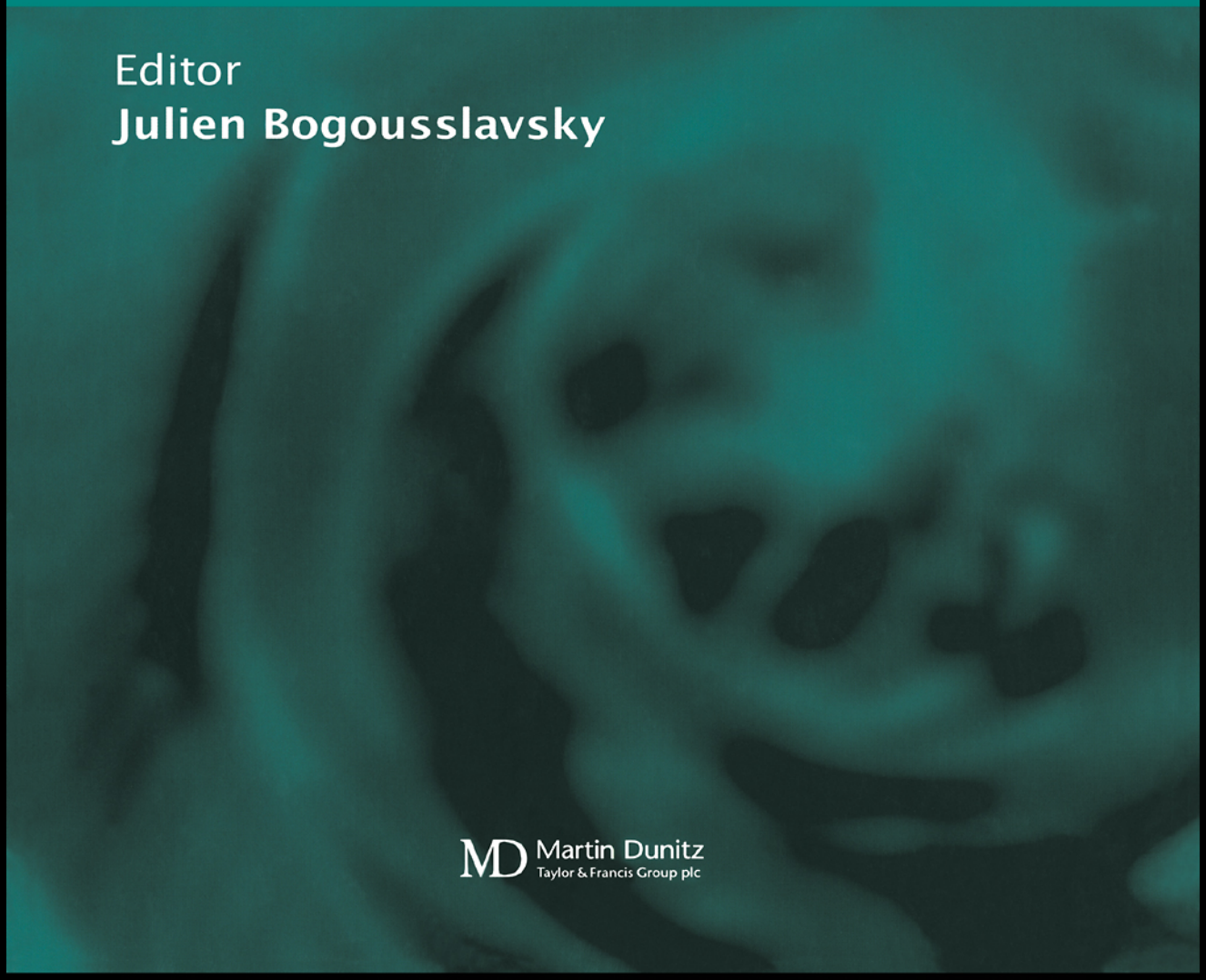
ACUTE STROKE TREATMENT

Second Edition



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Second Edition

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1.
Acute stroke management around the world

Stephen M Davis, David M Rosen and Geoffrey A Donnan

INTRODUCTION

There is substantial variability in the acute management of stroke within and between countries. Stroke clinicians are interested in studying variations in management, because this may help them choose better treatments that could improve outcomes. Health administrators are interested because evidence of better outcomes related to specific interventions could affect the allocation of scarce health resources to major diseases such as stroke.

Epidemiological studies of age-standardized stroke mortality rates in many countries indicate a dramatic reduction over the past 25 years, with up to 7% average annual declines.[1,2] This decrease appears to be at least partly due to falling 30-day case-fatality rates, as there are less clear changes in stroke incidence.[3] Falling case-fatality rates may in part reflect the greater clinical detection of milder strokes but could also reflect better acute stroke care.

There is very large variation in stroke mortality around the world. Despite these encouraging international trends, stroke mortality and morbidity remain high. Even in Western countries, 1-year stroke mortality remains a very high 40% at 12 months,[3–6] higher than most forms of cancer, which emphasizes the importance of international efforts to identify acute stroke therapies. In therapy for acute myocardial infarction, the positive results of large prospective, randomized, controlled trials in the 1980s were rapidly translated into clinical practice and have transformed clinical management.[7]

In recent years, three major evidence-based advances in acute stroke therapy have included the proven benefits of organised care in stroke units,[8,9] thrombolysis using intravenous tissue plasminogen activator (t-PA) within 3 hours of stroke onset,[10] and a modest reduction in adverse outcomes achieved with aspirin used in the first 48 hours after stroke onset.[11,12] These therapies should finally mark the end of the era of therapeutic nihilism for acute stroke.[13] It is now important to consider the current organization of stroke services and management of acute stroke around the world to understand the impact of the newer treatments.

Unlike acute myocardial infarction, stroke encompasses a heterogeneous group of pathologies, with variable outcomes and strategies for prevention and acute intervention. Differences in stroke around the world make it difficult to interpret the effects of different management strategies. First, there are important differences in stroke epidemiology and pathogenesis in different countries. For example, intracerebral hemorrhage is more prevalent in Chinese[14] and Japanese populations.[15] In many Asian countries stroke mortality is higher than the mortality rate of acute myocardial infarction, the reverse of the situation in Western societies. Intracranial atherosclerosis and small-vessel disease are more common in Black and Asian populations,[16,17] compared with the predominantly extracranial distribution in Caucasian individuals. Furthermore, in some countries, the proportion of stroke subtypes may be changing. In Japan, declining

rates of cerebral hemorrhage and increasing numbers of lacunar and extracranial large-vessel infarcts may reflect earlier antihypertensive treatment and dietary changes, with reduced salt but, conversely, increased meat consumption.[18] There has been a rapid increase in the prevalence of hypertension in a number of central and east Asian countries.[19]

Secondly, both population-based stroke mortality rates and case-fatality rates show significant differences in various parts of the world. Although acute stroke case-fatality rates are similar in many countries,[6,14,20–22] there is a huge 10-fold variation in age standardized, population-based stroke rates between countries with a very high rate, such as Bulgaria, Russia, and China, and countries with a low rate, such as France, the USA, and Switzerland.[1,2] The WHO MONICA (World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease) study showed a threefold variation in the 28-day stroke case-fatality rate between populations, lowest in Nordic countries and Germany, and highest in most Eastern European populations.[23] Swedish and Swiss case-fatality rates, in particular, appear to be lower than most countries.[24,25] It has been suggested that this may partially reflect a referral bias because of their high rates of hospitalization for acute stroke, including milder strokes not admitted in other countries.[22] However, differences in acute management, particularly the ready access to organized care in acute stroke units in some countries, could also explain some of this variation.

Applying the results of major stroke trials into clinical practice may therefore be limited by important international differences. These include geographical variations in the pathogenesis and outcome of stroke, differing organization of stroke services, variations in access to acute stroke treatment and investigations, emergency transport and hospital arrival times, admission procedures, expert stroke physician involvement, numbers of stroke units, consent procedures, and the use of unproven therapies.

To prepare this overview, pertinent literature was reviewed and information sought from stroke investigators involved in acute stroke management and clinical trials in Australia, Canada, China, Finland, France, Germany, Hong Kong, India, Indonesia, Israel, Italy, Japan, New Zealand, Singapore, South Africa, Sweden, Switzerland, the UK, and the USA. Much of the information provided regarding current practice in various countries is a qualitative impression, because detailed quantitative data are often lacking. Furthermore, as conveyed by one colleague, given the rapid changes in stroke care, what was standard management in 1 year may not be relevant in the next. Major international trends in acute stroke management are summarized in Table 1.1.

HEALTH SYSTEMS AND ACUTE STROKE ORGANIZATION

The organization of stroke services varies widely around the world. Deficiencies in services for acute stroke patients have long been recognized, in part because of professional nihilism as well as economic constraints. A UK report concluded some years ago that services for acute stroke were haphazard and fragmented, with a marked lack of data concerning the efficacy of interventions, including rehabilitation.[26] The organization of acute care varies, on one extreme, from the virtually total lack of resources in rural Africa, to helicopter transport and coordinated high-technology care in Switzerland and parts of the USA.

Table 1.1 International trends in acute stroke management

- Education of community and primary care doctors about acute stroke recognition, emergency management
- Coordinated emergency transport
- Rapid emergency department triage
- Acute stroke unit care
- Multicenter acute stroke trials

- Introduction of proven, interventional therapies—t-PA[a] and acute aspirin
- Emphasis on acute, multidisciplinary rehabilitation

[a] t-PA=tissue plasminogen activator.

In developed countries, financial strains are being imposed on the availability of acute care by the aging of the population, expensive new diagnostic therapeutic techniques, as well as increased patient expectations. In an effort to reform health delivery and optimize cost efficiencies, several countries have introduced managed competition with separate purchaser and provider roles. The effect of these changes could favor decentralization of acute stroke care, at odds with the common belief by stroke physicians that centralized, well-resourced, expert stroke centers are best suited to deliver acute stroke interventions such as thrombolysis.

The demand for acute stroke services will increase. However, new developments are likely to be hampered by cost constraints, unless cost-effectiveness can be shown. As a result, various national expert peer groups in the USA, the UK, Europe, Australia, and New Zealand have formulated evidence-based guidelines for optimal acute stroke management.[27–30]

STROKE PUBLIC AWARENESS AND INFORMATION STRATEGIES RELATED TO ACUTE STROKE

There is a global recognition of the enormous need to educate better both the public and health professionals in stroke diagnosis and management. Public ignorance about stroke is a worldwide problem. In the USA, the National Stroke Association estimated that 40% of people could not name the warning signs of stroke.[31] Stroke experts in most countries have an impression of widespread public ignorance about stroke and even confusion with myocardial infarction. In an Australian survey, 23% of people thought that stroke was associated with chest pain.[32] In response, many countries have developed public education and awareness campaigns directed at stroke prevention, acute stroke recognition, and treatment. In the USA, the concept of ‘brain attack’, analogous to heart attack, is promoted by the American Heart Association and the National Stroke Association and a Brain Attack Consortium has been formed. Similar strategies are being implemented in many European countries, Australia, and New Zealand. Such educational efforts have been shown to increase recognition of stroke symptoms and facilitate rapid emergency presentation of stroke patients.[33]

HOSPITALIZATION RATES FOR ACUTE STROKE

Expert opinion recommends that stroke be regarded as an emergency and that stroke patients should be urgently admitted to hospital to ensure accurate diagnosis, determination of likely pathogenesis and secondary prevention, enable coordinated acute medical care, and ensure appropriate rehabilitation.[27,34] There is considerable international variation in hospital admission rates after stroke. Around the world, approximately 80–90% of acute stroke patients are hospitalized,[35] although the proportion is much lower in developing nations such as India, where most patients are treated at home. In Oxfordshire, UK, only 55% of patients were admitted to hospital in the mid-1980s, although this is now much higher.[36] In South Africa, although stroke rates are similar in black and white populations, black patients, who are often indigent, tend

to be only briefly hospitalized before being discharged home without rehabilitation. In contrast, hospitalization of acute stroke patients approaches 100% in Sweden,[24] Switzerland,[25] and Russia.[35]

Hospitalization rates are also important for accrual in clinical stroke trials. Even in a small territory like Hong Kong, with only 5000 new strokes per year, it was possible to mount a successful clinical trial[37] because 30% of patients were admitted to hospitals participating in stroke trials. At least one-third of patients with acute stroke in Switzerland and Sweden are admitted to hospitals participating in clinical trials. In Australia, with a population of nearly 20 million, 40 urban and rural centers were involved in the Australian Streptokinase Trial.[38,39] These centers have now become coordinated through the Australasian Stroke Trials Network. The introduction of effective interventional therapies for acute stroke, based on clinical trial results, would be expected to further increase the demand for hospital-based care.

TRANSPORT, ARRIVAL TIME, AND TRIAGE OF STROKE TRIAL PATIENTS

Short hospital arrival times are crucial for acute stroke therapies, given the brief therapeutic windows.[40] Delayed stroke arrival times are a global problem, which largely reflect ignorance and nihilistic attitudes of patients, carers, and primary care practitioners. In contrast, rapid arrival times after trauma and acute myocardial infarction correlate with the anticipated benefits of early intervention. It should be remembered that urgent transport and the development of coronary care units predated proven therapy for acute myocardial infarction.

Hence, major changes are now necessary in most countries to develop the necessary infrastructure to accommodate the advent of acute interventional stroke therapies. Some of the current delays may reflect geographical factors, with large distances to stroke centers in some countries. Delays in stroke arrival are seen as a major problem both in developed countries such as the USA, Japan, Germany, and Australia, as well as in developing nations such as India and Indonesia. One older US study found that only 42% of patients presented to hospital within the first 24 hours.[41] In contrast, some small countries or cities, with well-coordinated emergency medical services, have achieved much shorter hospital arrival times for acute stroke patients. To optimize access to acute therapy, particularly t-PA, some cities in the USA, such as Houston and Cincinatti, have well-coordinated programs. In Finland, stroke cases are rapidly transported to a designated regional center, to increase the probability of receiving t-PA. In many Western countries, at least 50% patients arrive within 6 hours. A recent UK study showed that 50% patients arrived within 6 hours and that the use of emergency services reduces delays (K.Lees, pers. comm.). In Switzerland, all patients could potentially be admitted to hospital within 1 hour because of the large number of small, scattered hospitals and an active helicopter service.[25] In Japan, 37% of patients arrived within 3 hours. An Australian study showed that the median delay was 4 hours and delays were related independently to stroke type, the shortest being for cerebral hemorrhage.[42] In New Zealand, 52% of patients in the Auckland region arrive at hospital within 4 hours,[43] 69% of stroke patients arrive within 6 hours in the Tel Aviv area of Israel, whereas in Hong Kong 63% of stroke patients arrive within 12 hours.[14] In India, the time delay relates directly to geography, and is often as long as 48 hours in rural areas.

The experience of many hospitals is that involvement in clinical stroke trials has enhanced emergency transport, arrival times, triage, and emergency management. In centers participating in the US National Institutes of Health t-PA pilot studies, over 50% of patients arrived within 3 hours.[44,45] However, even with rapid transportation to hospitals participating in stroke trials, only a small proportion of patients are eligible for acute therapy protocols. Hence, only 17 of 222 patients in a Dutch study with cerebral infarction and an admission delay of less than 6 hours would have been eligible for an acute stroke trial[46] and, similarly, only 5% of patients arriving at the Multicentre Acute Stroke Trial-Europe centers fulfilled entry criteria.[47] In the

absence of the stringent eligibility and consent criteria required by controlled trials, a higher proportion of patients can, however, be treated.

Stroke arrival times should be shortened by better collaboration between patients, relatives, primary care doctors, ambulance services, and acute hospitals. A US study showed that the medical delivery system for acute stroke could be substantially improved with implementation of a coordinated strategy, together with in-hospital urgent management protocols.[40]

In most countries, stroke investigators consider that organization of stroke services is poor, impeding both trial entry and acute management. Accrual for the Multicentre Acute Stroke Trial-Europe[47] was particularly successful in smaller French cities. In the USA, although no national plan exists, each stroke center has its own enrolment strategies. The selection of 'preferred providers' by managed care organizations in the USA could affect these strategies. Important variation also exists in perceptions about stroke by referring family doctors in different countries concerning potentially useful drugs and their willingness to refer patients to stroke trial centers. This underscores the importance of educating family doctors about advances in stroke management, particularly t-PA, and involving them in the organization of acute stroke trials.[48]

Expert guidelines in many countries now recommend that the patient, relative, or bystander should call directly an emergency ambulance number, without the inherent delay involved in consulting a personal physician.[27] This has been shown in the USA to reduce arrival times.[45] An Australian study[42] indicated that median arrival delay was significantly increased if initial contact was made with the local doctor. In Russia, neurologic emergency ambulances have been set up in many large cities, similar to the coronary care ambulances already organized in most countries.

TRIAGE AND URGENT INVESTIGATIONS FOR ACUTE STROKE

Delays in recognition and communication in emergency departments of acute stroke patients are generally seen as common problems, particularly affecting stroke trial accrual. In some countries, it is perceived that house doctors, who have a low awareness of stroke trials, often cause delays. In Tel Aviv, Israel, a successful tactic has been to have a neurologist in the emergency department, strokes being seen as the first priority. In the USA, a suggested strategy has been to enlist emergency room physicians as trial co-investigators or even to link reimbursement to the interval from stroke onset. In some Australian hospitals, the triage nurse in the emergency department directly pages a stroke coordinator concerning all stroke arrivals, bypassing junior doctors. Other centers triage directly from the hospital arrival area to a stroke unit, avoiding emergency department delays.

In an effort to triage and to treat patients from the emergency departments of hospitals more rapidly, to reduce inefficiencies and delays, and to increase the proportion of patients eligible for acute interventions, in-hospital medical stroke treatment teams have been advocated by US studies.[49,50] The Houston study,[49] showed that the presence of a stroke team can shorten the time to physician examination and facilitate emergency management. Instituting rapid response systems, such as 'code stroke,' with a stroke team,[50] can reduce in-hospital treatment delays.

Urgent computed tomography (CT) scanning is mandatory in modern stroke care, both to distinguish ischemia from hemorrhage and to exclude non-cerebrovascular pathologies masquerading as stroke. In the late 1980s, CT scanning rates in the WHO MONICA study varied from zero in Russian centers to 17% in Poland and Lithuania, 67% in Beijing, China, and up to 75% in several Western European countries.[35] Access to CT scanning is still very limited in developing nations, but is rapidly increasing. It is now estimated to be 65% in those reaching hospital in India, although very low in Indonesia. Stroke patients admitted to hospital may be younger than Western cohorts.[51] Rates of CT scanning in stroke patients were

still surprisingly low in some developed countries until recent years. In a New Zealand study, only 42% of hospitalized stroke patients had CT scans in the early 1990s, although this proportion has recently increased to nearly 90% in the last few years.[43,52]

HOSPITAL ORGANIZATION OF ACUTE STROKE: NEUROLOGIC INVOLVEMENT AND STROKE UNITS

There is wide international variation in the hospital organization of acute stroke. Around the world, internal medicine physicians and geriatricians, with variable interest and expertise in stroke management, treat the great majority of acute stroke patients. In academic centers, early neurologic or stroke physician involvement is much more common. There are interesting geographical differences. For example, in Russia and Finland, neurologists generally manage stroke patients. In the USA, many are cared for by primary care physicians and this proportion is thought likely to increase given the emphasis being given to managed care plans in the community setting. In contrast, neurologists are responsible for most strokes in large, academic US centers, whereas neurosurgeons usually manage patients with large intracerebral or subarachnoid hemorrhage. Due to a shortage of neurosurgeons trained in vascular techniques in Argentina, endovascular techniques are used routinely for aneurysms and vascular malformations.

In the UK, only 5% of neurologists in one survey routinely managed acute stroke patients.[53] This low proportion, reflecting in part the very low number of neurologists in the UK, has generated controversy as to whether all stroke patients in that nation should be seen by a neurologist, rather than a geriatrician or general physician with an interest in stroke.[54,55] In a report from Sweden, only 9% of acute stroke patients were admitted to neurology departments, although stroke unit care is routine.[56] General physicians care for most acute stroke patients in New Zealand.[57] In contrast, neurologists in Germany generally manage stroke patients. In many countries, although internal medicine physicians manage most stroke patients, neurologic consultation is common. In Japan, about 50% of stroke patients are managed by neurosurgeons. A Swiss study showed that emergency neurologic evaluation of stroke enhanced diagnostic accuracy.[58]

A European survey reviewed acute stroke care in 22 countries in 1997 and confirmed an ‘East-West gap’. Hence, while stroke incidence and mortality rates were higher in Eastern Europe, hospitalization and CT scanning rates were lower.[59] It was thought that the higher 30-day case-fatality rates in Eastern Europe may have reflected differences in case mix, with the admission of a greater proportion of more severe ischemic strokes and cerebral hemorrhages.[59]

Around the world, the development of acute stroke units represents the single most important development in the organization of acute stroke management in recent years. Both geographically defined stroke units and mobile stroke teams have been shown to improve outcomes after acute stroke. Although many models have been described, it appears that relatively low-technology care by an expert, multidisciplinary stroke team is the key component of the measured benefits.[8,60,61] In a systematic overview, Langhorne et al.[8] identified 10 trials evaluating the management of stroke patients in a specialist unit compared with general medical ward care and found significant benefits in both acute and 12-month mortality rates. Most of the positive studies indicated that integrated stroke rehabilitation, including physiotherapy, occupational therapy, and speech therapy, were started earlier and provided more intensively to the patients in stroke units than control individuals on general medical wards. Since this overview, other individual studies and meta-analyses have shown that stroke unit care is associated with reduced mortality.[9,62,63] In addition, reduced costs have been linked linked to shorter length of stay.[63] A recent outcome cohort study showed long-term benefiits for those treated in stroke units, with survival advantages and less dependency for primary activities of daily living.[64]

Despite this compelling evidence of their benefits, the number of stroke units around the world is still very small and, until recently restricted to academic centers with stroke interest and expertise. For example, in the UK, only 5% of physicians looking after acute stroke patients reported having access to a stroke unit some years ago.[53] However, more recent information indicates that there are now approximately 40 acute stroke units and 100 stroke rehabilitation units in the UK. There are only 8 units in South Africa, all in major cities. In contrast, non-intensive stroke units and mobile stroke teams have been established in the great majority of hospitals in Scandinavia, stimulated by research in those countries into the benefits of organized stroke care. Sweden was the first country in the world to develop a national stroke registry to monitor all aspects of stroke care, termed *Riksstroke*. The registry manages parameters of quality of care, such as stroke unit access, CT rate, antithrombotic therapy, mortality, and functional outcomes.[64] Finland, also, has wellorganized acute stroke care. There has been a dramatic increase in the proportion of patients treated in stroke units. In Australia, a National Stroke Strategy was launched in 1996, emphasizing evidence-based best practice for stroke, particularly stroke units. There have been a number of state-based strategies aiming to implement these recommendations. A substantial proportion of Italian patients have access to stroke units.

The number of units in the USA is still small. A colleague estimates that less than 5% of patients are treated in acute stroke units, but this is likely to continue to increase following the recommendations of the American Heart Association expert panel on the management of acute stroke, which endorsed the development of acute stroke units as of proven value and a high priority.[27] In Hong Kong, there are regional stroke units. There are still very few stroke units in India, all in major urban centres. In Australia, approximately 25% of stroke patients are currently being admitted to stroke unit care. In New Zealand, only 6 of 41 hospitals admitting stroke patients had organized care in a recent review.[52] There are also few stroke units in Israel, although good access to rehabilitation facilities.

It is unclear which specific stroke unit strategies produce the measured benefits. Stroke unit patients have increased therapeutic contact with nurses and therapy staff, compared with those treated in general medical wards.[65] The structure of stroke units varies considerably. Neurologic intensive care units are often the model in Germany,[66] Switzerland, and Italy, whereas in Australia, the UK, and Sweden, stroke units are generally discrete ward areas with expert staffing but little high-technology monitoring equipment. Other stroke units are essentially neurorehabilitation wards as opposed to acute treatment facilities.

USE OF STROKE PROTOCOLS AND CLINICAL MANAGEMENT PLANS

Treatment for the acute stroke patient in a number of countries has seen the recent introduction of managed care paths, using various protocols that commence in the emergency department and incorporate medical, nursing, and allied health aspects of integrated team care. An experienced, multidisciplinary team, working in a specialized ward can facilitate the implementation of managed care paths (or clinical pathways). The use of such protocols has been shown to reduce acute hospital costs, chiefly as a result of reduced bedstay, without increasing the number of investigations.[67,68] Some studies have shown that the use of such protocols can also reduce complications after stroke, such as aspiration, urinary problems and infections.[69] Information from colleagues around the world suggests that such care plans are still limited to centers with stroke units.

There is increasing pressure in some countries, such as the USA and Australia, to reduce length of hospital stay for stroke patients, based on reduced reimbursement and diagnosticrelated group (DRG)-based funding mechanisms. In a US study, unjustified, protracted hospital stay for stroke patients was specifically related to delays in rehabilitation and other placements and delays in obtaining investigations.[70] Such

delays, termed exit block, are common in Australian teaching hospitals because of a shortage of inpatient rehabilitation resources and nursing home places, as well as a high demand for investigative services such as magnetic resonance imaging (MRI) and echocardiography.

INTERNATIONAL ACUTE STROKE TRIAL COLLABORATIONS

There has been an explosion in the number of stroke trials in recent years. Clinical trials aim to change medical practice. Ideally, a new therapy should accomplish significant and clinically relevant improvements in all measures of stroke outcome as well as a reduction in mortality. Generally, acute stroke trials have only been powered to show reduction in morbidity. These trials have increased the awareness of the potential for acute interventional strategies and the importance of the short time windows in which therapy needs to be initiated. Some acute stroke trials have been substantially confined to single countries, such as the Australian Streptokinase Trial,[38,39] the French-based Multicentre Acute Stroke Trial-Europe,[47] and the Italian Multicentre Acute Stroke Trial-Italy.[71] However, many have involved international collaboration, such as the International Stroke Trial,[11] the European Cooperative Acute Stroke Trials,[72,73] and many of the recent neuroprotective and secondary prevention trials. Stroke investigators continue to debate the optimal design for an acute stroke trial, particularly the necessary sample size. To show small but potentially important effects on stroke outcomes, very large patient numbers will be needed, similar to the successful acute myocardial infarction therapy protocols. Very large single country trials are only possible in those with large populations at risk of stroke, as in the USA and Japan. Accrual of large numbers of patients in mega-trials, such as the International Stroke Trial,[11] will usually require international collaboration between trial centers. Some countries or geographical regions have organized the coordination of stroke trials. These include the Canadian Stroke Consortium and the Australasian Stroke Trials Network. An Asian network involving Singapore, China, and other countries is being set up.

ETHICAL ISSUES IN STROKE MANAGEMENT: CONSENT PROCEDURES FOR STROKE TRIALS

Many stroke centers around the world are currently involved in clinical trials, the results of which will significantly alter acute stroke therapy. Reasonably simple, ethically sound consent procedures are most important for trial enrolment. There are important differences in approach to informed consent in different countries. The two key issues of relevance to stroke trials are (1) the complexity of the consent procedure and (2) whether surrogate consent (by spouse or next of kin) is permitted in those patients with aphasia or impaired conscious state. For example, the huge disparity between accrual for the ISIS-2 acute myocardial infarction trial in the UK and USA was thought to have reflected the far more complex consent protocol required in the USA.[17] The UK approach is typically a less formal one than in the USA, allowing far greater discretion by the individual doctor, with the view that excessively detailed consent can be inhumane and can impair trial recruitment. Furthermore, by delaying the discovery of effective treatments, this might potentially cause many deaths. While virtually all countries require some form of informed consent, many institutional ethics committees allow surrogate consent by spouse or next of kin if the patient cannot provide consent because of dysphasia or depressed conscious state. However, the legal status of surrogate consent appears to be unclear in many countries.

In some Asian countries such as Singapore, discussion and consent by the family is paramount. In contrast, in some countries, only the patient can consent to involvement. Hence, patients with dysphasia or altered conscious state are excluded from acute trials. In the USA, there are differences in legislation

between states and policies by individual institutional review boards, but evolving legal policies might well prohibit surrogate consent. Various patient advocacy and guardianship acts, which prohibit surrogate consent, are already in place in some Australian states. One American study indicated that such policies could reduce acute trial accruals by one-third and particularly affect entry of patients with more severe, and language-impairing strokes.[74]

ACUTE STROKE THERAPIES IN CURRENT PRACTICE

The results of the recent thrombolytic trials showed benefits in selected patients with acute ischemic stroke treated with intravenous t-PA within 3 hours of stroke onset in the US National Institute of Neurological Disorders and Stroke Trial[10] and a strong trend to improved outcomes for some patients treated within 6 hours in the absence of major early ischemic changes on CT in the ECASS trials.[72,73,75] Meta-analysis shows significant benefits of t-PA within 6 hours.[75,76] On the basis of these results, expert consensus panels, including the USA, Europe, and Australia, now advocate the use of t-PA within 3 hours in carefully selected and monitored patients in experienced centers.[27,30] However, currently the drug is not licensed for ischemic stroke in most countries outside of North America, with limited licensing in Europe. Even in the USA, it is estimated that only about 3% of patients receive t-PA and there remain many problems with physician acceptance and health system organization. In Germany, intravenous t-PA is now being widely used in anterior circulation stroke, whereas intra-arterial thrombolysis is often performed for basilar thrombosis. In most countries outside of North America and some European countries, t-PA is rarely used.

The Edinburgh group has proposed that this uncertainty can only be resolved if t-PA is evaluated in a mega-trial design, termed IST-3.[77] This is controversial. Opponents consider that there is an adequate level of proof of benefit within 3 hours, provided that the therapy is only administered within experienced stroke units, employing the safeguards used in the NINDS trial. Indeed, recent post-marketing experience with t-PA indicates the hazards of the therapy when these guidelines are breached. In one open study where there were protocol violations in 50% of patients, the symptomatic, intracerebral hemorrhage rate reached 16%, compared with 6.4% in the NINDS trial.[78] In contrast, the hemorrhage rate in experienced centers was found to be only 3.3% in the STARS study, evaluating t-PA experience with strict protocol adherence.[79] In summary, despite the accumulated evidence indicating significant benefits within 3 hours, t-PA is little used around the world because of a combination of factors, including very restricted licensing, emergency health system issues, and a variable degree of physician uncertainty

Two very large trials (the International Stroke trial[11] and the Chinese Acute Stroke Trial[12]) both showed that aspirin administered within 48 hours of stroke onset produced a modest improvement in outcomes at 6 months. Aspirin appears to be routinely used internationally in acute ischemic stroke, unless thrombolysis is being administered. Following a report of survival benefits after decompressive brain surgery for patients with life-threatening edema after stroke, this treatment is used for selected patients in Germany.[80]

A wide variety of currently unproven acute stroke therapies continue to be used around the world. There are significant differences in attitudes of both treating specialists and primary care doctors in different countries.[48] Few therapies in clinical medicine ignite as much controversy as the role of heparin in stroke. Many studies and information from colleagues indicate that heparin remains the most widely used unproven therapy in most countries. The great bulk of the evidence concerning heparin is based on the International Stroke Trial (IST),[11] which evaluated unmonitored, subcutaneous heparin up to 48 hours after stroke onset, rather than monitored, intravenous heparin delivered continuously in the acute setting. However, negative results have also been generated from studies with low-molecular-weight heparin and heparinoids.[81]

Heparin is frequently used in many countries, most often for cardio-embolic, basilar territory or progressive infarction. In the USA[5,82] 22% of patients with ischemic stroke were treated with heparin in the first 24 hours, despite their physicians' widespread concerns about both its safety and efficacy. Another US study found that 90% of neurologists recommended heparin therapy for progressing stroke and a majority anticoagulated most patients with partial stroke.[5] Information from colleagues indicates continued widespread use of heparin in the USA. In contrast, intravenous heparin is now rarely used in the UK.

Other acute stroke therapies are at odds with evidence-based guidelines. For example, in India and Argentina, calcium channel blockers and vasodilators are often used. In Argentina, use of cerebral 'energisers' such as carnitine is common. In Singapore, acupuncture and Chinese herbs are used, particularly after the acute phase. Traditional medicines are popular in China. In an earlier UK survey, approximately one-third of consultants used calcium channel antagonists or high-dose steroids in selected patients.[83] However, recent feedback from colleagues indicates that this is no longer the case. This study also found that active treatment of hypertension within 24 hours of acute stroke was practiced by over 25% of UK physicians, despite substantial evidence and expert opinion that acute antihypertensive therapy is likely to be hazardous in cerebral ischemia.[27,84] A New Zealand survey also showed that 23% of physicians instituted acute antihypertensive therapy.[57] Pentoxifylline is often used in India and Indonesia. In contrast, such therapies are rarely used in Finland and Sweden.

CONCLUSIONS

There is currently a revolution in stroke care around the world (Tables 1.1 and 1.2). Important developments include strategies to develop coordinated transport to facilitate earlier arrival times for acute stroke patients, the proven value of acute stroke units, and the first effective acute interventional therapies.

Nonetheless, there is still a widespread perception of therapeutic nihilism and inadequate organization of stroke care in many countries. There is a vast gulf in care standards between stroke patients in affluent, well-resourced countries and those in developing nations. Even in industrialized countries, cost constraints and changes in health care systems are likely to affect acute stroke services. Results of clinical trials are producing an impetus to change the clinical management of stroke. These evidencebased results will emphasize deficiencies in the ability of health organizations in different countries to deliver these new treatments. There will be increased emphasis on showing not only efficacy but also cost-effectiveness of new acute therapies. Increasingly, neurologists and other physicians with an interest in stroke are becoming involved in public education and policy formulation concerning stroke management. Future international differences in stroke outcomes are increasingly likely to reflect differences in the ability of health services to deliver effective therapies.

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Table 1.2 Factors that influence stroke management around the world

Factors	Benefits	Difficulties
Public education	• Stroke prevention, stroke recognition	• Increasing demands
	• Consumer and patient advocacy groups	• Increasing gap between expectations and reality
Professional education	• Interdisciplinary education	• Professional nihilism
	• Brain attack coalition	• Insufficient commitment to change
	• Practice guidelines	
Hospitalization	• Accurate diagnosis, acute therapy, multidisciplinary care, secondary prevention	• Arrival delays, lack of facilities in developing countries
Computed tomography (CT) scanning	• Accurate diagnosis, exclusion of non-stroke pathologies	• Inadequate CT scan access in poorer countries
Trials of acute stroke therapies	• Evidence-based treatments	• Complex consent procedures
		• Investigator-drug company dependence
		• Continued use of unproven therapies
Delineation of effective therapies	• Improved stroke outcomes	• Delay in hospital arrival
		• Lack of infrastructure
Stroke unit care	• Proven benefits	• Threat to non-stroke physicians
	• Improved stroke outcomes	
Organization of health services	• Needs-based resource allocation	• Increasing costs
	• Better delivery of stroke care	• Barriers to access of appropriate services
		• Decentralization of services

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2.
The behaviors of the acute stroke patient

Antonio Carota, Fabienne Staub and Julien Bogousslavsky

INTRODUCTION

The brain mediates and integrates all cognitive activities, emotional experiences and, finally, behaviors. Stroke is a clinical syndrome characterized by an acute loss of focal cerebral function with symptoms lasting more than 24 hours. Acute stroke has a deep impact on patients' behaviors.

In this chapter the focus is on acute ischemic lesions, because they better associate to stereotyped behaviors and allow more precise anatomoclinical correlations.

We will consider the acute phase the first 2 weeks after onset. During this interval, the core area of the infarct and the hypoperfusion zone are probably the more relevant factors for behavioral signs. In the later phases, during the recovery process, tissue (gliosis) and functional changes (plasticity) further contribute to behavioral symptoms. In both phases, other variables than lesion location may play a role (premorbid personality, pre-existing psychiatric and neurologic diseases, epidemiologic and genetic factors, psychological reaction to the impairment), resulting in great individual intervariability.

In acute stroke, cognitive syndromes such as aphasia or neglect are easily recognized and classified, but emotional, mood, and behavioral changes (psychosis, depressive reactions, anxiety, mania, apathy) are less well defined in their phenomenology, pathogenesis, and linkage to regional brain dysfunction. On many occasions they are also undiagnosed. In this period, behavioral changes are often transitory and fluctuating. Nevertheless, acute stroke undoubtedly remains a privileged disease for behavioral studies. It has a high incidence, and recent advances in high-resolution magnetic resonance imaging (MRI) techniques and functional neuroimaging allow precise lesion localization[1] as well as on-line visualization of cerebral areas and networks activity.[2]

HEMISPHERAL FUNCTIONS

More recent theories integrating neuropsychological and neuroanatomical data, and cognitive models, regroup hemispheral activities in three main functions: instrumental, fundamental, and executive.[3]

Instrumental functions comprise communication, motion, perceptual recognition, and praxis; fundamental functions include information-processing speed and regulation and motivation of mood and emotional states; and executive functions refer to abstract thinking, sequentiating analysis, ability to direct attention, and faculty of on-line answering to environmental actual changes.

Each function originates from the integrated activity of different cerebral areas and systems (node and networks in terms of neural circuitries), which have their own specific role (regulatory, enhancing, or inhibitory) in cognitive, emotional, and sensorimotor processing. This subdivision predicts precise

anatomicomedical correlation (such as in the case of aphasia or neglect) for acute lesions in the areas subserving instrumental functions, and less exact anatomoclinical matching for acute lesions within the network of fundamental and executive functions (such as in the case of depression, anxiety, and apathy).

The classification shown in Table 2.1 allows the systematization of acute behavioral changes due to stroke in a framework based on functional, anatomical, and phylogenetic data.

Table 2.1 Instrumental, fundamental, and executive functions (adapted by Cummings and Bogousslavsky[3])

	Instrumental	**Fundamental**	**Executive/integration**
Gray matter structures Cortical	Posterior heteromodal cortex (six-layered)	Hippocampus cingulated orbitofrontal cortex (three-layered and transitional)	Dorsolateral prefrontalheteromodal cortex (six-layered)
Thalamus Basal ganglion	Pulvinar None	Dorsomedial anterior Ventral striatum Pallidum	Dorsomedial Dorsal striatum Pallidum
White matter tracts	Long intrahemispheric and interhemispheric associations fibers	Medial forebrain bundle: mostly shorter tracts	Frontal-basal ganglia and thalamic-frontal connections
Neurotransmitters type	GABA (γ-aminobutyric acid) Glutamate Acetylcholine	GABA Glutamate Acetylcholine Dopamine Serotonin Norepinephrine	GABA Glutamate Acetylcholine Dopamine Serotonin Norepinephrine
Primary function	Direct information transfer	Modulation	Information transfer and modulation
Speed	Fast acting	Tonic	Fast acting and tonic
Organization	Serial linking of modules Hemisphere specialization (lateralization)	Little hemisphere specialization	Limited hemisphere specialization
Phylogeny	Recent evolutionary development	Primitive	Most recent evolutionary acquisition
Ontogeny	Incomplete at birth; development continues through childhood	Functional at birth	Incomplete at birth, development continues through early adulthood
Neuropsychological disorders	Aphasia Agnosia Apraxia	Bradyphrenia Avolition Reduced arousal Limbic system syndromes	Concrete thinking Distractibility Environmental dependency Frontal-subcortex circuit syndromes
Neuropsychiatric conditions	Anosognosia	Deficit: apathy Productive: irritability, depression, mania, anxiety, psychosis, obsessive-compulsive disorder	Deficit: loss of empathy
Emotional disorders	Disorders of emotional vocal and facial comprehension	Disorders of emotional experience—mood, threat	Disorders of emotional expression (aprosodias) and of emotional control (pseudobulbar palsy)

	Instrumental	Fundamental	Executive/integration
Dementia associated	Cortical dementia (especially Alzheimer's disease)	Limbic system dementia	Frontal and subcortical dementia
Pharmacological treatment	Limited response	Responsive	Limited response

ACUTE BEHAVIORAL CHANGES RELATED TO IMPAIRMENT OF INSTRUMENTAL FUNCTIONS

APHASIA

Acute aphasia has great time-dependent (hours or days) variability (Fig. 2.1), which makes it difficult to compare studies on the incidence of aphasia subtypes and related emotional displays.

In a preliminary study, we evaluated daily, during 7 days, 48 consecutive aphasic patients with first-ever uncomplicated stroke. Results showed early major aphasia changes (Fig. 2.2).

Global aphasia was the more frequent syndrome at the onset, and comprehension was the first linguistic domain to improve. Rapid and complete recovery is frequent with subcortical lesions.

Global aphasia is the more severe form of aphasia, with almost complete abolition of all linguistic faculties, a phenomenon that leads to speculation about the nature of a nonverbal thought. Patients are also unable to use gestures for purposeful communication. In global aphasia, the recording of event-related brain potentials might be useful to assess emotions and cognition.[4]

Patients with Broca's aphasia show intense emotional behaviors, often with a depressive content. The psychological states due to the frustration of aborted social contacts can be devastating.

In a study population of 326 patients with first-ever stroke[5] we found, by the mean of a pure observational method, that, in the first 4 days, among patients with left hemispheral lesion, aphasics show depressive behaviors more often. They attenuate with comprehension recovery (Fig. 2.3). Aphasia is known to increase the risk of developing depression in the late phases of stroke.[6]

Patients with Wernicke's aphasia (WA) show severe unawareness of their condition. In the acute phase, their behaviors have a high emotional content (aggressiveness, irritability, refusal, rage) and contention measures might be necessary. Fluctuations in comprehension are important in the first days. Later narratives show that cognitive and emotional process, not measured by aphasia examination, may exist independently of language.[7] During recovery, patients attribute their aggressiveness to the assumption that the examiner was deliberately speaking in an incomprehensible way. According to the valence theory (Fig. 2.4) the right hemisphere could be predominantly involved in negative and unpleasant types of emotional experiences such as fear, anger, panic, and melancholia.[8]

Wernicke's aphasia related displays could be the consequence of the shifting of emotional experience, especially that involved in language and personal communication, from the left to the right hemisphere.

Thalamic aphasia, usually observed with left thalamic lesions, in the acute phase, is often tinged with confusion (aphasic delirium).[9]

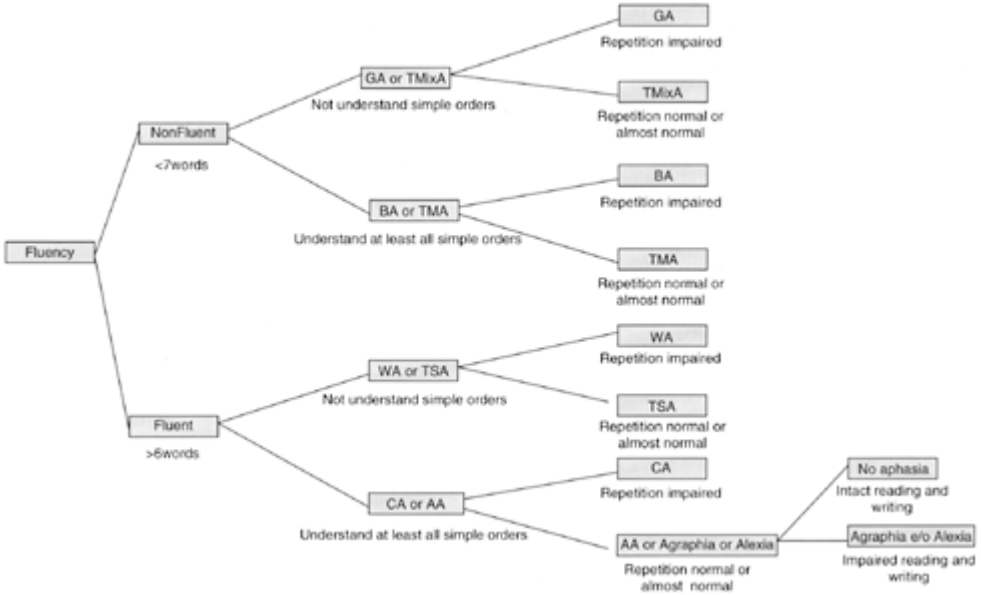

Figure 2.1 Algorithms for the diagnosis of aphasia in the acute stroke.

AA: anomic or amnestic aphasia; BA: Broca's aphasia; CA: conduction aphasia; GA: global aphasia; TMA: transcortical motor aphasia; TmixA: transcortical mixed aphasia; TSA: transcortical sensory aphasia; WA: Wernicke's aphasia.

AGNOSIA

Agnosia indicates a recognition deficit in one sensory modality that is not accounted for by sensory or oculomotor disorders, attentional impairment, aphasia, or mental deterioration. Stroke locations associated with agnosia are reported in Table 2.2.

Among visual agnosias, apperceptive agnosia corresponds to the disruption of visuo-perceptual processing: patient fails to recognize the object or its shape, to draw it, to isolate it from the background (Fig. 2.5), or to match it with a similar figure in different perspectives.

The patient sometimes looks as a blind person and, for recognition, uses other strategies than visual, such as tracing the contours with finger or head movements. In other cases, recognition failure emerges only with detailed testing, and perceptual and sensory deficits could be extremely difficult to separate.

Apperceptive agnosia has to be distinguished from simultaneoagnosia (impaired visual recognition of objects presented simultaneously), which is caused by a disturbance in orienting visual attention and not to visual fields' deficits or neglect. Simultaneoagnosia, gaze apraxia, optic ataxia, and impaired distance and depth perception constitute Balint's syndrome, which results from bilateral lesions of the parietooccipital junction.

Specific tests[10] allow identification of shape agnosia (discrimination of figures from the background), agnosia for object orientation, integrative agnosia (whole object misidentification with

Table 2.2 Agnosia—lesion location in stroke

Visual agnosia (associative apperceptive)	Left medial occipitotemporal areas[13]

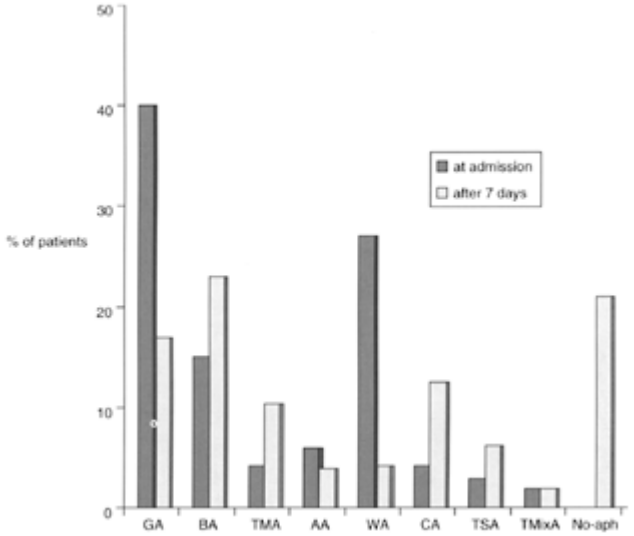

Figure 2.2 Aphasia acute changes.

AA: anomic or amnestic aphasia; BA: Broca's aphasia; CA: conduction aphasia; GA: global aphasia; TMA: transcortical motor aphasia; TmixA: transcortical mixed aphasia; TSA: transcortical sensory aphasia; WA: Wernicke's aphasia.

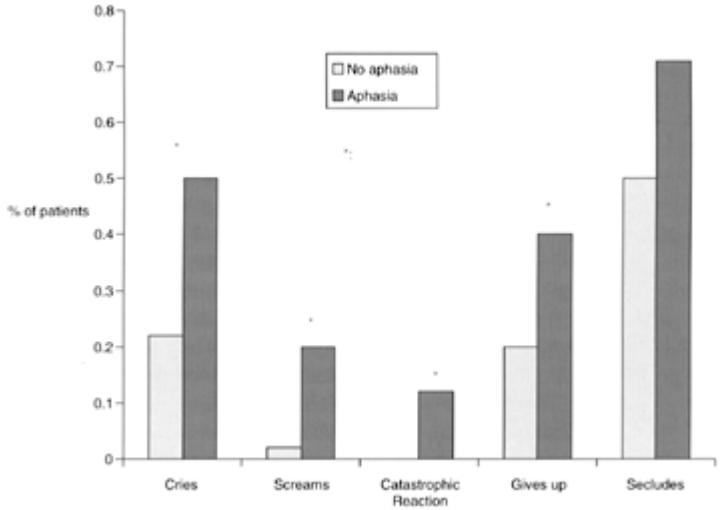

Figure 2.3 Observed behaviors in patients with left hemispheral stroke.

Optic aphasia	Left medial occipitotemporal areas[14]
Prosopagnosia	Bilateral occipitotemporal lesion[15]
	Right occipitotemporal lesion[16–18]
	Right temporal[19]
	Right lingual and fusiform gyri[20]

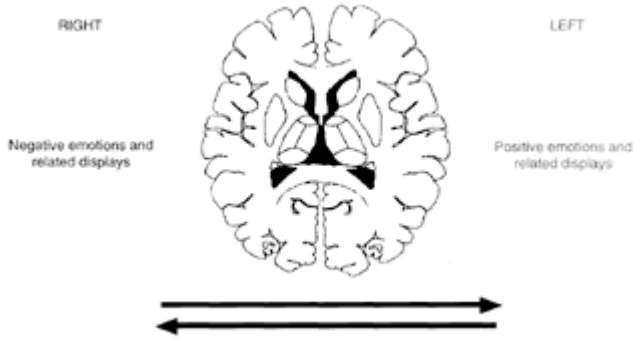

Figure 2.4 The valence hypothesis.

Figure 2.5 Example of figure which requires elemental visual-perceptive analysis

	Right fusiform gyrus and inferio and fourth occipital gyrus[21]
	Right thalamus[12]
Mirror agnosia	Right parietal lobe[11]
Olfactory agnosia	Right temporal lobe[19]
Topoagnosia	Right occipital lobe[22]
	Right parahippocampal gyrus[23]
Color agnosia	Bilateral occipitotemporal region [24,25]
	Fusiforme and lingual gyrus[26]
	Bilateral temporal and left inferomedial-occipital[27]
Music agnosia	Right superior temporal lobe and insula[28]
Auditory agnosia	Right temporal lobe[29]

sparing of details recognition), and agnosia for internal representation (the recognition process comparing the structured description of the object with its representation stored in the semantic memory). Internal representation (mental imagery) is evaluated by requiring the patient to decide whether a stimulus corresponds to a real object or not. Associative agnosia represents recognition failure of meaningful visual stimuli even when the perceptual structure is adequately encoded. Patients are often unaware of the acute deficit, and specific tasks—visual naming, miming the object use, semantic categorization and association tasks, and acknowledgment of semantic attributes—are diagnostic. Optic aphasia is the inability to name objects under visual guidance even if visual recognition is spared. The patient can name objects placed in his hands, reject wrong names for a visual presented object, and have no comprehension difficulties. Mirror agnosia, a very rare form of visual agnosia, refers to the inability of the patient to recognize that the object in the mirror is an image and not real; the patient usually tries to grasp the object.[11]

Prosopagnosia is the inability to recognize faces without non-physiognomic cues. In severe cases, patients cannot recognize relatives' faces or their own in the mirror. In milder forms, failure is limited to friends and acquaintances met in an unusual context, or to famous people, or it may only concern faces known after stroke onset. Patients with prosopagnosia in acute stroke usually don't complain about visual prob lems. They know that a 'face is a face' and are usually able to differentiate sex, race, and age, or emotional expression, but they fail to recognize its ownership. Prosopagnosia, could be further differentiated in apperceptive and associative forms. Two different systems process face recognition and facial emotional expression recognition because double dissociations (prosopoaffective agnosia without prosopagnosia and vice versa) have been reported.[12]

Visual agnosia is the more frequent form of agnosia in acute stroke but recognition failure may manifest in all the other sensory modalities (tactile, auditory, olfactive, gustative). One or several categories might be involved—objects, objects' orientation, color, faces, places, words, sounds, music, mental images, living/nonliving, familiar/nonfamiliar, canonical/noncanononical view, environmental/non-environmental—and double dissociations are possible but extremely rare.

Finger (or toe) recognition failure, right-left disorientation, acalculia, and peripheral agraphia constitute—when they associate and are not accounted for by other cognitive deficits (linguistic, visuospatial, attentional)—the elements of Gerstmann's syndrome. The lesion is limited to the superior angular and supramarginal gyrus. We observe this very rare syndrome more often in the recovery phase of a fluent aphasic syndrome.

UNILATERAL NEGLECT

Unilateral neglect represents a failure to attend, represent, orient, or respond to lateralized stimuli (generally on the left). In acute stroke, unilateral neglect may be noticed simply by observing spontaneous behaviors. The head and eyes deviate toward the right, and eye movements are reduced or absent on the left. Bed position is often unusual—lateral (on the right or on the left) or diagonal—and allows prompt diagnosis. Hyperneglect[30] denotes orientating toward the right for any stimuli given from the left, a phenomenon that substantially recovers in the first hours or days. In unilateral neglect, participation of left limbs in semiautomatic activities may be present, but most patients seem to forget what it is on the left. Patients forget to put on the left sleeve of their jacket, the left leg of their trousers, or the left shoe; they shave or make up only on the right side of the face, they eat in the right space of the dish. If not apparent in spontaneous behavior, unilateral neglect could be easily confirmed and quantified by crossing outline segments, bisecting line, spelling, writing, reading, or drawing. In copying or drawing from memory, patients omit, misarrange, or distort left details. In order to increase test sensitivity and to allow precise

quantification, the arrangement, the target ratios, and distracters of cancellation or bisection tasks could be modified. The typical rightward error on bisection of horizontal lines progressively reduces and then reverses with diminishing lines or words length (the crossover effect).[31–33] Diagonal and vertical neglect are other possible variants.[34–36]

It is better to use all possible tests because dissociations or specific test failure locations could be found.[37,38] A patient may only read the last two letters of any word in any possible placement, but he perfectly executes a cancellation task. Visual attention tests combined with distracter activity (such as stepping) can represent the neglect impact on daily living activities more effectively than conventional tests.[39] It is also advisable to repeat test administration because of the remarkable variability of patients' performance in the acute phase, a variability that is independent from vigilance or cooperation. Motivation, attention, affective stimuli,[40] and reward can also modify performances.

Unilateral neglect could also depend on the distance of the stimuli and may be evident only when a motor response is produced and not in merely visuo-perceptive tests.[41] Patients could ignore stimuli presented on the body (somatic space) or near the body (peripersonal space) but normally respond to distant stimuli (extrapersonal space) or vice versa.[42–44] The somatic space could be tested by asking blindfolded patients to touch, with the right hand, parts of the left body. Peripersonal space could also be assessed by avoiding obstacles with a wheelchair. Double dissociations may be found across different sensory modalities.

In the auditory modality, a neglect-related phenomenon is the misallocation of dichotic stimuli (in their spatial or representational meaning) toward the ipsilesional side.[45]

Unilateral neglect should also be defined with respect to ego- and allocentric coordinates. Egocentric frames may be retinal or correspond to the sagittal midplanes of the head or the trunk, or to the axis of a limb ready to move. Allocentric coordinates refer to the way stimulus arrays are parsed into perceptual limits: unilateral neglect may affect the contralesional side of separate components of a complex figure drawn by the patient (object-based neglect), rather than the contralesional side of the entire drawing (scene or viewer-based neglect).

Neglect phenomena may be found in the domain of mental representation and dissociate from any current sensory or attentional bias.[46–50]

Representation unilateral neglect is revealed by asking the patient to form the image of a familiar place and to describe its details from a given perspective point or even in forward or backward mental spelling. In these paradigms, patients omit left-side details, no matter what their relevance. If, subsequently, a description is required from the opposite perspective, then, previously omitted details are recalled.

Motor neglect is the loss of motivation or reluctance to initiate or carry out motor activities on one side of the body (hypokinesia), a unilateral overall decrease in the amplitude of all motion (hypometria), and difficulty in maintaining fixed postures or repetitive movements (impersistance). Motor neglect is manifest in crossed paradigms (asking with open or closed eyes to raise the limb controlateral to a stimulus). Motor neglect could be prominent and dissociate from spatial neglect with promotor and medial frontal areas lesions.[51]

Unilateral neglect could be the consequence of errors in space representation, spatial and non-spatial attention resources, space exploration, and movement programming.[52,53] Unilateral neglect is probably a multicomponent syndrome because, in the acute stroke, the recovery of the different sub-types hitherto reported is asynchronous.

Unilateral neglect is frequently associated with anosognosia. Both could improve fast, but anosognosia generally precedes unilateral neglect in the first weeks or months.

Despite the multiple variety of unilateral neglect signs, the responsible acute ischemic lesions cluster over the inferior parietal lobule at the temporoparietal junction[54] and less frequently on dorsolateral lesions in the

premotor cortex.[55] Subcortical and thalamic lesions can induce neglect possibly by a diaschisis phenomemon.[56–58] Several cases with other lesion locations are also reported.[59,60]

Interestingly, a right anterior parietal stroke could also liberate a behavior of acute hemiconcern that refers to an over-interest for the left body (patients relentlessly rub, touch, pinch, press, lift, and manipulate parts of the left arm, trunk, and leg with their right hand or foot). This behavior is manifest only in the first days after stroke onset and is strictly associated with severe left hemisensory loss and the absence of neglect signs.[61]

Allied neglect disorders are the extinction on double simultaneous stimulation (in auditory, visual, tactile modalities) and allochiria (the misallocation of contralesional stimuli to symmetrical or, less frequently, asymmetrical points of the ipsilesional somatic or extrasomatic space). Extinction and allochiria may reflect dysfunction at different levels of the sensory processing because they can be observed after both spinal cord[62] and cerebral lesions. Illusory transposal of stimulus location from the contralateral to the ipsilesional side has also been found in the uncrossed olfactory modality.[63,64] The relationship of extinction and allochiria with neglect is still unclear because double dissociations are frequent, especially in the early recovery phase. Unilateral neglect signs usually disappear before extinction phenomena or sensory and motor deficits.[65]

ANOSOGNOSIA

Anosognosia is an hyperacute behavior in stroke because, compared with other neurobehavioral syndromes, recovery is fast. It refers to partial or complete unawareness of a deficit due to the stroke.

Anosognosia and depression may coexist in the same patient,[66] suggesting the existence of two systems for emotional assessment, of which only one has direct access to cognition.

Patients with anosognosia for hemiplegia have no spontaneous complaints and the refusal of the deficit is obstinate. They may also claim unreal movements of the paralyzed limb. The presence of illusory limb movements correlates to anosognosia degree[67] but is not directly explained by a proprioceptive deficit.[68] Other patients admit weakness of only one limb despite complete side hemiplegia. Patient behaviors might be congruent (will to walk or perform activities) or incongruent (mysterious acceptance of bed or wheel-chair). The ownership, the existence, or even the human nature of the affected limbs could be denied (somatopraphrenia). Somatic illusions such as reduplications of body parts (pseudopolymelia) or supernumerary phantom limb sensations could be present. These absurd misbeliefs are generally expressed without particular concern, but, less frequently, the patient may be annoyed or demand insistently the removal of the limb (misoplegia).

The multiple contrasting dissociations for knowledge of weakness, location, and body parts identity are arguments for the existence of multiple causal mechanisms.[69–72] These processes include inattention to the left hemibody, reduced sensory feedback, impaired attention resources, defect in body schemata or in self-awareness, internal representation, mental flexibility, and diffuse mental deterioration. A feedforward or intentional theory attributes unawareness of the motor deficit to the loss of expectancy of movement that is the failure to update an internal comparator about impending movement.[73,74] This last hypothesis, however, does not explain the dissociation of anosognosia and illusory limb movements in Wada tests.[68] Furthermore, none of these theories—either psychological, or denial or emotional changes—adequately explains the more common occurrence of anosognosia with right hemisphere stroke. Wada tests show that, although aphasia may confound the reported rate of anosognosia following left-hemisphere dysfunction, frequency is still higher with right-side dysfunction.[75] Presentation and manipulation of the paretic extremity in the right visual field do not alleviate anosognosia and fail to support a interhemispheral disconnection hypothesis.[76] Confabulations or misbeliefs, somatic illusions, and delusions strongly contrast

with the integrity of all other cognitive processes. Actually, the exact nature of their relationship with anosognosia remains mysterious.

Confabulations are supposed to correspond to gap filler or to a compensatory mechanism for the conscious mind that is unaware of the deficit, or might suggest a failure to inhibit incorrect responses, or impairment of self-monitoring. In the acute phase, a great fluctuation of symptoms is a constant feature.

Anosognosia for hemiplegia could dramatically improve in a few hours or days, more rapidly and completely than spatial neglect to which it is generally associated.[42] Unawareness of illness and anosognosia for hemiparesis disappear rapidly (within the first 3 months)[69] and its role for poor long-term recovery is a matter of debate.[42,69,77]

Even patients without anosognosia or cognitive impairment, and with dramatic recovery for hemiplegia after thrombolysis, seem unaware of the improvement and often, strangely, sound unemotional.[78]

Anosognosia for neglect (which has been the object of fewer investigations) may be more lasting and results in poor outcome.[69]

In acute stroke, anosognosia for hemianopia is more common (about 20–30% of all hemianopic patients and 70–90% of patients with left hemianopia) than anosognosia for hemiplegia (33% of patients with hemiplegia) but the two conditions, which might dissociate,[79] share similar behaviors and contrasting dissociations. Patients with acute hemianopia or quadranopia rarely report that one-half of the visual field is obscured and that they see only half of objects and faces. When hemiplegia and hemianopia co-occur, anosognosia is usually more severe. Anosognosia for hemiparesis and anosognosia for hemianopia overlap for lesion site in parietal and subcortical areas of the right hemisphere, in the middle cerebral artery territory. Anosognosia for hemianopia is less frequent in pure occipital lesions (PCA territory) and in left parieto-occipital lesions.[79] Anosognosia has been also reported in right thalamic,[80] capsular-lenticular,[81] and pontine stroke,[82] and a frontal or parietal diaschisis has been suggested as a causal mechanism.

Patients with cortical blindness are unaware of blindness, deny any visual disturbance or, if they recognize some deficit, attribute it to external and improbable reasons. Many patients report unreal visual experiences, others can describe only surrounding parts and misname objects, whereas others may pretend to watch television and try to grab unreal things. A confusion or translation of acoustic or tactile perceptions in mental images is probably at the origin of these misbeliefs. While some patients attempt to walk and bump into objects, the behavior of others suggests some unconscious knowledge (no objections to remaining in bed or request help to walk). Blindsight is the presence of remnant visual function despite denial of perception. This phenomenon is probably explained by indirect visual input in tectal projections to the pulvinar and then to extrastriate cortex (for pattern and motion)[83] and in lateral geniculate afferents to extrastriate cortex.[84]

Anosognosia for aphasia occurs in patients with fluent aphasia (WA, transcortical sensory aphasia). Patients produce abundant phonemic, semantic paraphasias and neologisms but they seem to believe that they communicate satisfactorily and show anger when they realize that the examiner does not understand. Some authors have interpreted the jargon as the result of co-occurrence of aphasia and anosognosia; i.e., amnestic confabulations might be due to the co-occurrence of amnesia and anosognosia for amnesia.

AFFECTIVE DYSPROSODIA

Affective dysprosodia (AD) refers to the impairment of both production and comprehension of language components (stress, pauses, cadences, accent, melody, intonation) that allow translation of internal states (fear, happiness, sadness, anger) in speech. Ability to experience emotions is, nevertheless, spared. While talking, patients usually give the impression of a lack of affection and are, therefore, considered depressed,

even when they are not. Affective dysprosodia is frequent in the acute phase of stroke and, as for aphasias, rapid improvement usually occurs. Diagnosis of AD is dependent, in milder forms, on the examiner's ability to recognize the patient's failure to give emotional vocal expression to sentences. Identification of failure of comprehension of prosodic cues is even more problematic, because it is not manifest in overt behaviors and requires specific testing.

The right hemisphere has a dominant function and seven dysprosodic syndromes have been described.[85] They mirror the aphasic syndromes produced by left lesions (Table 2.3) and major changes occur in the acute stroke such as for aphasia.

Affective dysprosodia is probably organized at the level of the neocortex as part of the languagerelated neurocognitive networks and is usually under volitional control. Affective production seems to be compromised in lesions involving the right posterior-inferior frontal lobe whereas lesions of the right basal ganglia, temporal and parietal operculum are more relevant for prosodic comprehension.[86]

APRAXIA

Apraxia refers to the inability to perform skilled acts movements that cannot be accounted for by weakness, sensory loss, incoordination, inattention, and perceptual and comprehension impair

Table 2.3 The dysprosodias (adapted from Ross[85])

Type of dysprosodia	Spontaneous fluency	Repetition	Comprehension
Motor	Poor	Poor	Good
Sensory	Good	Poor	Poor
Conduction	Good	Poor	Good
Global	Poor	Poor	Poor
Transcortical motor	Poor	Good	Good
Transcortical sensory	Good	Good	Poor
Mixed transcortical	Poor	Good	Poor

ment. The first step is to be sure that the object, command has been understood, because most patients with apraxia also have language impairment. Other specific features are the loss of the purposeful character of the action and the automatic-voluntary dissociation.

In some cases, apraxia can be detected only by appropriate tests, whereas in others it manifests in ecological situations such as mealtime actions.[87] A gradient of difficulty generally exists, with greatest difficulties on command, minor on imitation and, lastly, when the patient is given the object to use.

Gestural disorganization can take two forms— ideational and ideomotor—but this dichotomy is often not easy to apply at the bedside. Patients with pure ideational apraxia (which is a quite rare condition) fail to retrieve the movement formula typical for a certain objects use; i.e. they do not know what to do. The patient is able to recognize objects but looks hesitantly at them, makes some attempts to use, then tries with another, or makes omissions. The action is inappropriate, carried out in the wrong place, or the order of gestures may be illogical. Actually, ideational apraxia describes the loss of tool-action (e.g., screwdrivers are twisted) or tool-object associations (e.g., hammer-nail).[88] A case of pure apraxia for the single tool use has been reported.[89] Conceptual apraxia denotes both tool-movement associative errors and the loss of mechanical knowledge.[90] Tactile apraxia is characterized by an isolated disturbance of hand movements for use of and interaction with an object, while intransitive movements (movements without the use of an

object) are preserved.[91,92] Ideational apraxia is frequently but not exclusively observed with damage to the left posterior temporoparietal junction.[88]

Ideomotor apraxia is the failure to implement gestures' representation in a motor program. The shape, order, and spatial features of the movement are distorted but their intention is correct, a fact that is proved by the ability of matching a gesture of the examiner with the related object. These patients know 'what' to do but they do not 'how' to do, and they fail on imitation, a condition when retrieval of the plan of the action is not necessary.

Liepmann's model, of which validity persists despite some controversies, identifies four syndromes:

1. bilateral ideomotor apraxia with a lesion of the left parietal lobe
2. sympathetic left limb apraxia associated to right limb hemiplegia if infarction involves areas close to the motor area
3. a 'melokinetic apraxia' when the left motor area damage is mild and the right limb shows unrefined movements (the existence of this latter form has been questioned because distinction from mild paresis may be problematic)
4. left limb apraxia due to the interruption of anterior callosal pathways.

When apraxia and aphasia are associated, there is also a correlation between praxis ability and spontaneous gestural communication.[93]

Oral apraxia involves every intentional buccal movement on command or on imitation. Its frequent association with phonetic-articulatory disorders leads some authors to consider aphasia as the consequence of oral apraxia. Oral apraxia is found in the great majority of Broca aphasics and overlaps speech apraxia, but dissociations are reported.[94] Speech apraxia is a form of oral apraxia limited to speech. It refers to a phonetic-motor rather than to a linguistic disorder and affects the translation of an intact phonological representation into the bucco-phonatory kinematic parameters. In speech apraxia, articulatory efforts vary according to the complexity of sentences and improve with the recitation of automatic series (counting, months of the year), which allows distinction from dysarthria. Dissociation from aphasia has been reported in rare cases.[95]

Swallowing apraxia, a peculiar from of oral apraxia, is exceptional in a pure form.[96] Eyelid closure or opening apraxia is an uncommon condition, generally evident in the first days after stroke, characterized by difficulties in voluntary eye closing or opening while involuntary blinking, closing or opening eyes in response to a perceived threat are preserved.[97–99] This condition probably corresponds to a 'motor impersistence' behavior and may correlate more to advancing age, mental impairment, and disorientation than to a localizable lesion. Some authors consider simultanapraxia (i.e. the inability to perform simultaneously two motor tasks, such as closing the eyes and protruding the tongue) a sign more specific for non-dominant hemisphere dysfunction.[100]

The alien hand consists of unintended gestures of one hand, which occur in isolation or reproduce movements of the other hand or interfere with them. This last condition is called diagonistic dyspraxia. Alien hand could be the consequence of simultaneous damage of the contralateral supplementary motor area and corpus callosum,[101] whereas diagonistic dyspraxia has been interpreted as the result of the disconnection of the two superior parietal lobes.[102]

Gaze apraxia is one component of Balint's syndrome and is associated with damage to the posterior parietal lobe, a region critical for integrating visual signals with information about eye position. Gaze apraxia denotes a chaotic oculomotor behavior due to dysfunction of fixation, saccade initiation, and accuracy, and of smooth pursuit eye movements. This disorder affects eye movements under the visual

guide, whereas they are accurate under sonor or tactile stimuli. Patient with Balint's syndrome show optic ataxia (difficulty in reaching objects under visual guidance that is not explained by motor, somatosensory, visual acuity, or visual field deficits). Optic ataxia is an overt behavior strictly related to gaze apraxia.

Constructional apraxia, in right braindamaged patients, reflects an impairment of visuospatial analysis and motor execution in drawing. Constructional apraxia includes different constructional abilities sustained by various cognitive mechanisms (sustained attention, reasoning, working memory, perceptual and visuospatial skills) that are usually more impaired in the acute than in the late phase of stroke. It could also occur after left parietal lesions and, in this case, the main mechanism is a loss of programmation with impoverishing of details.[103]

Gait apraxia (loss of gait movements programmation) has rarely been described as an isolated symptom in acute stroke.[104]

ALEXIA WITHOUT AGRAPHIA

This syndrome, otherwise known as pure alexia, is considered due to word visual misperception (peripheral alexia) and not to an aphasic disorder (central alexia).

The deficit results in impaired mapping of the visual structure of the word into its encoded representation in the long-term memory store (lexicon). Patients usually read with a letter-byletter strategy. Peripheral alexia, in acute stroke, invariably points out to posterior cerebral artery territory involvement and hemianopsia, dyschromatopsia, color anomia or agnosia, and color or visual mental imagery impairment are common associated findings. According to the specific type of reading error (predominantly reading— semantic, visual, or neglect), it is possible to differentiate with specific testing alexia without agraphia (pure alexia), hemianopic alexia, and neglect alexia. Pure alexia is due to a lesion of the occipitotemporal junction, of corpus callosum splenium, and of left forceps major or of their fibers, with the disconnection of afferences from right occipital cortex to the left occipitotemporal junction. This disconnection is not present in the case of hemianopsic or neglect alexia or in patients with hemianopia without alexia.[105]

ACUTE SYNDROMES DUE TO IMPAIRMENT OF FUNDAMENTAL FUNCTIONS

AMNESIA

Amnesia should only refer to a loss of past memories, as well as to an inability to form new ones, in the absence of significant impairment of alertness, attention, language, comprehension, visual recognition, and motivation to learn and to recall. Conversely, in acute confusion and delirium, events have probably never been adequately perceived.

There are few syndromes in acute stroke that correspond to true amnesia. Transient global amnesia is extremely rare.[106,107] Hippocampal damage alone is probably insufficient to produce persistent amnesia if it is not associated with damage to the enthorhinal and perirhinal cortex, collateral isthmus, or parahippocampal gyrus. Lesions are usually bilateral. Amnesia due to a lesion in the medial temporal lobe corresponds to a deficit of declarative and episodic memory and mainly produces anterograde amnesia, whereas retrieval of previously learned data is almost adequate and working and procedural memory are spared. Damage to the hippocampus and to its projections results in deficits in recall of episodic information, whereas damage to other regions, such as the rhinal cortex, disrupts recognition based on familiarity judgments.[108] Most patients are aware of the defect. Confabulations are infrequent.[109] Left-side

infarcts predominantly cause a verbal memory deficit, often associated with pure color and object agnosia or anomia,[110] while right-side lesions affect visuospatial, face, and spatial memory.[111]

In the case of anterior nuclei thalamic infarcts, amnesia is associated with abulia, decreased expression of emotions, language disturbances, or neglect.[112] After mediodorsal infarcts, memory defects are combined with drowsiness, abulia, flattened emotions, and vertical gaze disturbances;[113,114] amnesia usually becomes apparent when vigilance improves. In memory tasks, patients with dorsomedial infarcts show severe distractibility[115] and alternating good-bad performances. The best performance is generally on the first attempts, suggesting the role of motivation and attention in the encoding.[116] Thalamic amnesia predominantly affects episodic and declarative memory, whereas retrograde amnesia is generally rapidly reversible. Motor learning, implicit memory, and priming are generally spared.[117] A patient with bilateral paramedian thalamic infarction presented in the chronic phase a dissociation between personal and extrapersonal episodic memory impairment.[118] Some patients are aware of the defects but others are not. The main defect is in encoding new memories, whereas there is no evidence of rapid decay or forgetting. The memory defect consequent to thalamic lesion is verbal,[119] or both verbal and visual in the case of left-side infarcts, and only visual memory, for right-side lesions.[120] However, both right[121] and left[113] unilateral thalamic lesions with global amnesia have been described.

For some authors, amnesia is more severe and stable with anterior nuclei infarcts in comparison to dorsomedian nuclei damage unless the lesion extends rostrally enough to include the mamillothalamic tract, the ventral portion of the lamina medullaris interna, and the inferior thalamic peduncle.[122]

ATHYMHORMIA

Athymhormia or 'loss of self psychic activation' refers to a lack of motivation, characterized by apathetic, aspontaneous, and indifferent behavior, with motor and affective drive loss but without anxiety or suffering, with mental emptiness but without cognitive impairment. The affective indifference is remarkable even to emotional life events. Adequate activity can be obtained on stimulation, underlying the contrast between impaired self-activation and intact hetero-activation. There are no studies, to our knowledge, indicating the prevalence of this syndrome in the early and late phases of stroke.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies in patients with bipallidal, with paramedian mesencephalo-diencephalic, and with bilateral genu capsula infarcts, point to a frontal cortex deactivation (Table 2.4).

Habib proposes the role of a specific corticosubcortical circuit connecting, in a loop, gyrus cinguli with limbic striatum pallidum and mediodorsal thalamus.[129] Several dopaminergic networks convert motivation—related to a positive reinforcement—to behavioral or emotional displays with motor and affective components. In Habib's model, a selective lesion in the frontosubcortical system results in the disconnection of the striato-limbic from the motor and association loops, by sparing of the motor and mental activity, but dysfunction in the initiation.

APATHY

Patients with apathy show little spontaneous actions or speech, have delayed, and short, slow, or absent responses and flat affect. Differently than athymhormia, apathy is frequently associated with hypophonia, perseverations, grasp reflex, magnetic reactions, compulsive manipulations, utilization behaviors, cognitive and funcbe distinguished from depression, even if both tional impairment, and older age. Apathy should conditions generally co-occur.

Table 2.4 Athyhormia and stroke: lesion topography

Bilateral lesions of pallidum and putamen,[123]
Bilateral lesions of caudate nucleus[124,125]
Bithalamic infarcts,[126,127] left thalamus[128]
Disseminated cortical and subcortical lesions (antiphospholipid syndrome, personal observation)

Table 2.5 Apathy and stroke: lesion topography

Frontal lobe[133]
Cingulate gyrus[133]
Supplementary motor area[133]
Mesial motor area, amygdala[133]
Capsular lesions[134]
Insula[135]
Bilateral or unilateral right or left caudate[59,124]
Bilateral thalamic infarcts[136]
Anterior thalamus[137]
Right thalamic infarct[138]

Hypoactivity of frontal and anterior temporal regions have been observed by SPECT imaging.[130] A reduced faculty to direct attention to novelty is likely to contribute to the apathy after lesions of the frontal lobes.[131] Apathy is a common and persistent symptom in the case of anterior thalamic infarcts (Table 2.5).[132]

KLÜVER-BUCY SYNDROME

The diagnosis of Klüver-Bucy syndrome (KBS) requires the presence of at least three of the following symptoms: tameness with loss of fear or anxiety, dietary changes (bulimia and loss of alimentary selectivity), aberrant sexual behaviors (increased autoerotic, homosexual, or heterosexual activities, or inappropriate sexual object choice), hypermetamorphosis (excessive visual exploration of the environment), hyperorality (tendency to examine all objects by mouth), and 'psychic blindness' (failure in recognizing emotional visual stimuli). It is a very rare syndrome in stroke because of its peculiar lesion topogra phy (bitemporal). Incomplete forms (e.g. isolated hypersexuality) can occur with a unilateral temporal lesion,[139] bilateral amygdala damage,[140] or a bithalamic lesion.[141]

Patients with KBS also generally have severe cognitive deficits such as amnesia, loss of semantic knowledge, aphasia, and visual or multimodal agnosia.

DEPRESSIVE CHANGES

The diagnosis of depression cannot always be set down in the very acute phase of stroke because DSM criteria require the presence of persistent symptoms. Furthermore, the neurobehavioral sequelae of stroke syndromes (such as aphasia, indifference or denial, and cognitive impairment) compromise the validity of patients' answers to the scales.

Even when language and attentive functions are not involved, patients may still fail to respond in a reliable fashion to standardized tests, such as the neurobehavioral cognitive status examination[142] or the

visual analog mood scales (VAMS).[143] Tests to check the validity of replies in interviews are rarely performed. Caution in the use of rating scales is also required, since patients might be more sensitive to the stressor event of stroke than affected by depression and anxiety.[144] The presence of misleading neurologic and neurocognitive conditions (Table 2.6) should be also carefully evaluated.

Various scales and questionnaires have been constructed and tested in order to objectify mood changes in patients with aphasia. The Stroke Aphasic Depression Questionnaire[145] and a modified analogue dysphoria scale[146] make it possible to report, together with verbal items, vegetative and other symptoms independently of language ability (i.e. eating and sleep disturbances). These scales show a good validity compared to other standard mood disorder questionnaires, especially the Hamilton Depression Rating Scale. The VAMS assess mood (sad, happy, tense, afraid, tired, energetic, confused, and angry) on a 10-cm vertical line (to avoid

Table 2.6 Diagnostic confounders of depressive syndromes after stroke

1. Indirect
Common to many severely ill hospitalized patients
Controlled appetite (e.g. NPO and tube feeding)
Frequently awakened
Confined to bed
Acute confusional states
Of special concern in stroke patients
Immobility (potential confusion with apathy)
Dysphagia (interferes with eating habits)
Slurred speech (and resultant miscommunication)
2. Direct
Aphasia
Amnesia and cognitive impairment
Anosognosia and denial of depressive signs
Aprosody
Neurologic apathy syndromes
Isolated abulia/apathia
Loss of psychic autoactivation
Frontal lobe syndrome
Klüver-Bucy syndrome
Korsakoff's syndrome
Poststroke fatigue
Special behavioral syndromes
Emotional lability or emotionalism
Catastrophic reaction
Dementia
Pseudobulbar syndrome

neglect effects) with two pictures at the bottom (e.g. a smiling and a sad face for happiness and sadness). Some studies[147,148] have demonstrated their validity as standardized measurements, whereas others have

criticized their utility because their administration is not completely independent of linguistic cues and the test-retest variability may be surprisingly great, even for short time intervals.[149]

Observational methods can be used to diagnose depression in order to reduce bias in patients' answers but they also have limitations.

The emotional behavior index form (EBIF), a simple observational method that is independent of language abilities, has been designed and employed in our center to define the emotional profile of patients during the acute phase of first-ever stroke.[150] The EBIF, scored daily by the stroke unit nurses caring for the patient, consists of 38 rated items in the classes of overt sadness, passivity, aggressiveness, indifference, disinhibition, and adaptation.

We assessed depressive changes with both the EBIF and the HDRs. Our study population consisted of 64 consecutive patients (mean age= 56±15 years) admitted within 48 hours after a first-ever stroke with a single lesion on neuroimaging. In this population 33% (n=21) were aphasic and 33% (n=21) showed anosognosia or neglect. Only 27% (n=17) had no significant cognitive impairment. Depressive feelings were verbally reported by 19% of patients (n=11) who could communicate (n=57), whereas depressive signs (crying, overt sadness) were observed in 19% (n=13) and were independent from verbal reports. Only 5% (n=4) had both subjective and objective depressive changes. This study confirmed the early dissociation of depressive changes from subjective feelings, and the limit of diagnosis with standardized verbal questionnaires. Early depressive signs correlated with aphasia (11/21 vs 10/42; $p<0.04$) and with left hemispheral lesion (14/28 vs 7/34; $p<0.01$). Nevertheless, acute depressive changes did not predict the risk to develop PSD at 3 months and at 1 year follow-up.

Several risks factors for poststroke depression (PSD) have already been investigated (Table 2.7) with conflicting results. Recently, a meta-analysis study[151] failed to individuate determinant and independent factors.

There are no conclusive data concerning the time of the introduction of antidepressant drugs. Early prophylactic treatment with mianserin started in the acute phase does not reduce, at 1 year follow-up, the prevalence of PSD and does not improve the neurologic outcome.[166] Wiart et al. found that fluoxetine improved depression in 60–70% of the patients but without significant impact on motor, cognitive, and functional outcome.[167] Many other studies demonstrated that mood improvement enhanced recovery of neurologic deficits.[168] Nevertheless, a placebo effect may also account for 35–75% of the thera

Table 2.7 Factors associated with poststroke depression in 16 clinical studies

Factors	Significance in 16 studies	
	Significant	**Nonsignificant**
Age	6	6
Gender (F)	6	6
Prior stroke	3	2
Prior disability	0	2
Prior depression	3	1
Stroke severity	5	0
Stroke side	1	7
Lesion volume	1	2
Anterior circulation	4	2
Cognition	5	2
Functional outcome	11	1

Factors	Significance in 16 studies

Sources: Wade et al.,[151a] Ebrahims et al.,[152] Andersen et al.,[153] Burvill et al.,[154] Hermann et al.,[155], Kotila et al.,[156] Paradiso et al.,[157] Ramasubbu et al.,[158] Pohjasvaara et al.,[159] Kauhanen et al.,[6] Robinson et al.,[160] Sato et al.,[161] Dennis et al.,[162] Singh et al.,[163] Pohjasvaara et al.,[164] Paolucci et al.[165]

peutic response in trials of antidepressants[169] and spontaneous remissions might be frequent for minor depression in the immediate period after stroke;[170] therefore, the therapeutic properties of SSRIs could be overemphasized in the early phases of stroke, but their efficaciousness seems more consistent in the chronic phase.

The natural course of depressive changes in stroke and the role of pharmacological therapy appear to be not completely understood.

In conclusion, the diagnosis of depression cannot be set down in a standardized way during the acute phase of stroke, and clinical evaluation should be performed on an individual basis.

The more prominent risk factor, at any delay after stroke, is the degree of the functional impairment.

FATIGUE

Poststroke fatigue is a frequent but neglected symptom that has been misleadingly regarded as a mere component of PSD. Fatigue is reported by up to 70% of stroke patients, even at a considerable time after stroke, and can have a great impact on cognitive, physical, and social functions, and on rehabilitation.[171] Whereas the few existing series[171–173] did not show significant cor-relations between fatigue and stroke severity, lesion location, cognitive and neurologic impairment, and depression, a study performed in our department points to an association between fatigue and brainstem and thalamic lesions. Fatigue may be linked to the interruption of neural networks involved in tonic attention, such as the reticular activating system. Several fatigue subtypes may develop after stroke according to the presence of specific cognitive and neurologic impairment, psychological factors, and sleep disorders. In the acute phase of stroke it is difficult to investigate the fatigue syndrome because of many interfering conditions such as pain, sleep changes, and new drugs. On the other hand, the study of fatigue in the chronic phase might prove a very interesting subject, especially when fatigue and depression dissociate and when other neurologic or neuropsychological after-effects do not completely explain the symptoms.

ANXIETY

Anxiety is an emotional state involving physiological arousal (increased heart rate), verbal reports of feelings of distress, overt behavior of avoidance, and cognitive disruption (i.e. maladaptative shifts in attention due to off-target thinking), hyperawareness about possible threatevents are occurring in an unpredictable manner. ening cues, and the perception that adverse Approximately 25–50% of patients manifest anxiety in acute phase of stroke.[174] Existing data about the relationship of anxiety with location site are not conclusive. Anxiety after stroke shares many features with post-traumatic stress disorders, both corresponding to a sudden and unpredictable life-threatening stressor. In these disorders, the extension and volume of the lesion do not correlate with anxiety level, which probably results from the co-occurrence of individual traits, psychosocial dynamics, and a deregulatory lesion effect on the limbic system with autonomic changes.

MANIA

The incidence of mania in acute stroke is about 1%[175] and most cases are associated with right hemispheral infarcts. A nondisabling mania with hyperphagia and a specific preference for fine food ('Gourmand syndrome') has been reported in a few patients following right anterior frontal lesions.[176] Hypometabolism involving the right inferior temporal lobe was seen in a PET study of three patients with subcortical lesions and manic behaviors, leading to the hypothesis of a direct or indirect role (diaschisis) of the temporal lobe.[177]

The right basofrontal and temporobasal regions have heavy connections with the more dorsal cortical and associative areas involved in visuospatial, somatosensorial and spatial processing, and cognition. This supports the hypothesis that dysfunction of these heteromodal ventral brain areas may result in disinhibited behavior because of an impaired emotional/cognition processing.

PSYCHOSIS

Behavioral symptoms of psychosis have been frequently reported in acute stroke but the real prevalence is unknown. In presenile or senile

Table 2.8 Mania and stroke: lesion topography

Bifrontal lesions[178]
Right hemisphere:
Frontal lobe[177]
Temporal lobe[179]
Caudate[177,179]
Subcortical[177]
Thalamus[12,180]
Ventral pons[181]
Left hemisphere[182]
Basal ganglia[183]

patients presenting with behavioral or psychiatric manifestations without any previous history of mental illness, acute stroke should be a diagnostic consideration. At least four symptom clusters have been identified: namely, affective, paranoid delusional, confusional state, and changes in mood with behavioral disturbances, but the mechanisms involved are unclear. Reduplicative paramnesia, Capgras's and Frégoli's syndromes are special forms of delusions (delusional misidentification syndromes). Reduplicative paramnesia is a bizarre disturbance where the patient believes to be in a different place against all possible evidence. It can take three forms (which may coexist): namely, place reduplication (the patient believes the existence of two identical places with the same name but geographically distinct); 'chimeric' assimilation between house and hospital (the patient claims to be in his house which has been transformed into a hospital); and extravagant spatial localization (the patient thinks he is in another place, generally familiar). This misbelief of familiarity may be associated with visuospatial defects and neglect but is not entirely explained by these disturbances. The duration of symptoms is generally brief (some hours, days, rarely weeks), but chronic cases have been reported.[184]

Capgras's syndrome describes the patient's belief that some familiar or known persons, or the patient himself, has been substituted or replaced by a sosia. Although elements of prosopagnosia or visual agnosia

could be present, they are not sufficient to explain symptoms. Patients with Frégoli's syndrome attribute the displacement of some psychological characteristic from one person to another.

In acute stroke, delusional misidentification syndromes may be the result of a disconnection of cerebral areas specialized in face (fusiform gyrus) and place (parahippocampal gyrus) recognition, with the most anterior inferior and medial part of the right temporal lobe where long-term memory, retrieval, and visual recognition mechanisms of faces and scenes are stored.[185,186]

Table 2.9 Psychosis and stroke: lesion topography

Reduplicative paramnesia	Righthemisphere[184,189,190,191]
	Frontal[186,192]
	Parieto-occipital[193]
	Parahippocampal gyrus[186]
	Thalamic[194]
	Subcortical[195]
Capgras's syndrome	Right hemisphere[196]
	Watershed infarct[197]
Frégoli's syndrome	Right hemisphere[198]
Psychosis	Right hemisphere[199]
	Frontoparietal[200]
	Thalamic[180]

Psychosis has been generally reported with right hemispheral stroke, especially in the temporoparieto-occipital junction regions or in the thalamus (Table 2.9). Old age and pre-existing degenerative disease or cerebral atrophy increases the risk.[187,188] Manic delirium has been reported as the main symptom of a right-sided thalamic infarct with SPECT findings, suggesting a frontal or limbic disconnection as the causal mechanism.[180]

The hallucinatory experience of such patients probably reflects pathological activation of neural ensembles in regions bordering an occipital lesion. These regions are presumed to contain records of visual feature fragments that are coactivated by feedback projections in the earliest visual association cortices, where they produce meaningful patterns during normal recall.[201]

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) includes a broad range of symptoms such as intrusive thoughts, preoccupations, rituals, and diverse motor behaviors. Obsessive compulsive disorder is reported after a period varying from days to years following cerebral lesions, often with progressive worsening over time. Few cases have been reported with stroke, almost all with basal ganglia lesions,[202–204] whereas OCD is more frequent with cranial trauma.

The dorsolateral frontal zones allow monitoring of ongoing activities according to environmental changes. Disruption of this system may result in difficulty terminating abnormal behavioral acts. The basal ganglia and ventral caudate are thought to be a 'gating station' for sensory information. Their dysfunction may leave the afferent information from the frontal lobes improperly regulated, with consequent inappropriate responses. The mediodorsal thalamic nucleus probably also exerts a regulatory control. Its lesion allows wrong information to flow back-ward to the orbitofrontal cortex. Orbitothalamic overactivity contributes to

the compulsive component, whereas basal ganglia and thalamic dysfunction reduces an inhibitory control on symptoms.[205]

ACUTE BEHAVIORAL CHANGES DUE TO IMPAIRMENT OF EXECUTIVE FUNCTIONS

INHIBITION AND ATTENTION DEFICITS

The signs of the environmental dependency syndrome in acute stroke are remarkable and generally improve in some weeks. Behaviors are impulsive, compulsive, involuntary, and slightly limited by command. Patients with 'utilization behavior' display an exaggerated dependency on the environment for cues or objects that predispose to an action. Hyperphasia or forced language is a rare variant and specifically refers to the inability to prevent speaking about objects or events.[206] Hypergraphia is an excessive and unsuitable utilization of writing with severe spatial and syntactical inattentiveness, stereotypes, ideational incontinence, and semantic incoherence. It is due to right frontal, right premotor areas, and/or right parietal lobe dysfunction. The automatic writing behavior and the visuospatial stimulus-bound automatic writing behavior[207] are variants, with perseveration in copying or writing letters, words, and signs. A persistent olfactory utilization behavior has also been reported.[208] Imitation behavior refers to a compulsive imitation of examiner's gestures, facial expressions, or speech. Patients with forced grasp reflex behavior grasp any object touching their hands, making impossible any purposeful activity. Palipsychism refers to an overlap of sequential cognitive processes in two or more domains and seems consequent to frontal disconnection by anterior thalamic infarcts.[137]

In echoing approval,[208a] the patient replies to questions by echoing them despite changes in the meaning. In the response-to-the-next patient stimulation,[209] the patient answers to questions directed to other patients or comments on their conversation. All the aforementioned behaviors seem to correspond to a 'pull to stimulus' that is typical in children and disappears with frontal lobe maturation. The neural network that guarantees this control in an automatic mode should be very diffuse in the frontal lobes because large infarcts are necessary for their emergency.

LOSS OF EMPATHY AND PERSONALITY CHANGES

There are no systematic studies on the prevalence of this disorder in acute stroke, because of the difficulties of testing and because of the presence of other relevant behavioral or cognitive changes.

Empathy is a faculty necessary to human relationships. It refers to cognitive processes such as identifying a behavioral perspective or adopting a role that takes part in the 'theory of the mind' (the ability to infer the intentions and mental states of others). The majority of studies in this area, performed on normal subjects with experimental paradigms partially reproducing echological situations, suggest that the prefrontal cortex mainly supervises the cognitive aspects of empathy[210] and the orbitofrontal cortex probably regulates autonomic activation or visceralsomatic states. In a functional MRI study,[211] empathic judgments activate the left superior and inferior frontal gyrus and the orbitofrontal gyrus, whereas another study[212] suggests a role for the right hemisphere in the attribution of mental states. In patients with stroke bilateral but not unilateral, orbitofrontal lesions are associated with deficits on tasks requiring the faculties of the theory of the mind.[213]

The difficulty in understanding and adapting to others may confer sociopathic traits. Empathy loss is probably at the origin of emotional and personality disorders due to frontal lesions.

Emotional and personality disorders in patients with frontal lobe lesions vary from the absence of tact and inhibition, inappropriate familiarity, childish behavior, and sexual disinhibition, to lack of initiative and spontaneity, bradypsychism, and poverty of emotional expressions. Other patients appear capricious, unstable, egocentric, and show lack of concern for the environment and other persons, and they may be aggressive and transgress ethical rules.

EMOTIONALISM

Emotionalism or emotional lability is an increase in the frequency of crying or laughing, starting with little or no warning. This syndrome is frequent in acute stroke (40% in personal data), at 1 month follow-up (21%),[214] but prevalence declines over the first 6 months (15–21%).[192,214] Emotionalism is often associated with depression,[215] irritability, ideas of references, and other psychiatric conditions.[214] Several locations have been reported, e.g. anterior lesions,[216] or frontal and temporal lesions,[217] subcortical lesions,[218] lenticulocapsular,[215,216] but a specific link between lesion location and the emergence of emotionalism has not yet been demonstrated.

According to Wilson's theory, the voluntary and involuntary control on laughter are determined by two relatively independent systems: the first connects the frontal lobe or critical cortical area to brainstem nuclei necessary for motor behaviors and coordination; the second is an unknown location. This theory explains why even small or unilateral lesions that result in imbalance in the whole system may cause involuntary crying or laughter. The underlying abnormalities may be serotoninergic, since some patients respond to SSRI drugs.[219]

CATASTROPHIC REACTION

Catastrophic reaction (CR) manifests as a disruptive emotional behavior when the patient is confronted with an unsolvable task. We identified 12 aphasic patients with a CR in a prospective cohort population (n=326) with first-ever stroke.[220] The abnormal emotional content of CR, its stereotyped character and dissociation from physical impairment suggest a specific lesioninduced neural dysfunction. Only patients with left hemispheral lesion manifested catastrophic behaviors. The CR may be the behavioral translation of a 'paleological thinking,' emerging by homologous areas of the right hemisphere when language areas are damaged in the left. In this study the cerebral areas more frequently associated with CR (temporal lobe cortex and insula, frontal opercular, and parietal cortex) along with the gyrus cinguli and the thalamic nuclei, project massively to the amygdala. The amygdala is a critical region forming stimulus-reinforced modality-specific associations in order to enhance behavioral responses through basal ganglia output.

Bilateral amygdala activation is known to be significant in the processing of danger elicited by language. In CR patients, damage of critical language areas in the left hemisphere may cause loss of the modulatory amygdala effect. Catastrophic reaction was not associated with depression early after stroke but most patients (8/12=66%) developed 3 months later, emotionalism or poststroke depression, a finding which suggests a time-related correlation among these disorders, possibly originating from an imbalance of a frontal/temporal lobe-limbic-basal ganglia circuitries with left dominance.

BEHAVIORS RELATED TO AWARENESS AND ALERTNESS DISTURBANCE

Consciousness may be defined as 'the state of awareness of the self and the environment' and coma is a total absence of such awareness. Consciousness is dependent on the functioning of the ascending reticular

activating system (ARAS), which groups neural structures in the brainstem, and the subthalamic and thalamic regions. Loss of consciousness during stroke is extremely unusual and is due to direct lesion to the ARAS or to large supratentorial lesions with secondary brainstem compression (generally in 1–3 days).

The locked-in-syndrome is a state of motor de-efferentation with generalized paralysis sparing awareness, cognition, vertical eye movements, blinking, vision, hearing, and sensation. Akinetic mutism refers to a condition of extreme limited responsiveness to the environment with relatively unimpaired arousal and alertness. Patients lie with open eyes, follow objects, become agitated and could react verbally to intense stimuli but in normal condition do not respond to the environment. Akinetic mutism and abulia share the same lesion location and neurotransmettorial dysfunction (i.e dopaminergic, down-regulation of frontal-subcortical circuitries).[221]

In the persistent vegetative state, wakefulness, preserved autonomic functions and the sleep-wake cycle contrast with the total lack of cognition. The patient is awake with eye opening and with electroencephalogram (EEG) arousal, but he doesn't follow objects, has no perception, no comprehension, and no meaningful behavioral response. He is mute and loses any interaction with the environment. Diagnosis requires that 12 months have elapsed from the onset. Residual cortical processing could be detected but it is dissociated from the integrative processes that are needed in order to maintain awareness.

The patient in the acute confusional state loses the customary speed, clarity, and coherence of thinking. The symptoms develop in a short period, fluctuate during the day, and cannot be explained by pre-existing dementia. Attention and concentration resources are depleted or unavailable: the patient is unable to register and recall events; spatiotemporal coordinates are lost, irrelevant thoughts intrude, and language may be impaired (anomia and incoherent speech). The patient shows daytime sleepiness, nocturnal agitation, and fragmented sleep or insomnia. Delirium reproduces the same symptoms but is characterized by increased psychomotor and vegetative activity, by a severe perception disorder (vivid dreams and hallucinations), by intense emotional changes, and by a tendency to convulse. Stroke without lateralizing deficit is a relatively infrequent cause of acute confusional state and delirium[222] and for this reason should be considered as an exclusion diagnostic. Strategic lesions involve, usually in the right hemisphere,[119,223] cerebral areas subserving polysensorial or polymodal integration. Elderly patients, or those with previous dementia or minor cognitive impairment, or severe neurologic deficit are at increased risk. Hypersomnia indicates a prolonged and deep state of sleep and could be the main behavioral disturbance in the acute bilateral paramedian thalamic stroke. Hypersomnia is the consequence of a deficient diurnal arousal and of a insufficient nocturnal spindling and slow-wave production at night (Table 2.10).[224]

CONCLUSIONS

In this chapter we have reviewed the principal behavioral signs and symptoms occurring in the acute phase of ischemic stroke by using an operational framework that groups hemispheral activities in instrumental, fundamental, and executive functions.

This model is supported by neuroanatomical, neurotransmittorial, and phylogenetic data and enhances an operational concept of modularity for brain functions. This concept includes the relative specialization, or the domain specificity of a given brain system, which may involve several

Table 2.10 Lesion topography for awareness and alertness disturbancies

	Lesion location	Arterial territory involved and mechanisms
Loss of consciousness	ARAS[203]	Vertebrobasilar infarcts

	Lesion location	Arterial territory involved and mechanisms
		Bilateral MCA infarcts or cerebellar infarcts with brainstem compression Subarachnoid or brainstem hemorrhage
Locked-in syndrome	Pontine ARAS[225]	Vertebrobasilar territory
Akinetic mutism	Usually hemispheric bilateral, cingulated cortex, caudate nuclei, anterior limb of the internal capsule, limbic thalamus	Anterior communicating artery aneurysmal subarachnoid hemorrhage Multiinfarct states Recurrent artery of Heubner
Persistent vegetative state	This condition is consequent to a diffuse insult to the cerebral cortex (hypoxia) with relative sparing of brainstem fimctions[226]	Multiple hemispheric bilateral infarcts or diffuse hypoxia (CO_2 poisoning)
Acute confusional state and delirium[227,228]	Thalamus[229,230] Caudate[124] Inferior part of the genu of the internal capsule[231] Frontal[228] Bilateral occipital[228]	Uni- or bilateral PCA, Top of the basilar[23] Right MCA[232] Right ACA[233]
Hypersomnia	Bilateral paramedian thalamus[224]	Perforantes branches of PCA Top of the basilar artery

ACA: Anterior cerebral artery; ARAS: ascending reticular activating system; MCA: Middle cerebral artery; PCA: Posterior cerebral artery

connected regions. Any such system is likely to be modulated by other components of the brain (e.g. attention, motivation, affective states) but not at such a degree of complete interconnectivity to abolish any specificity of the processing domain.

The other important point is that earliest syndromes of the acute phase of stroke give a great opportunity for studying the cerebral functions because of the relative absence of learning and plasticity phenomena. Actually, in the acute phase, behavioral changes are more florid but often transitory and fluctuating. Analytical protocols should be specifically constructed in order to perform a complete neuropsychiatric evaluation. They should take into account, as much as possible, all the complex variables that are independent of lesion location (premorbid personality, pre-existing psychiatric and neurologic diseases, epidemiological and genetic factors, psychological reactions to the physical or cognitive impairment). These protocols should be evaluated on-line with neuroimaging studies. The goal is to correlate early behavioral changes to modifications of the ischemic lesion by means of perfusion/diffusion MRI parameters. Only in this context, could functional neuroimaging (fMRI, PET, SPECT) studies pinpoint the precise role of critical cerebral regions which are involved or take part in determining behaviors (which is a highly dynamic process in acute stroke) but that are distant from the lesion.

It would be interesting, in order to reduce inter-individual variability, to apply the voxelbased morphometric analysis on large stroke populations. Diagnosis and treatment of behavioral changes are a priority in the acute phase of stroke.

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3.
What is the place of clinical assessment in acute stroke management?

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INTRODUCTION

Given the technological advances in neuroimaging, one could ask whether clinical examination is still of value. Although computed tomography (CT) and conventional magnetic resonance imaging (MRI) results may be normal during the first hours of ischemic stroke, new developments in MRI—namely, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI)— can show brain injury minutes after the clinical symptoms, and even hypoperfused, but uninfarcted, areas (penumbra).[1] However, the history and physical examination remain the cornerstones of neurologic diagnosis.

First, although DWI is considered the gold— standard examination for ischemic stroke by certain authors, there are several reported cases of patients with ischemic stroke and 'negative' DWI.[2] Secondly, the clinical assessment directs the diagnostic work-up, deciding which laboratory studies are essential. Thirdly, although neuroimaging can help to determine which patients are most vulnerable to treatment complications,[3] therapeutic decisions are currently based on the neurologic deficit, not on its image. Fourthly, the clinical assessment is currently the best guide for defining prognosis; in addition, the effect of personal contact with a doctor at a time when the patient is feeling particularly vulnerable must not be underestimated.[4] Finally, high-technology MRI is only available in a few stroke centers and is not available to the majority of stroke patients worldwide.

CLINICAL ASSESSMENT

A detailed and systematic history and neurologic, neurovascular, and general examinations are essential in the assessment of patients with suspected stroke. Details, such as Horner's syndrome in a patient with carotid artery dissection or livedo reticularis in a patient with Sneddon's syndrome, may provide substantial clues to the final diagnosis.[5] However, the short time limit imposed by novel therapeutic options (namely thrombolysis) makes a rapid, directed evaluation essential. Although there is no consensus on which elements of the history and physical examination are the most effective in providing the diagnosis, some should be evaluated routinely (Tables 3.1 and 3.2). One possible approach is to make a rapid, systematic examination within the therapeutic time window and then to assess further details during, or just after, treatment.

HISTORY

A detailed history is the most important element in the diagnosis. Disturbances in the level of consciousness, memory, language, and attention (e.g. anosognosia) caused by the stroke can make it difficult to obtain a

satisfactory history; in this situation, family member, co-workers, or other witnesses should also be interviewed. In most instances, the physician should initially listen to the patient's description of his main symptoms (passive process). This should be followed by an active process in which the physician asks about specific symptoms that often have less impact for the patient and are not mentioned spontaneously (for example, the patient may forget to report a loss of vision in the right eye that occurred months before the development of a left hemiparesis).

Characteristics of stroke onset and other elements, such as the presence of headache, amaurosis fugax, and transient ischemic attacks

Table 3.1 Important items of the history

Items	Importance
Time of onset	There seems to be circadian variation in stroke onset (i.e. ischemic stroke often occurs during repose and in the morning)
Precipitating events	Aneurysm rupture and artery dissection during physical activity, embolization through patent foramen ovale during Valsalva's maneuver
Temporal profile	Often abrupt in embolic stroke. There may be fluctuation of symptoms in small-vessel disease
Level of consciousness	Impairment often associated with hemorrhagic stroke. Related to prognosis
Presence of headache	Suggests SAH and intracranial hemorrhage. In ischemic stroke, frequent in artery dissection and more common after posterior than anterior circulation infarcts
Presence of vomiting	Related to SAH, intracranial hemorrhage, and brainstem infarcts
Presence of seizures	Suggests cortical strokes, especially embolism and hemorrhage
Presence of vertigo or hiccups	Associated with posterior circulation stroke
Presence of visual changes (diplopia, uni- or bilateral visual loss)	Helps in identifying lesion localization and etiology (e.g. amaurosis fugax and carotid artery disease)
Risk factors (age, hypertension, diabetes, hypercholesterolemia, cardiac disease, peripheral artery disease, TIA, alcohol consumption, oral contraceptives, familial history, etc.)	Help in establishing stroke etiology and prognosis

SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

Table 3.2 Important items of the physical examination

General examination (e.g. blood pressure, peripheral arterial pulses, skin examination, cardiac auscultation, and palpation)

Neurovascular examination (e.g. palpation and auscultation of cervical and facial arteries)

Neurologic examination

- Cranial nerves (including ophthalmoscopy)
- Meningeal signs
- Motor system

- Posture and gait
- Reflexes
- Coordination
- Sensation
- Cognitive function
  - Language (spontaneous speech, comprehension, naming, repetition, writing, and reading)
  - Memory

Orientation
Attention
Arithmetic calculation
Praxis
Gnosia

(TIA), listed in Table 3.1, may help in differentiating between hemorrhagic and ischemic stroke and also subtypes of ischemic stroke.[6,7] Information on past medical history, such as cardiovascular risk factors, recent head or neck trauma, alcohol consumption, and contraceptive use, is of primary importance.

Unfortunately, there are few reports on the extent of agreement between observers in obtaining the neurologic history.[8–11] Moreover, for many specific items of the neurologic history, agreement between expert physicians is very low.[8] In one study, the agreement on the history of TIA, measured using the kappa (γ) coefficient, was very low, barely greater than chance (γ= 0.11) (see chapter Appendix for kappa values): the same study showed moderate agreement for only 2 variables, fair agreement for 9, and only chance agreement for 6. However, training and the uniformization of methods for recording symptoms resulted in a better agreement.[12]

PHYSICAL EXAMINATION

The general examination should be directed at finding evidence of disease of the cardiovascular system. Auscultation and palpation of the arteries of the neck, face, and limbs should also be performed. The evaluation of other organs should be driven by the hypothesis developed during the history (e.g. screening for telangiectasy or adenopathy). In terms of the neurologic examination, some items must be systematically assessed and the search for other signs should be guided by the hypothesis elicited.

As with the history, for certain items of the neurologic examination, agreement between physicians is very low.[8,13] Agreement is fair for some elements, such as visual fields (γ=0.40),[8] extraocular movements (γ=0.30),[13] and sensory loss (γ=0.19).[13] However, in general, there is more agreement between physicians in the neurologic examination than in the items in the neurologic history;[8] for some items, such as weakness and orientation, agreement is very good (γ=0.67[8] and 0.83,[13] respectively).

DIAGNOSIS

Having completed the history and physical examination, the neurologist should be able to answer five questions with some degree of confidence.

IS THIS CEREBROVASCULAR DISEASE (STROKE OR TIA)?

Many conditions can mimic the presentation of stroke,[14–16] and there have been very few studies on the precision of the diagnosis of stroke[17] and TIA.[11,12] In clinical trials of thrombolytic agents, many conditions have been distinguished from stroke only by CT or MRI. Among patients admitted to an acute stroke unit, the initial diagnosis of stroke proved incorrect in 13%,[15] and a similar result (9%) was obtained in a recent study.[16]

Primary and metastatic neoplasm can simulate cerebrovascular disease, and this seems to happen more often with glioblastoma and metastatic tumors.[15] This misdiagnosis may be more frequent in patients in whom the symptoms evolved over a time period longer than 12 hours and in a more gradual manner.[14,18] Seizure is one of the commonest disorders misdiagnosed as stroke, with 39% misdiagnosis in one study.[15] It can be primary (idiopathic) or secondary to old infarcts, tumors, alcohol withdrawal, or subdural hematoma. The differential diagnosis may be especially difficult when the seizure had not been witnessed and there is residual Todd's paralysis. Migraine, mainly hemiplegic migraine or aura without headache, can also be confounded with cerebrovascular disease. An adequate history may help in the differentiation in some cases. Classically, the progression of focal seizures takes approximately 2–3 min and the progression of the 'aura' is often longer (15–20 min), whereas, in cerebrovascular disorders, progression is instantaneous or lasts only a few seconds.

Moreover, cerebrovascular disorders tend to produce negative phenomena (e.g. weakness, hemianopia, and aphasia), whereas, in seizures, the phenomena are often positive (e.g. tonic-clonic movements and visual hallucinations); migraine can produce either, although positive phenomena, e.g. teichopsia, are more common. However, in the experience of the authors, differentiation may be rather difficult in some cases, and the observations above must not be taken as rules.

Abnormal movements simulating seizures may be present after carotid ('limb-shaking' TIA)[19] or vertebrobasilar[20,21] ischemia. Vertigo is a common symptom in vertebrobasilar ischemia, which should be differentiated from vestibular neuronitis. Vertigo can be caused by lesions anywhere along the vestibular pathways, and, usually, the diagnosis can be made on the basis of the history and special maneuvers. Although there is an established view that isolated vertigo is rarely vascular,[22] there are reports opposing this view.[23] These and other diseases that cannot always be differentiated from stroke solely on clinical grounds are presented in Table 3.3.

IS THIS AN ISCHEMIC OR HEMORRHAGIC STROKE?

Distinguishing between ischemic and hemorrhagic stroke is the most important step in the management of acute stroke, as the clinical management of these two disorders differs substantially. Neuroimaging (CT scan and novel MRI sequences) is the most accurate method of distinguishing cerebral hemorrhage from ischemia.

However, in the 1980s, few CT scans were available and the examination was too expensive to be performed in every stroke patient, limitations which still exist in some rural communities and developing countries. Consequently, several studies addressed the efficacy of differentiating between these entities using only clinical features.[18,24–26] Decreased level of consciousness, acute onset, vomiting, headache, neck stiffness, a bilateral Babinski sign, hemiplegia involving the lower limb, severe hypertension on admission, a history of hypertension, hyperglycemia in the absence of a previous history of diabetes, warfarin therapy, alcohol consumption, and absence of TIA, hyperlipidemia, atheroma markers, or cardiac disease are all characteristics that have been associated with intracranial hemorrhage[18,24–28] and scores based on these items have been developed (Table 3.4).[18,25,26]

The Allen score (also called the Guy's Hospital score) is derived from 11 variables, and had an accuracy of 90% in identifying infarcts and hemorrhages in the original study.[18] One shortcoming of this score is that it cannot be calculated until 24 hours after the beginning of symptoms, so it is of no use in making decisions in the very first hours after stroke. The Siriraj score was

Table 3.3 Differential diagnosis of stroke and transient ischemic attack (TIA)

Neoplasm (primary or metastasis)
Subdural hematoma
Seizures (partial or Todd's paresis)
Hypoglycemia and other metabolic disturbances
Migraine
Hypertensive and other encephalopathies
Infections (brain abscess, encephalitis)
Vertigo (vestibular neuronitis and benign paroxysmal positional vertigo)
Syncope
Transient global amnesia
Multiple sclerosis
Peripheral nerve palsy
Psychological disorders (hyperventilation, somatization, and conversion)

Table 3.4 Clinical scores for distinguishing between hemorrhagic and ischemic stroke

Allen[18]	Siriraj[25]	Besson et al.[26]
1. Apoplectic onset: (a) Loss of consciousness (b) Headache within 2 h (c) Vomiting (d) Neck stiffness 2 or more=+21.9	1. Consciousness (×2.5): (a) Alert=0 (b) Drowsy, stupor=1 (c) Semicoma, coma=2	1. History of hypertension (×3): Absent or unknown=0 Present=1
2. Level of consciousness (24 h after admission): (a) Alert=0 (b) Drowsy=+7.3 (c) Unconscious=+14.6	2. Vomiting (×2): No=0 Yes=1	2. History of transient neurologic deficit (×5): Absent or unknown=0 Present=-1
3. Plantar responses: Both extensor=+7.1	3. Headache within 2 h (×2): No=0 Yes=1	3. History of hyperlipidemia (×1.5): Absent or unknown=0 Present=-1
4. Diastolic BP (24 h after admission): +(BP×0.17)	4. Diastolic BP (×0.1)	4. Alcohol consumption (×2): Absent or unknown=0 Present=1
5. Atheroma markers (angina, claudication, diabetes): One or more=-3.7	5. Atheroma markers (×3) (angina, claudication, diabetes): One or more=-1	5. Headache (×3): Absent or unknown=0 Present=1
6. History of hypertension: Present=-4.1		6. Peripheral arterial disease (×1): Absent=0

Allen[18]	Siriraj[25]	Besson et al.[26]
		History or loss of ankle pulse=-1
7. Previous TIA or stroke: Any number=-6.9		7. Atrial fibrillation on admission (×2.5): Absent=0 Present=-1
8. Heart disease (aortic or mitral murmur, cardiac failure, cardiomyopathy, atrial fibrillation, cardiomegaly on chest radiograph, MI within 6 months): Each=-4.3		8. Plantar response (×1.5): Flexion=0 Extension ipsilateral to the deficit=1 Extension contralateral to the deficit=2 Bilateral extension=3
Score=sum of variables-12.6: Infarct <+4 Hemorrhage >+24	Score=sum of variables (multiplied by factor)-12: Infarct <-1 Hemorrhage >+1	Score=sum of variables (multiplied by factor): Infarct <+1

BP, blood pressure; MI, myocardial infarction; TIA, transient ischemic attack.

developed and initially tested in Thailand.[25] Its simplified version is easy to calculate and is based on five clinical variables assessed at the bedside. It achieved a sensitivity for cerebral hemorrhage and infarction of 89.3% and 93.2%, respectively, with an overall predictive accuracy of 90.3%. However, when these two scales were tested for validation in populations other than those used in the original studies, in whom the frequency of hemorrhage was different, they led to conflicting results.[29–33] The predictive accuracy of these scores ranged from fair (64%)[31] to very good (93%).[30] In one study, the clinical impression of the neurologist was more accurate than either score.[33] More recently, another score, based on eight variables, was developed by Besson et al.[26] and achieved 100% accuracy for ischemic stroke; however, this high level of accuracy was obtained at the expense of making the diagnosis with confidence in only 36% of the patients admitted to the stroke unit.

In cerebral infarction, neurologic dysfunction can be attributed to main arterial territories on the basis of clinical criteria, but these rules may not apply to many brain hemorrhages, because the bleeding usually involves more than one arterial territory. Indeed, the fact that the typical association of neurologic features which would suggest involvement of a specific territory is lacking or becomes atypical may be one of the most important clues suggesting hemorrhage rather than infarct.[34] For example, the association of hemiparesis with vertical gaze palsy is strongly indicative of thalamocapsular hemorrhage, as it suggests involvement of structures that have a different arterial supply, making cerebral infarct unlikely.

These scores described above seem to be useful in epidemiological studies. However, their utility in the clinical management of individual patients is disputable, since therapeutic decisions, notably when more risky options, such as thrombolysis and surgery, are considered, should be made on methods with 100% accuracy. However, it has been suggested that they may be useful in deciding which patients should have priority for neuroimaging when resources are scarce.[18,26]

WHAT IS THE LOCATION OF THE LESION?

It is important to determine whether the lesion is in the anterior or posterior circulation, and whether it is cortical or subcortical, since the management and prognosis differ markedly in these different situations (Table 3.5). For instance, thrombolysis can be less efficacious for small subcortical infarcts than for cortical

Table 3.5 Common patterns of neurologic characteristics in patients with acute ischemic stroke

Anterior circulation/cortical:

- Left (dominant) hemisphere Aphasia, right hemiparesis, right-sided sensory loss, right visual field deficit, poor right conjugate gaze, dysarthria, and difficulty in reading, writing, and calculating
- Right (non-dominant) hemisphere Neglect of the left visual space, left hemiparesis, left-sided sensory loss, left visual field defect, poor left conjugate gaze, extinction of left-sided stimuli, dysarthria, and spatial disorientation

Posterior circulation (brainstem, cerebellum, and territory of the posterior cerebral artery):

- Motor or sensory loss in all four limbs, crossed signs, limb or gait ataxia, dysarthria, dysconjugate gaze, nystagmus, amnesia, and unior bilateral hemianopia

Subcortical (small lesion in the anterior or posterior circulation):

- Pure motor hemiparesis: weakness of face and limbs on one side of the body without abnormalities of higher brain function, sensation, or vision
- Pure sensory stroke: decreases sensation of face and limbs on one side of the body without abnormalities of higher brain function, sensation, or vision
- Sensory motor stroke: weakness and decreases sensation of face and limbs on one side of the body without abnormalities of higher brain function, sensation, or vision
- Ataxic hemiparesis: weakness and ataxia of face and limbs on one side of the body without abnormalities of higher brain function, sensation, or vision. Dysarthria-clumsy hand syndrome is considered a variety of ataxic hemiparesis.

infarcts, and a wider time window for treatment can be accepted in catastrophic vertebrobasilar lesions than in carotid territory stroke.

Although certain symptoms (e.g. vertigo and diplopia) have a localizing value for posterior circulation strokes, the diagnosis may be difficult during the very early phase. Moreover, patients with hemodynamically important obstruction of the internal carotid artery may present classical vertebrobasilar symptoms, even in the absence of atheromatosis of the posterior circulation arteries.[35] These events are probably due to hemodynamic disturbances with an intracranialcarotid-vertebrobasilar steal effect ('vertebrobasilar insufficiency'). In some cases, bilateral carotid territory ischemia may mimic vertebrobasilar symptoms.[36,37] Conversely, when the carotid territory is filled by the basilar artery through the posterior communicating artery, embolization through the vertebrobasilar system may cause carotid territory ischemia.[38] In addition, a posterior cerebral artery infarct may be misclassified as a middle cerebral artery infarct, since it can lead to aphasia, hemianopia, and hemiparesis due to involvement of the posterior limb of the internal capsule or motor fibers in the brainstem.[39,40] Thus, the combination of symptoms (e.g. diplopia plus vertigo in the absence of a history of carotid territory symptoms), rather than isolated information, should be considered when ascertaining the location of the lesion.

The characterization of cortical and subcortical syndromes is also difficult, since, in the very acute stage, the clinical signs may evolve over time. In particular, subcortical lesions (e.g. thalamic lesions) may result in some 'cortical' signs, such as aphasia, neglect, and apraxia. Conversely, classical small subcortical (lacunar) syndromes may be seen after cortical lesions, and are not good predictors of lesion localization in the early phase. Although brachiofachial weakness is suggestive of infarct in the cortical territory irrigated by the middle cerebral artery, it may also be seen after subcortical and other lesions.[28] There have been very few reports about the accuracy of lesion localization during the acute phase of stroke.[5,41,42] Two studies showed that, even when combined with early CT findings, the clinical presentation as a lacunar syndrome (i.e. pure motor hemiparesis or sensorimotor stroke) was of little value in the differential diagnosis of lacunar infarction.[41,42] Using patients enrolled in the ECASS I study, the positive predictive value of pure motor

hemiparesis and sensorimotor stroke combined with CT findings was 36% in the placebo group and 33% in tissue plasminogen activator (t-PA)—treated patients.[42] Greater accuracy was obtained in another study, in which the neurologic picture was used instead of rigid stroke syndromes, and the diagnosis was discussed by the stroke team neurologists;[5] the topography was correct in 88 of 96 patients (96%) when both the first-choice and second-choice clinical diagnosis of topography were considered and in 68 of 92 (74%) when only the first-choice diagnosis was considered.

Satisfactory results were also obtained using the Oxfordshire Community Stroke Project (OCSP) clinical classification.[43] However, patients who had suffered a previous stroke within the previous 3 months were included and the results cannot be extrapolated to the acute setting, since, as stated by the authors, there have been no studies validating the OCSP scale in the acute phase.

WHAT IS THE ETIOLOGY OF THE STROKE?

The recognition of the etiology of the lesion is of great therapeutic importance. It may be useful in stratifying patients for therapeutic decisions, especially in the very acute phase of stroke when imaging may still be normal and the laboratory work-up (e.g. Doppler and echocardiography) not yet available. Although initial results with intravenous thrombolysis suggest that the benefit is independent of stroke etiology,[44,45] novel developments in therapeutics (e.g. intra-arterial thrombolysis) will be more efficacious in certain stroke subtypes than others. Moreover, the clinical impression in the acute phase dictates the laboratory investigations. Several classifications for stroke etiology exist. In the Lausanne Stroke Registry, etiology is classified into five main groups: namely, large-artery disease (atherosclerosis), cardioembolic stroke, small-artery disease (lacune), undetermined etiology (cause not identified or more than one cause), and other (e.g. arterial dissection and vasculitis).[46]

Accuracy[5,17,47] and interobserver agreement[13,48] on the classification of stroke etiology have been evaluated in the acute phase. A poor agreement (γ=0.41) between observers was obtained when acute stroke was studied using the OCSP classification.[13] Differences in the assessment of some commonly neurologic signs result in only moderate (γ=0.39 for hemianopia) or poor (γ=0.15 for sensory loss) interobserver agreement. Similar results for interobserver agreement (γ=0.38) were achieved in the Stroke Data Bank when only the history and clinical examination were used to establish the stroke mechanism.[48] Studies comparing the initial clinical impression of stroke subtype and the final diagnosis after laboratory evaluation (accuracy of initial diagnosis) yielded conflicting results.[5,17,47] The clinical impression of stroke experts agreed with the final diagnosis in only 62% of patients in the TOAST study.[48] Greater accuracy was obtained by von Arbin et al. (87%)[17] and in the Lausanne Stroke Registry (92%).[5]

WHAT IS THE PROGNOSIS OF THE PATIENT?

At the very beginning of the evaluation of a stroke patient, it would be useful to have some idea of the prognosis. It is important not only to determine whether the patient is going to live or not (mortality) but also to estimate his quality of life (disability). It has been known for a long time that certain characteristics in the presentation of stroke are related to death and disability. For example, in 1893, Gowers stressed the importance of altered level of consciousness in the prognosis.[49] Several studies have attempted to identify criteria for functional prognosis after stroke. Most reported that impaired consciousness was the strongest predictor of mortality and severe disability after stroke.[27,50–52] Other clinical characteristics often correlated with a poor prognosis are lower limb weakness,[28,50–52] conjugate eye deviation,[27,50] hemianopia,[52] a history of ischemic heart disease,[53] and a history of atrial fibrillation.[52,54] Contradictory results were found for other

items, such as age,[27,51,52]sex,27 and admission blood pressure.[52,53] Scores based on these characteristics have been developed to predict mortality[53] and disability.[50] The score developed by Allen predicted the clinical outcome (poor outcome=moderate to severe disability or death) with high accuracy (Table 3.6).[50] Social network and emotional responses, which may have a strong effect on the prognosis, are usually neglected in clinical studies.

CLINICAL SCALES

The neurologic examination is uniquely suited to the accurate description of a single patient, but has limitations for group description over time, as required in large-scale clinical investigations.[55] In response to the need for more precise measurements, a number of stroke scales have been developed. Although such scales have been used for decades, few have passed the rigorous clinimetric process required to ensure their reliability and validity.[56,57] Reliability refers to the reproducibility of a measurement at two different points in time (intraobserver reliability) and between two or more observers (interobserver reliability), whereas validity reflects the ability of the scale to reflect as closely as possible the clinical phenomenon under study. Ideally, a stroke scale should be valid, reliable, and simple.

Stroke scales can be used for different purposes:[58]

1. to evaluate a new therapy in randomized clinical trials
2. to guide management (e.g. use of thrombolytics)

Table 3.6 Allen score for predicting outcome

Clinical feature	Score
Complete limb paresis (MRC scale 0 or 1)	−12
Combination of high cerebral dysfunction, hemianopia, and hemiplegia	−11
Drowsy or comatose (after 24 h)	−10
Age (years)	−(age x0.4)
Loss of consciousness at onset of deficit	−9
Uncomplicated hemiparesis	+8
	+40 (constant)
	Total:
	>+10=good outcome
	<−15=poor outcome

3. to monitor the neurologic evolution of patients after admission or the use of specific treatments
4. to determine the prognosis at an early stage.

One of the first and previously most frequently hemiplegia due to middle cerebral artery infarcused scales, the Mathew stroke scale, was first reported in 1972 in an evaluation of glycerol therapy.[59] It measures the level of consciousness, orientation, speech, cranial nerve function, motor power, global disability status, reflexes, and sensation, with a range from 100 (normal) to 0 (death).

The Scandinavian Stroke Scale, reported in 1985, was originally created for a study of hemodilution in acute stroke by non-neurologists.[60] It contains nine items (consciousness, orientation, gaze palsy, motor power of the arm, hand and leg, speech, facial palsy, and gait) and has a maximal score of 58 points (normal). It can be divided into two parts: one for prognosis and the other for long-term follow-up.

The Canadian neurological scale was developed by Côté on the basis of a review of the literature and clinical experience.[10] It was designed to be used by both neurologists and by non-neurologists such as nurses, and measures 8 items, with 8.5 as the maximal score. A different version was developed for patients with comprehension problems.

The Toronto stroke scale was used in 1976 in a study of steroid therapy for acute ischemic stroke.[61] It contains 11 items, with 0 as the normal score and 281 the worst score.

The middle cerebral artery neurologic scale, also called the Orgongozo scale, presented in 1983, was specially developed for the study of tion.[62] Initially, it contained 13 items, but 3 were unreliable and were omitted in the last version, which therefore contains 10 items.

The hemispheric stroke scale was designed for ischemic strokes in the anterior circulation and was presented in 1987.[63] It contains 23 items, graded from 0 (normal) to 100 (worse).

The unified stroke scale is composed of the middle cerebral artery stroke scale and the Scandinavian Stroke Scale. Its scoring format permits the generation of a score for one or both stroke scales.[64]

The European stroke scale, developed by European neurologists for studies of middle cerebral artery infarction, was published in 1995.[65] It contains 14 items, each graded from 0 (worst) to 100 (normal).

The National Institutes of Health stroke scale (NIHSS) was presented in 1989, and is based on several previous scales—the Toronto scale, Oxbury scale, Cincinnati stroke scale, Edinburgh2 coma scale, and the Boston diagnostic aphasia examination.[66] It contains 13 items, with higher scores indicating a greater deficit (Table 3.7). Over recent years, the NIHSS has been the instrument most widely used in clinical trials to assess

Table 3.7 The National Institutes of Health stroke scale (NIHSS) and its simplified version (mNIHSS)

Item	NIHSS	mNIHSS
1A. Level of consciousness	0=Alert 2=Not alert, obtunded 3=Unresponsive	–
1B. Questions[a]	0=Answers both correctly 1=Answers one correctly 2=Answers neither correctly	0=Answers both correctly 1=Answers one correctly 2=Answers neither correctly
1C. Commands[b]	0=Performs both tasks correctly 1=Performs one task correctly 2=Performs neither task correctly	0=Performs both tasks correctly 1=Performs one task correctly 2=Performs neither task correctly
2. Gaze	0=Normal 1=Partial gaze palsy 2=Total gaze palsy	0=Normal 1=Partial gaze palsy 2=Total gaze palsy
3. Visual fields	0=No visual loss 1=Partial hemianopia 2=Complete hemianopia 3=Bilateral hemianopia	0=No visual loss 1=Partial hemianopia 2=Complete hemianopia 3=Bilateral hemianopia
4. Facial palsy	0=Normal 1=Minor paralysis 2=Partial paralysis 3=Complete paralysis	–
5. Motor arm: (a) Left (b) Right	0=No drift 1=Drift before 10s 2=Falls before 10s 3=No effort against gravity	0=No drift 1=Drift before 10s 2=Falls before 10 s 3=No effort against gravity

Item	NIHSS	mNIHSS
	4=No movement	4=No movement
6. Motor leg: (a) Left (b) Right	0=No drift 1=Drift before 5 s 2=Falls before 5 s 3=No effort against gravity 4=No movement	0=No drift 1=Drift before 5 s 2=Falls before 5 s 3=No effort against gravity 4=No movement
7. Ataxia	0=Absent 1=One limb 2=Two limbs	–
8. Sensory	0=Normal 1=Mild loss 2=Severe loss	0=Normal 1=Abnormal
9. Language	0=Normal 1=Mild aphasia 2=Severe aphasia 3=Mute or global aphasia	0=Normal 1=Mild aphasia 2=Severe aphasia 3=Mute or global aphasia
10. Dysarthria	0=Normal 1=Mild 2=Severe	–
11. Neglect	0=Normal 1=Mild 2=Severe	0=Normal 1=Mild 2=Severe

[a] The patient is asked the month and his age.
[b] The patients is asked to open and close his eyes, then to grip and release the non-paretic hand.

therapeutic interventions in acute stroke. One study showed it to be a good predictor of the 3-month outcome, performing better than the Canadian neurological scale and the middle cerebral artery neurologic scale.[67] Recently, a modified version of this scale (mNIHSS) has been presented;[68] items with poor reliability or redundance were excluded and the choices for the sensory item collapsed, this version therefore contains 11 items (Table 3.7). Although simpler than the original version, the mNIHSS has still to be tested in a prospective fashion.

Scales developed for the evaluation of activities of daily living (disability scales) are used for outcome evaluation, those most frequently used being the Barthel index[69] and the Rankin scale.[27] The Barthel index contains 10 items (feeding, bathing, grooming, dressing, bowel control, bladder control, toilet transfer, chair/bed transfer, ambulation, and stair climbing), and a maximal score of 100 indicates competence in all 10 items (Table 3.8). The Rankin scale was presented in 1957 for use in stroke in patients over 60 years of age. Initially, it had five grades,[27] but a modified version included a class for 'death'[70] (Table 3.9).

CONCLUSIONS

The neurologic examination has certain limitations, but is far from obsolete, providing important information for the neurologist who is aware of its utility.[71–73] It guides therapy, provides valuable data regarding prognosis, and dictates which laboratory tests or technical methods of examination should be used. However, it should be complemented by neuroimaging to differentiate with certainty between cerebral hemorrhage and infarct.

Although the authors employ stroke scales, particularly the Orgogozo scale, NIHSS, Barthel index, and modified Rankin scale, these are not a substitute for neurologic examination, but a complement to it, being particularly useful for research. No classification or score has been shown to be a better predictor of the final findings (e.g. hemorrhage vs infarct, lesion topography, and stroke etiology) than clinical judgment.[5] The reasons for this are not clear, but clinical problem solving is a complex skill.[74] Clinical reasoning involves the generation and testing of sequential hypotheses. A clinical case involves so many individual variables and possible combinations of these variables that a mathematical formula cannot include and process all of them, something which the clinician does subconsciously. In addition, experienced neurologists may quickly recognize a syndrome because of their previous experience of identical situations.

In some instances, technology may not clarify the diagnosis, and it may be of great value to go back and collect a more detailed history and perform a more complete physical examination.

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Table 3.8 The Barthel index

Item	Score
1.Feeding	10. Independent 5. Needs help (e.g. cutting food, spreading butter) 0. Totally dependent
2. Moving from wheelchair to bed	15. Independent, including looking the wheelchair and lifting the footrests 10. Minimal help or supervision

Item	Score
	5. Able to sit, but needs maximal assistance for transfer 0. Completely bedridden, use of chair not possible
3. Grooming	5. Washes hands and face, combs hair, brushes teeth, and shaves 0. Needs assistance
4. Toilet transfer	10. Independent with toilet or bedpan 5. Needs help for balance or handling clothes or toilet paper 0. Dependent
5. Bathing	5. Independent 0. Dependent
6. Walking/motility	15. Independent, may use aids other than a rolling walker 10. Walks with help 5. Independent with wheelchair 0. Unable to move
7. Stair-climbing	10. Independent 5. Needs help 0. Unable to climb stairs
8. Dressing	10. Independent 5. Needs help, but does at least half of the task within a reasonable period of time 0. Dependent
9. Bowel	10. Continent and able to use enema or suppository 5. Occasional accidents or needs help with enema or suppository 0. Frequent accidents
10. Bladder	10. Continent 5. Occasional accidents 0. Incontinent or needs indwelling catheter Maximum 100

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Table 3.9 The modified Rankin scale

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

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APPENDIX

The kappa score (γ) is preferred over general measures of agreement because it accounts for agreement expected by chance. The degree of assessment is conventionally interpreted as follows: γ=0.0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect agreement.

4.
Acute stroke units and teams

Philippe Lyrer

INTRODUCTION

Stroke represents a major cause of death, cognitive impairment and disability. The type of care patients receive varies from country to country also, depending on the local habits, political issues and resources available. The sensitivity of the brain to brief episodes of profound ischemia or prolonged periods of modest ischemia requires an aggressive approach to acute stroke care. Often patients do not receive the appropriate care in time. In Germany, as well as in the United States, patients are more likely to get acute stroke intensive care treatment during the first days, while in France, Switzerland, Norway, Sweden, and some other European countries, patients are more likely to be treated initially by means of different, individually modeled stroke service pathways. It is therefore crucial to first determine what aim should be targeted when managing stroke patients. The focus of this chapter is the treatment of patients with focal cerebral ischemia, which accounts for about 85% of most etiologies of strokes.

The common goals of the management of patients affected by possible symptoms of transient ischemic attacks or stroke are:[1–3]

- prompt and accurate diagnosis of the stroke and the underlying etiology
- specific medical and surgical treatment
- assessment of patients' stroke-related medical problems in the acute phase and providing adequate care
- terminal care for patients that are unlikely to survive
- comprehensive rehabilitation
- continuing long-term care for severely disabled patients
- hospital discharge and placement
- adequate secondary prevention of further vascular events
- educational and research programs
- established guidelines.

DEFINITIONS

It is crucial to first outline the different existing types of stroke care, which range from services providing acute stroke care during the first days after stroke to the service only providing rehabilitation. The various aspects may refer to the following items:

- geographic location of stroke treatment, such as the emergency ward, intensive care unit, specialized ward, and the general ward
- consistency of the diagnostic and treatment process
- expertise of the treating physicians and staff members involved
- availability of diagnostic facilities and general infrastructure
- focus of activities, e.g. emergency treatment only, rehabilitation only, comprehensive treatment covering all needs
- social and political requirements or commitments.

Different opinions regarding stroke treatment pathways and infrastructure exist. The maximal solution may consist of a comprehensive stroke care, i.e. treatment covering the whole period from the acute phase to the end of rehabilitation.[4] The minimal, but not necessarily the least solution, is community-based home treatment.[5]

A recent systematic meta-analysis identified several types of stroke services. The most important finding was that all services should provide an organized care and use defined path ways.[6] So-called dedicated stroke units can be distinguished as follows.

ACUTE STROKE UNIT AND ACUTE STROKE INTENSIVE CARE UNIT

This setting is defined by geographically clearly marked/restricted wards, where stroke patients are admitted and cared for. This category includes the 'acute intensive stroke unit' or 'acute stroke intensive care unit,' which accepts patients acutely but discharges early, i.e. usually within 7 days. Acute stroke units seem to improve care by themselves by alternating investigations as well as secondary prevention and reducing length of stay.[7]

ACUTE STROKE TEAM

One approach for reducing the in-hospital delays by obtaining specialized medical care and by providing acute stroke care for stroke patients is the formation of so-called acute stroke teams, which are also referred to as stroke code teams in analogy to cardiac code teams. This is a common approach in the United States[8] and in some hospitals in the United Kingdom.[9] Different specialists collaborate in stroke care and are available on request to advise on specific stroke-related issues. The team is thus based on organization not on geography, and the patient may be treated in the most extreme case on any ward of any appropriate hospital.

STROKE REHABILITATION UNITS

Stroke rehabilitation units only accept patients after the acute phase of the disease, i.e. with a delay of usually 7 days or more, and focus exclusively on rehabilitation. This type of organization will not be discussed further in this chapter.

COMPREHENSIVE STROKE UNITS

Comprehensive stroke units combine acute and rehabilitation stroke care. Here, patients may also be treated for a prolonged time.[6]

MANDATORY COMPONENTS AND GOALS

Any of the above-mentioned facilities can only work efficaciously provided that a clear organization scheme is present. It is mandatory to establish algorithms that determine patients, evaluation, any diagnostic work-up, treatment, and rehabilitation procedures as well as staff responsibilities and duties.

RESPONSIBLE PHYSICIAN

One responsible physician with specialized knowledge has to be appointed to lead the stroke unit. This raises the question about the mandatory qualification. This person should implement the stroke unit, adopt and develop the concept to the local needs, select and supervise the staff and is responsible for the continuous training of the stroke team members. This issue has not often been addressed so far. A neurologist with training in stroke medicine or an internist or geriatrician with a strong interest in neurology might be regarded as particularly suitable if they acquired specialized knowledge.[2] Warlow et al.[1] do not specify what kind of physician is most able to give treatment to stroke patients. They state that the physician should have broad knowledge about pathologies underlying stroke as well as the functional problems related to this disease. His broad knowledge qualifies him to lead the stroke team. The neurologist can provide knowledge on clinical diagnosis, interpretation, and consequences of neurologic impairment. Moreover, a neurologist may be more aware of stroke in the posterior fossa than untrained physicians.[10] Recent reports suggest that treatment by neurologists in the acute phase may be more expensive, but outcome is better over all.[8,11] As stroke patients suffer from a broad range of symptoms, their care demands input from several disciplines.

TYPE OF ORGANIZATION

Different types of stroke unit organization can be identified. Several models have been described, but only a few have been evaluated. Stroke units are far from being homogeneous. On the one hand, there are acute stroke units[12] or intensive care units[13,14] mainly designed to provide care for patients in the acute phase and not focusing on rehabilitation. Their aim is to avoid systemic complications and to rapidly detect deteriorating stroke as changes in a patient's assessment often occur in the first few hours after onset. On the other hand, non-intensive stroke units or stroke rehabilitation units exist, where a patient is transferred to for rehabilitation, which is regarded as the main aim. These units are usually discrete stroke wards. Furthermore, there are the stroke wards taking care of patients starting in the acute phase until full rehabilitation. A further approach is to create mobile stroke teams in acute care hospital as well as in rehabilitation hospitals with the aim of providing skilled treatment at every stage of the illness.

Every stroke unit should, in any case, be dedicated to provide: [13,14]

- a comprehensive assessment of the patient's illness and disability
- development, and implementation of a collaborative policy for stroke management
- identification and awareness of objectives of rehabilitation
- close multidisciplinary collaboration
- education and research activity.

An easy access to a stroke service for patients has to be aimed at. Furthermore, a reduction of inhospital delays of stroke treatment by adequate measures, e.g. by establishing a phone call system, is regarded as essential.[15]

INFRASTRUCTURE AND FACILITIES TO RUN A STROKE UNIT

As strokes occur at any time of the day and are to be considered as medical emergencies, an emergency room should be accessible on a 24-hour basis. The assessment of patients and close monitoring have to be warranted. A minimal amount of diagnostic tools should be available on site, i.e. a 24-hour cranial computer tomography (CCT)— scan facility, a 24-hour neurosonology examination on request, routine laboratory tests, cerebral angiography, and an intensive care unit. Emergency CCT diagnosis is mandatory to diagnose intracerebral hemorrhage and will be used on an emergency basis, especially for ischemic stroke patients qualifying for thrombolytic treatment. Neurosonology examinations are needed to perform screening of large-artery cerebrovascular diseases, and are requested as soon as emboli from large arteries are suspected. Laboratory facilities are mandatory for blood cell count and to detect electrolyte and metabolic disturbances in the acute stage. The option of transferring a patient to an intensive care ward if necessary is essential to avoid early systemic complications and to closely monitor impairment as well as cardiovascular functions. A rapid access to neurosurgical operation procedures is also mandatory.[4]

EVIDENCE OF EFFICACY

SPECIFICALLY ESTABLISHED PATHWAYS FOR STROKE CARE

With the aim of establishing a meta-analysis for stroke care, the stroke unit trialist's collaboration identified stroke pathways that provided information by randomized controlled trials. The dedicated stroke unit is a disease-specific service provided by a discrete stroke ward or stroke team working exclusively in the care of stroke patients. The service can be based in a geographically discrete ward or comprise a peripatetic team. This category included the following:

- acute (intensive) stroke units which accept patients acutely but discharge early (usually within 7 days)
- rehabilitation stroke units, which accept patients after a delay of usually 7 days or more and focus on rehabilitation
- comprehensive stroke units (i.e. combined acute and rehabilitation), which accept patients acutely but also provide rehabilitation for at least several weeks if necessary.

Both the rehabilitation unit and the comprehensive unit offer prolonged periods of rehabilitation.

CONTROLLED RANDOMIZED TRIALS

Several controlled randomized trials aimed at showing the efficacy of different types of stroke unit care. By themselves, the results of each trial give a very heterogeneous picture, and no definite conclusion can be drawn. For a few years, the stroke trialists' collaboration has provided data from meta-analysis of all available data on stroke unit care. Data could be extracted from more than 25 controlled randomized trials and allowed the following estimate of efficacy.[6]

EFFECT ON DEATH

In the cited meta-analysis, data from 20 trials on the principal outcome of death at final review were available. This analysis is based on the service comparisons within the original trials where a novel

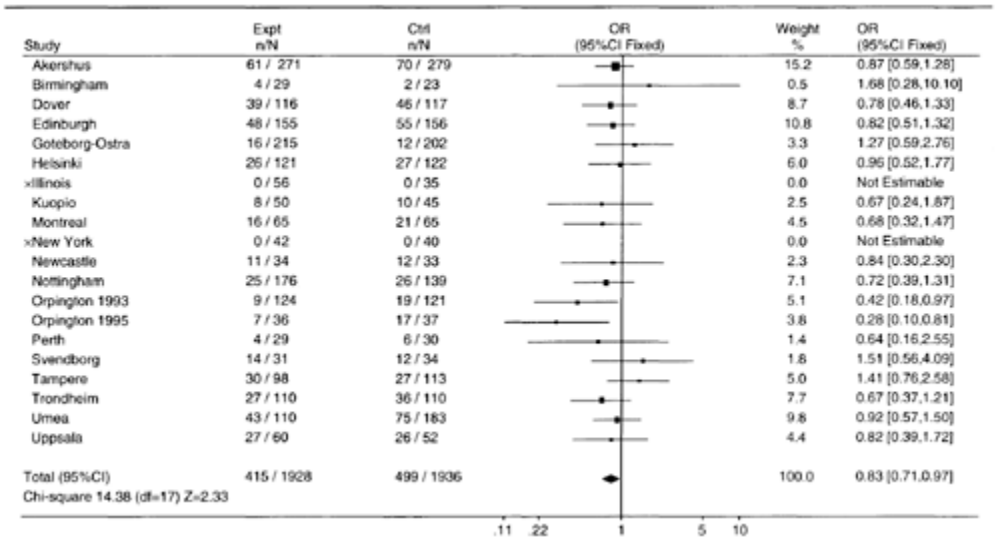

Figure 4.1 Compari son of organized stroke unit care vs conventional care outcome: death by the end of scheduled follow-up.[6]

intervention was compared with the contemporary conventional care. Case fatality recorded at final review (median follow-up 12 months; range 6 weeks to 12 months) was lower in the organized (stroke unit) care in 14 of the 20 trials. The overall estimate gives an odds ratio (OR) of 0.83 (95% confidence interval (CI) 0.71–0.97). The odds of death was not considerably changed if the analysis was restricted to trials where scheduled follow-up was continued for a fixed period of 6 months or 1 year (Fig. 4.1).

EFFECT ON DEATH OR INSTITUTIONAL CARE

The second outcome examined was the OR of death or condition requiring institutional care at the end of follow-up (median=1 year after stroke). Institutional care is an important outcome, as it may be unbiased. The summary result was highly significant (0.77, CI 0.68–0.88; $p<0.0001$), but some heterogeneity existed between trials attributable to five analyzed trials that had a very short or variable period of followup. Trials with a fixed prolonged period of follow-up showed a significant reduction in death or institutionalization with less heterogeneity (Fig. 4.2).

EFFECT ON DEATH OR DEPENDENCY

The third outcome examined in the meta-analysis was the combined adverse outcome of being dead or dependent in activities of daily living at the end of follow-up. The overall OR for being dead or dependent if receiving organized (stroke unit) care rather than conventional care was 0.75 (0.65–0.87; $p<0.0001$), and the summary result showed some minor heterogeneity. The main reason for this may lie in the nature of the control group. The results were less heterogeneous and the odds ratio remained significant where organized (stroke unit) care was compared to conventional care provided in a general medical ward. The conclusions were not altered by the exclusion of trials with a variable followup period or informal randomization procedure. The main methodological difficulty when using dependency as an outcome is the degree of blinding at final assessment and the potential for bias if the assessor is aware of the treatment allocation (Fig. 4.3).

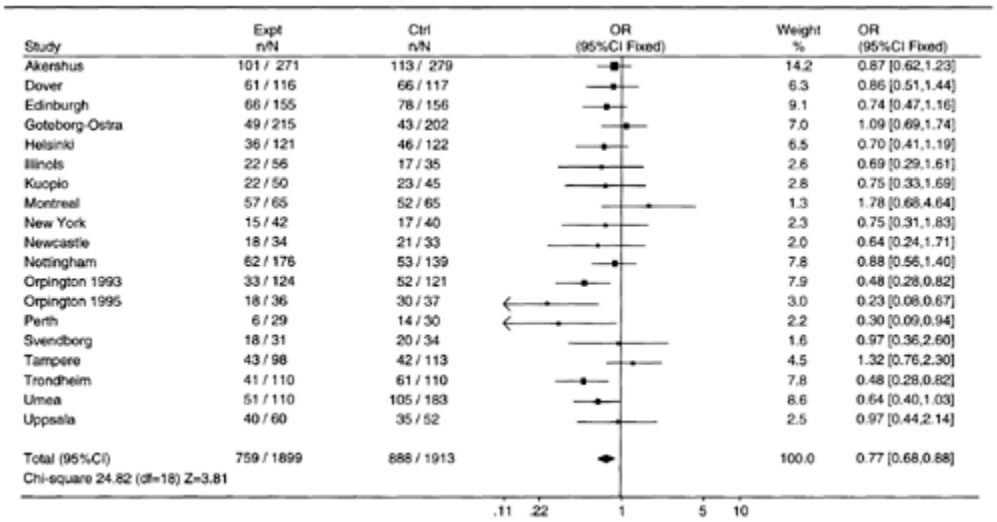

Figure 4.2 Comparison of organized stroke unit care vs conventional care outcome: death or institutional care by the end of scheduled follow-up.[6]

AGE

As the severity of stroke is not age-related, age should not be taken into account for decision making as far as admission to a stroke unit is concerned. Elderly people, however, are more likely to have a less favorable outcome. Still, each individual should get a maximal treatment to reduce disability. As prognosis may depend very significantly on the clinical syndrome, priority should be given to patients with certain specific syndromes. There is no clear evidence so far whether any clinical neurologic syndrome should be excluded from treatment in stroke units. Patients with lacunar syndromes are likely to be less disabled compared with patients with cortical syndromes, even though there are exceptions. As the etiology is usually still unknown when the patient enters an emergency room, etiologic factors cannot be taken into account for decision making whether a patient should be admitted to a stroke unit or not. Etiological factors are the basis of secondary stroke prevention, but not for decision making.

In the previously mentioned meta-analysis, the patient subgroup analysis for death or institutional care showed a similar OR (95% CI) for the age group up to 75 years of 0.77 (CI 0.63–0.94) and an even more favorable value for the elderly, i.e. over 75 years, of 0.71 (0.57–0.90).

LONG-TERM FOLLOW-UP

Until now, one clinical controlled trial could recall data from patients 10 years after initial treatment. The effect of stroke unit treatment was still present 10 years after admission for an initial stroke. It is therefore concluded that stroke unit care has a long-term benefit that is measurable until 10 years later.[16]

NUMBER NEEDED TO TREAT

The risk difference for each outcome was calculated as the absolute difference in outcome in each trial pooled for all available trials. This information was used to calculate the number needed to treat to prevent one adverse event. On average, the number needed to treat to prevent one death was calculated to be 32

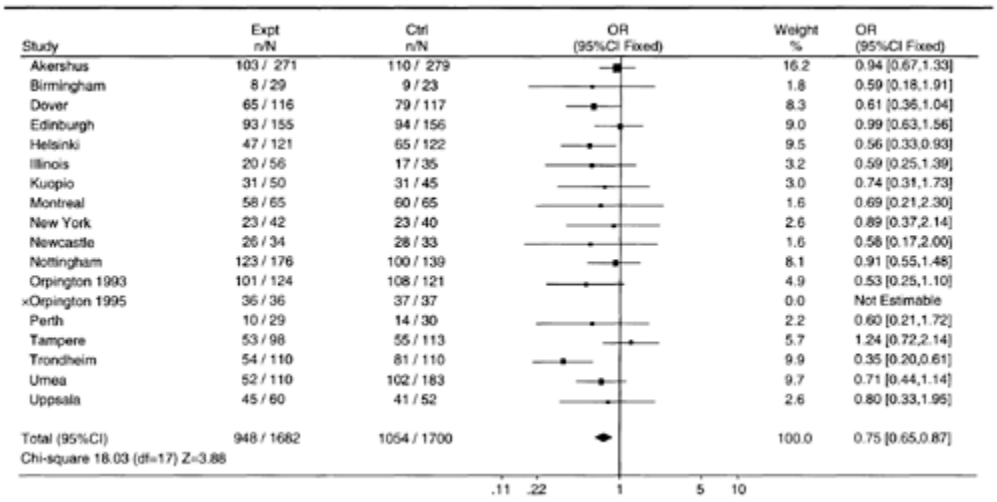

Figure 4.3 Comparison of organized stroke unit care vs conventional care outcome: death or dependency by the end of scheduled follow-up.[6]

(95% CI 18–200), that to prevent one patient from being unable to live at home was 16 (10–43) and that to prevent one patient from failing to regain independence was 18 (11–45). There could, however, be a wide range of results as both the confidence intervals and the baseline outcome rates vary considerably.

PATIENT SATISFACTION AND QUALITY OF LIFE

Only two trials[17,18] recorded outcome measures related to patients' quality of life. In both cases, there was a pattern of improved results within the stroke unit survivors, with the results attaining statistical significance in the Trondheim trial.[18] There was no information on any systematically gathered information on patients' preferences.

LENGTH OF STAY

Length of stay data were available for 16 individual trials from the meta-analysis. Mean (or median) length of stay ranged from 13 to 162 days in the stroke unit groups and 14 to 137 days in the control groups. Nine trials reported a shorter length of stay in the stroke unit group, and seven a more prolonged stay. The calculation of a summary result for the length of stay was subject to major methodological limitations, such as different ways of calculation of the length of stay or trials that recorded median rather than mean length of stay. Overall, there was a modest reduction in the length of stay in the stroke unit group, which approximately corresponded to a reduction ranging from 2 to 11 days. Finally, the length of stay is mainly determined by local conditions and organization. It seems not warranted to claim that stroke patients should stay at one place from entry to discharge. It may be equally effective to separate an acute phase of a few days, designated to the treatment of the initial lesion as well as consecutive acute complications, from a second phase dedicated to rehabilitation.[6]

At present, there are also services following the strategy of discharging home early, but at the same time offering community-based rehabilitation. However, there is neither clear evidence of risk and benefits nor

of cost-effectiveness.[19] So far, these models need further evaluation and cannot be propagated at the present stage.

PRE-HOSPITAL TREATMENT

There are virtually no data on admission pathways. By empirical decision making it seems rational to avoid any delay in transfer of patients to an adequate institution. This requires a higher awareness of the possibility of potentially efficacious treatment of stroke in public and among family physicians and emergency organizations. In order to optimize therapeutic potential, the highest number possible of patients should be admitted.[2] Of course, many of these patients will eventually not require immediate treatment, but will need appropriate diagnostic work-up and start of secondary prevention. This is true in the case of existing institutions, that are able to treat acute stroke patients.

AVOIDING HOSPITALIZATION AFTER STROKE

Another systematic Cochrane review deals with the need for hospitalization of stroke patients.[20] In the United Kingdom, it has become increasingly fashionable to develop alternatives to hospital-based care for a number of conditions, including stroke, which are often called 'hospitalat-home.' In a recent UK survey, over 100 schemes of this type were planned or underway.[21] The underlying rationale is that these services not only provide equivalent or better patients' outcome at lower cost but are also preferred by patients and caregivers. The corresponding trials are characterized by considerable heterogeneity hardly allowing specific conclusions. Therefore, drawing conclusions seems only reasonable for broad policy choices rather than for specific service designs, e.g. whether the availability of home-based alternatives to hospital care does improve outcome and does reduce resource use. The review indicates that such an approach has yet to prove to have an advantage over conventional services (which often involve hospital admission). The authors have not been able to identify any significant differences in patient or caregivers' outcomes. Further, despite an apparent reduction in the number of patients admitted to hospital, there was no overall reduction in hospital bed use, which suggests that the novel (intervention) services are not cheaper and might be even more costly than conventional care.[20] However, there are concerns about the heterogeneity of the control service provision. The control services usually included the option of admission to hospital to a general medical service, which is no longer regarded as adequate.[6] Any future trials should compare home care services to the best available inpatient care (organized stroke unit care). In view of the heterogeneous nature of the trials reviewed, it might be argued that no pooling of data should be attempted. Even if this recommendation were followed, we would still be left with the conclusion that the availability of home care services to acute stroke patients has neither been shown to improve patients' outcomes nor reduce the costs of care.[14] Thus, there is currently no evidence to support a radical shift of acute care from the conventional hospital-based setting to a home-based one for the majority of stroke patients.

A further recently published trial addressed this question. It aimed to compare the efficacy of stroke unit, stroke team, and domiciliary stroke care in reducing mortality, dependence and institutionalization in patients with moderately severe stroke. It finally showed that organized stroke units are more effective than a specialist stroke team or a specialist domiciliary stroke care.[9] Mortality was significantly lower, with 14% for stroke team care after 12 months, than for stroke team or domiciliary stroke care, with 24% and 30% respectively (OR 0.5, CI 0.29–0.87, $p<0.01$). This study provides further support for early specialist care on dedicated units for stroke patients.

DISCHARGE AND REHABILITATION

Any type of follow-up treatment has to be carefully planned. It is important to adjust and coordinate patients' daily requirements in cases of discharge home. In cases of inpatient rehabilitation, it is important to prepare the patient for this next step, to choose the adequate institution, and to warrant information on follow-up as well as on final outcome. It is not the aim of this chapter to describe rehabilitation-related procedures.

ECONOMIC ISSUES

Stroke units appear to improve outcomes, but at what cost? No detailed cost-benefit analysis of stroke units has been carried out up to now[22] nor have the published trials provided enough detailed information to allow a detailed formal analysis. In cost terms, length of stay is likely to dominate any individual component of patient care. Studies from several developed countries[23] have shown that fixed cost (particularly nursing staff salaries) account for over 90% of spending on patients with acute stroke. Remedial therapy represents only a small proportion of the total cost of hospitalization. In a recent analysis,[24] stroke unit care was not apparently associated with an increase in total health and social care cost but these conclusions were sensitive to some variations in cost estimates. More research is required to elucidate the cost implications of stroke units. Setting up a stroke critical pathway leads to significant savings due to a decrease of length of stay.[25]

Inpatient costs vary, depending on the type of stroke. In a recent estimate on stroke costs, patients with subarachnoid hemorrhage had the most cost-intensive treatment, followed by patients with intracerebral hemorrhage.[26] The least expensive were those with ischemic stroke and transient ischemic attacks. The average costs amounted to US$23 777 for subarachnoid hemorrhage, US$10 241 for intracerebral hemorrhage, US$5837 for ischemic stroke and US$3350 for transient ischemic attack, respectively. It has to be taken into account that this estimate was issued by the United States, and that costs vary among institutions, e.g. the costs were higher in teaching hospitals than in non-teaching hospitals. These data provide a judgment of hospital costs, but it will be much more difficult to estimate the personal costs as well as those of relatives and society. So far, there are no data available on cost-effectiveness for acute stroke treatment by prospectively collected data. Prospectively collected uncontrolled data on cost are able to demonstrate that hospitals' cost in the first days of occurrence are determined by a few predictors, such as length of stay, stroke severity, atrial fibrillation ischemic cardiac disease, male sex, and use of heparin.[27]

Overall, the costs for stroke treatment vary a lot between different countries and different types of stroke care. At least in Europe there is a great variation of the processes of care, resources used and, thus, in stroke unit cost. The costs for one stroke within 3 months after onset vary from less than US$1000 in eastern Europe to approximately US$8000–9000 in London or Copenhagen.[28] At present, it is not clear what kind of stroke care is the most cost-effective.[28]

The formation of an acute stroke team creates no or only minimal additional cost. From this point of view, it will be wise to operate as many acute stroke teams as possible, as this seems to be one of the most cost-effective interventions.[8] Modeling costs for a stroke unit gives estimates that costs for stroke care decrease by approximately 3%. The transformation of a general ward to a stroke unit would then result in an amortization of investments within the first year.[29] Overall, there would be a saving in hospital as well as in community resources as patients are better off after a shorter hospital stay.

ESTABLISHING GUIDELINES AND EDUCATION

Guidelines are mandatory to any clinic that treats stroke patients, in the way that is compatible with a stroke unit pathway. Guidelines have to implement local habits specifically and they have to consider the possibilities of the present infrastructure. It is not only important to create guidelines but also to disseminate them and to teach their application.[13,14]

CONTINUOUS EVALUATION PROCESS

Once a stroke unit care pathway is established, quality control of the care given is mandatory. The availability of data draws attention to possible lacks or failures and enables changes where required. Quality improvement proceeds most effectively if all elements of the quality triad — structures, processes, and outcomes—are used in the assessment, provided that the structures and processes chosen have been demonstrated to be associated with the desired outcome of care.[30] One of the most suitable tools is the use of a stroke database that holds the predefined and relevant items on processes and outcomes.

CONCLUSIONS

It can be stated that patients receiving organized inpatient (stroke unit) care are more likely to survive, regain independence, and return home than those receiving contemporary conventional care. This apparent effect is of marginal statistical significance for case fatality. However, the observed reduction in the combined adverse outcomes (death or institutionalization, death, or dependency) are much more statistically robust and warrant the institutionalization of stroke unit care. The requirement for long-term care is a useful surrogate for disability and is likely to show good interobserver agreement. However, the absolute rates of institutionalization will be influenced by a variety of national and cultural factors.[6] This is also true for the cost.

Methodological limitations may also have had an influence on the analysis of descriptive information about service organization.[6,31] Service descriptions are collated retrospectively The above-mentioned findings may therefore be biased in regard to the expectations of the authors, who ran organized stroke unit care. One has to keep in mind that subgroup analyses indicate that the observed benefits of organized stroke unit care are not limited to any one subgroup of patients or models of stroke unit organization. Apparent benefits are seen in patients of both sexes, aged under and over 75 years, and across a range of stroke severities. Therefore there is no reason to deny stroke unit treatment to any stroke patient at present.

The type of organization is of secondary importance. Many different approaches to stroke unit care exist (e.g. comprehensive stroke units, stroke teams, acute stroke units, rehabilitation stroke units, and rehabilitation units). A considerable part of them tends to be more effective than conventional care in a general medical ward, by scientific evidence. Apparent benefits can be shown for units with acute admission policies as well as for those with delayed admission policies and for units offering a period of rehabilitation of several weeks.

Stroke units appear to improve outcomes, but at what cost? No detailed cost-benefit analysis of stroke units has been carried out.[22] Available information on detailed cost analyses showed a heterogeneous picture, with huge differences in stroke case costs within Europe. There is not sufficient information to allow a detailed formal analysis of cost-effectiveness. In cost terms, length of stay is likely to dominate any individual component of patient care. Studies from several developed countries[32] have shown that fixed costs (particularly nursing staff salaries) account for over 90% of spending on patients with acute stroke. Remedial therapy represents only a small proportion of the total costs of hospitalization. In a recent analysis,[24]

stroke unit care was not apparently associated with an increase in total health and social care costs but these conclusions were sensitive to some variations in cost estimates. More research is required to elucidate the cost implications of stroke units.

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5.
Computed tomography in acute stroke

Rüdiger von Kummer

INTRODUCTION

Computed tomography (CT) was the first modality to image the brain and its pathology. It is today regarded as a safe and simple method to quickly image the skull and its content. It confirms the definite diagnosis of ischemic stroke and detects the stroke pathology of the individual patient. Brain imaging with CT is consequently widely used and considered as the method of first choice for differentiating the stroke syndrome. Moreover, imaging of stroke pathology by CT can identify patients who may benefit from specific treatment.

A CT image of acute stroke patients is not difficult to read; it is, however, not self-evident. Reading of a CT image needs training and instruction, on how to recognize anatomy and pathology, combined with some knowledge about the physical conditions of image contrast.[1]

In this chapter, we discuss what kind of stroke pathology CT can assess, how accurate this information is, and whether imaging with CT has any impact on stroke diagnosis, stroke treatment, and finally on the clinical outcome of patients. After describing how to read CT, we discuss the levels of clinical efficacy of CT: technical capacity, diagnostic accuracy, diagnostic impact, therapeutic impact, and the effect on the clinical outcome of stroke patients.[2] Technical capacity is the capability of CT to reproducibly display recognizable images that demonstrate pathology with good intra- and interobserver reliability.[3] Diagnostic accuracy is measured in terms of sensitivity and specificity if a gold standard is available. The levels of clinical efficacy will be described for each individual stroke pathology that is depicted by CT.

KAPPA STATISTICS FOR IMAGE INTERPRETATION

The kappa statistics is regarded as the best measure for the assessment of chance-adjusted agreement and interobserver reliability.

The technical capacity is best measured by testing the intra- and interobserver agreement in detecting a specific pathology. If two observers agree on a proportion of cases, some of this agreement can be expected by chance alone. Cohen, therefore, introduced kappa as a chance-adjusted measure of agreement between two observers.[4] Kappa, however, does not only measure agreement; it is also affected by the presence of bias between observers and by the distribution of data across the categories that are used. If two observers differ in their assessment of the frequency of a specific state, there is a bias between the observers. This bias and the prevalence of specific findings may cause the paradox of high agreement, but low kappa[5] that was observed in studies of early CT findings in acute stroke.[6,7] Byrt et al., therefore, recently suggested the use of prevalence- and bias-adjusted kappa (PABAK).[8]

BASIC PRINCIPLES FOR THE INTERPRETATION OF CT IN ACUTE STROKE

The image provided by CT consists of a limited number of volume units (voxels). Matrix and slice thickness determine spatial resolution. A typical matrix has 256×256 voxels or 512×512 voxels. A recommended slice thickness is 4–5 mm for the base of the brain and 8–10 mm for the upper portions of the brain. The X-ray attenuation of each voxel is electronically detected, grouped in relative attenuation values —in Hounsfield units (HU) between −1023 and +3072, calibrated by the attenuation of water (HU=0) and air (HU=−1000)—and translated into 20 levels of a gray scale, which can be distinguished by the human eye. To enhance contrast resolution, the entire gray scale is used to represent exclusively the attenuation of the brain tissue, which normally varies between 20 and 50 HU. Another section ('window width') of the entire HU scale is used if structures with different attenuation, e.g. the temporal bones, are examined. The typical CT window width for the head is 80 HU. The mean value of such CT windows is called 'level' and is responsible for the brightness of the image. X-ray attenuation below the range of the CT window (e.g. air in nasal sinus) appears as black on the image; above this range (e.g. bone or clotted blood) it's white. A broader window diminishes the contrast between gray and white matter and impairs the detection of subtle changes in X-ray attenuation. If a CT window width of 80 HU is used, each gray level represents 4 HU. The contrast resolution is thus limited to 4 HU and could be enhanced by a reduction of the window width. However, a smaller window causes more image noise.[9]

CT scanners with one row of X-ray detectors image the brain slice by slice while the head is moved through the scanner by the increments of slice thickness. Helical CT means continuous CT scanning while the head is moved through the scanner. It achieves the X-ray attenuations of a tissue volume from which single slices can be computed. Modern CT scanners have more than one row of detectors and allow the simultaneous imaging of up to 16 slices and reduction of the imaging time by a factor of 2–16, providing CT images of the entire head in less than 1 s. The electron densities of the substrate under study attenuate X-rays.[10] In biological tissue, X-ray attenuation is directly correlated with its specific gravity.[11] Gray matter appears a bit brighter than white matter, because its X-ray attenuation is in the range of 35–45 Hounsfield units (HU), whereas white matter measures 20–30 HU. This difference allows differentiating subcortical white matter from cortex and from deep gray matter structures. CT can thus well depict the inner and outer anatomy of the brain. It detects changes in tissue water content (edema) and a shift of structures due to space-occupying processes. The X-ray attenuation of clotted blood is in the range of 70–90 HU: therefore CT easily detects blood clots.

The injection of contrast agents enhances X-ray attenuation of the cerebral vessels under normal conditions for the time period of brain circulation. Imaging during this period detects the intense contrast enhancement of arteries or veins, depending on the delay between contrast bolus injection and CT. Electronic segmentation then achieves CT angiography (CTA) of the brain's arteries or veins. (Fig. 5.1) Repeated scanning of one slice provides contrast concentration curves over time and thus hemodynamic information.

Pathological findings detected by unenhanced CT in acute stroke may be ischemic edema, thromboembolic occlusion of large vessels, focal brain tissue swelling caused by a focal increase in cerebral blood volume (CBV), intracranial hemorrhage, or tumor-like lesions that may mimic stroke. Computed tomography identifies these findings by detecting a change in X-ray attenuation of normal brain structures or a shift or replacement of brain structures by pathological substrates. A pathological increase in X-ray attenuation is called 'hyperdensity,' a pathological decrease 'hypodensity.' These terms are somewhat confusing because they do not define a fixed degree of X-ray attenuation. They are commonly used to characterize the attenuation of a structure in comparison to other tissue, e.g. in saying that a parenchymal hematoma is identified by its hyperdensity if compared with gray matter. They are best used, however, to

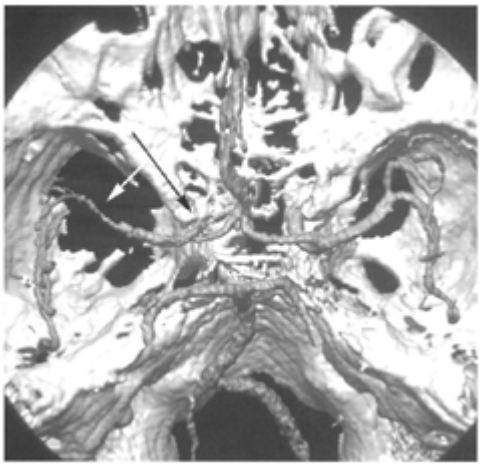

Figure 5.1 CT angiography in a patient with occlusions of the left internal carotid artery (black arrow, view from above) and of branches of the left middle cerebral artery (white arrow).

characterize a change in X-ray attenuation by comparing the 'density' of an affected structure to its normal 'density.' The symmetry of the brain structures in transverse planes facilitates this comparison. For example, the putamen is best evaluated by comparing its attenuation to that of the contralateral putamen and to that of the head of the caudate nucleus, because the caudate nucleus and the putamen are portions of the same anatomical structure, the striatum. It is obvious, that low technical quality of the scan (motion artifacts, wrong window or level), and in particular any obliquity of the scan, impairs the recognition of real changes in X-ray attenuation.

CT DETECTION OF INTRACRANIAL HEMORRHAGE AND STROKE MIMICS

The first step towards an effective treatment is the diagnosis of the cause of stroke. Clinically, acute parenchymal hemorrhage cannot reliably be distinguished from ischemic stroke. Other conditions that mimick ischemic stroke, such as focal encephalitis, demyelination, tumor, seizure, and hypoglycemia, may be identified by a careful analysis of concomitant symptoms. In patients with acute stroke, blood may be present in one or more cranial compartments: brain parenchyma, ventricles, subarachnoid space, and subdural or epidural space. After acute hemorrhage, blood represents as a hyperattenuating, often space-occupying mass. The degree of hyperattenuation depends on the amount of blood, whether it is clotted or not, and whether the blood is intermixed with cerebrospinal fluid (CSF) or brain tissue. Figure 5.2 shows an example of acute temporal hemorrhage in a patient with amyloid angiopathy where CT detects only portions of the acute blood clot. Moreover, CT does not detect blood degradation products like hemosiderin and cannot identify patients with old brain hemorrhages, e.g. with amyloid angiopathy. Hemorrhages related to coagulopathies or treatment with anticoagulants or thrombolytics are often inhomogeneous with fluid levels. CT may detect such bleeding after thrombolytic treatment for stroke or myocardial infarction (Fig. 5.3). Sensitivity of CT for detection of parenchymal hemorrhage is considered as nearly 100%, but small hemorrhages into the brain parenchyma or subarachnoid space can be missed.

The investigators of the European Cooperative Acute Stroke Studies (ECASS I and II) missed only a small parenchymal hemorrhage and a subarachnoid hemorrhage (SAH) in 1420 patients (0.1%) that was later

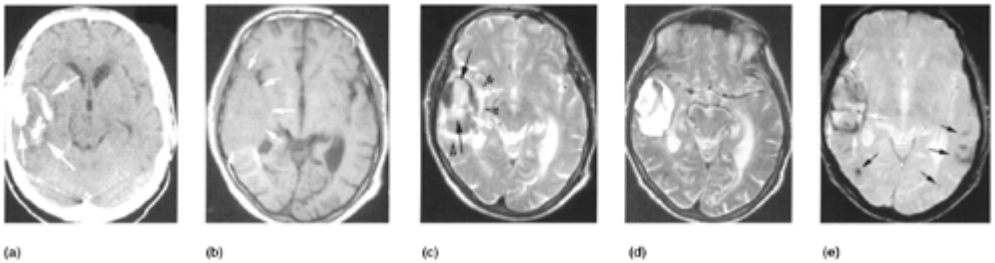

Figure 5.2 Imaging of acute temporal hemorrhage in a 72-year-old man with memory disturbance.

(a) The computed tomography (CT) scan shows three hyperattenuating areas (arrows) within the right temporal lobe intermixed with tissue of normal X-ray attenuation. The remaining brain looks normal. (b) The magnetic resonance imaging (MRI) scan was obtained 1 hour before the CT scan. The T1-weighted spin-echo sequence shows slight signal hypointensity (arrows) of the anterior temporal lobe. (c) On the T2-weighted spin-echo sequence, the signal of the anterior temporal lobe is heterogenous with areas of decreased signal (white arrows) representing deoxyhemoglobin, intermixed with areas of increased signal (black arrows) representing oxyhemoglobin, and surrounded by zones of markedly increased signal (black arrowheads) representing edema. (d) The follow-up MRI scan 3 weeks later shows the temporal hemorrhage with bright signal and a dark rim on T2-weighted spin-echo sequences representing methemoglobin and hemosiderin. (e) On T2*-weighted gradient echo sequences, the rim of hemosiderin deposit surrounding the hemorrhage appears more marked (white arrows). Moreover, more hemosiderin deposits become visible (black arrows) that were not detected by CT or spin echo MRI. This finding allows the diagnosis of amyloid angiopathy.

detected by neuroradiologists. Emergency physicians in another study had an error rate in stroke detection by CT twice that of neurologists and radiologists, and only 17% of emergency physicians, 40% of neurologists, and 52% of radiologists achieved a 100% sensitivity for the identification of intracranial hemorrhage.[12] These observations underline that hemorrhages can be subtle or in a stage undetectable for CT. Inter-observer reliability reflects the technical capacity of CT, but also the training and experience of the observer. The exclusion of brain hemorrhage requires special training and experience.

Acute hemorrhages usually show hyperattenuation without surrounding edema. If marked edema is present under these circumstances, underlying neoplasm or venous obstruction should be suspected. The location of the hematoma often provides clues about its underlying etiology. Multiple hemorrhagic lesions should make one think about metastatic disease, coagulopathy, or cerebral amyloid angiopathy (See Fig. 5.2).

CT is 90% sensitive for the detection of SAH within the first 24 hours of bleeding. When blood later intermixes with CSF, the density will be similar to the adjacent brain and difficult to visualize. If the hemorrhage is small, it may be missed entirely by the scan, necessitating lumbar puncture for definitive diagnosis in patients with a history and a syndrome highly suspicious for SAH. The sensitivity of CT in detecting subarachnoid blood declines to approximately 50% at 1 week after SAH.[13]

Calcification of the basal ganglia can occasionally be mistaken for deep intraparenchymal hemorrhage. It has a similar degree of attenuation as acute blood, but may be distinguished by its characteristic location and tendency to be bilateral.

The impact of the CT finding of intracranial hemorrhage and other diseases mimicking ischemic stroke on diagnosis and treatment is clear and important. Space-occupying lesions may require surgery; patients with hemorrhages will not be treated with thrombolytics.

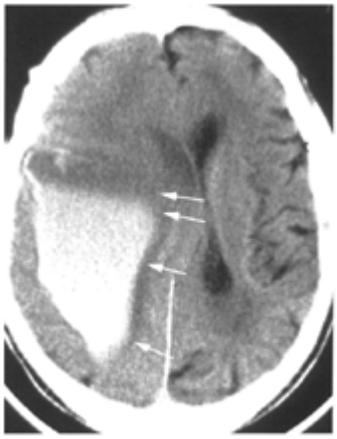

Figure 5.3 Brain hemorrhage after myocardial infarction and treatment with thrombolytics.

Note the increasing X-ray attenuation from anterior to posterior (arrows) and the fluid level indicating non-clotted blood.

CT DETECTION OF OBSTRUCTED ARTERIES AND THE ISCHEMIC TERRITORY

The assessment of arterial obstruction has certain advantages: it confirms the diagnosis of ischemic stroke, enables the differentiation between arteriosclerotic and embolic occlusion, allows an estimate of the territory that is ischemic, and may underline the urgency of reperfusion therapy. If arterial obstruction is excluded, e.g. because of spontaneous recanalization, reperfusion therapy is no longer necessary. Perfusion CT enables a direct assessment of the ischemic tissue volume using iodine or xenon as contrast agent.[14–20]

CT offers two possibilities to depict arterial obstruction: the unenhanced cross-sectional images and CTA. Thromboembolic occlusion of major brain arteries may represent as a hyperattenuating arterial segment in comparison to other arterial segments on unenhanced CT (Fig. 5.4a). The segment is either tubularshaped or dot-shaped, depending where the slice cuts the occluded artery. On slices parallel to the orbito-meatal plane, the thrombosed MCA trunk will appear tubular-shaped, and thrombosed insular MCA branches as dotshaped. The inter-observer agreement on such 'hyperdense artery signs' varied between poor and moderate (γ=0.20 and 0.63).[21–23] It should be noted, however, that all these kappa values were not adjusted for prevalence.

The determination of the specificity of a hyperattenuating arterial segment requires the comparison with digital subtraction angiography (DSA) as a gold standard for the assessment of arterial occlusion. We studied the 'hyperdense middle cerebral artery sign' (HMCAS) in 53 patients with DSA-proven unilateral MCA trunk occlusions.[24] The HMCAS was positive in 25 patients (sensitivity: 47%) and 100% specific (no false-positive findings). Tomsick et al.[21] described a sensitivity of 79% and a specificity of 93% in 25 patients. The HMCAS may be false positive in patients with calcification of the arterial wall or high hematocrit.

The diagnostic and therapeutic impact of arterial occlusion as depicted by CT should not be underestimated. We recently treated a 54-year-old man who was admitted to another hospital because of a slight paresis of his left hand for 2 hours. The CT (Fig. 5.4a-d) was judged as normal, and the patient was not treated or further evaluated. The radiologist missed the hyperattenuating segment of the distal right MCA trunk and the dot-shaped hyperdensity of one M2 segment. The patient deteriorated 8 hours later and developed a leftsided hemiplegia and impairment of consciousness. He was transferred to our stroke unit.

The CT obtained 2 hours after clinical deterioration showed hyperattenuation of the complete right MCA trunk and slight hypoattenuation of the right lentiform nucleus and precentral gyrus (Fig. 5.5). CTA revealed right ICA and MCA occlusion that was confirmed by DSA. We could pass a 5F catheter through the fresh thrombus within the right ICA and get a microcatheter into the MCA trunk. After infusion of 20 mg recombinant tissue plasminogen activator (rtPA) the right MCA was recanalized and orthograde blood flow into the MCA territory was restored. The patient became immediately responsive, but remained hemiplegic. The follow-up CT 4 days after stroke onset showed an infarct of the right basal ganglia and precentral gyrus with hemorrhagic transformation of the striatum (Fig. 5.6). One could speculate that the finding of the hyperdense MCA on the initial CT would have alarmed the physicians in charge and caused a further evaluation of the brain arteries and early treatment before clinical deterioration.

With regard to the low sensitivity of unenhanced CT for arterial obstruction, we recently proposed CTA for the diagnostic workup in acute stroke patients.[25] CTA can be obtained immediately after the unenhanced scan. It depicts reliably the occlusions of major brain arteries (see Fig. 5.1).[26] CTA has an important diagnostic impact in patients with basilar artery occlusion. The clinical picture often allows a broad differential diagnosis. Doppler ultrasound can hardly assess oral basilar artery occlusion. Therefore, CTA is, of special value for all patients with impaired consciousness and other brainstem symptoms.

The detection and measurement of cerebral blood flow (CBF) require a tracer that represents whole blood, that stays within the vascular system, that does not affect brain metabolism and function, and that can be directly measured during its passage through the region of interest. The repeated measurements of X-ray attenuation affected by a tracer provide a concentration curve over time if concentration and X-ray attenuation are directly correlated. The time to the concentration peak (TTP) can be used to create a parameter image that is relatively robust and can depict brain areas of impaired blood flow. The quantification of CBF, CBV, and mean transit time (MTT) require the measurement of the tracer's input function into the region under measurement, which is hardly feasible. Another disadvantage of perfusion CT is the radiation dose that is required by repeated measurements.

Xenon has been used as a CBF tracer for CT in single institutions for years, although it is not metabolically inert.[14] Using xenon CT, it was shown that a CBF below 21 ml per 100 g per min is 100% specific for cerebral infarction and a CBF above 15 ml per 100 g per min excludes the risk of midbrain herniation. It was shown that the brain tissue volume with a CBF <6 ml per 100 g per min was closely associated with the volume of infarction whether the patients were treated with intrarterial thrombolysis or not.[17–20] Kilpatrick et al. recently showed that the assessment of ICA or MCA obstruction with CTA has the same prospective value as perfusion CT.[16] Koenig et al. suggested the use of iodinated contrast agents to image CBF with CT and provided a computer program for CBF quantification.[15]

The target of reperfusion therapy in acute stroke is ischemic brain tissue that will not survive without reperfusion. Such tissue is functionally impaired, but morphologically intact. Moreover, its volume may vary with time. A firm definition of brain tissue at risk from hypoperfusion is, therefore, hardly possible and has to rely on functional tests like the measurement of CBF, CBV, and MTT and the assessment of irreversible tissue injury. One may question, however, whether a firm definition of such tissue is necessary. Nevertheless, many attempts were made with imaging to assess the tissue at risk from hypoperfusion.

CT DETECTION OF BRAIN TISSUE SWELLING

Enlargements of anatomical structures such as the cerebral cortex and the effacement of CSF spaces suggest brain tissue swelling. In acute stroke, CT may detect brain tissue swelling without hypoattenuation for a short period early after arterial or venous obstruction (Fig. 5.7a). Compensatory arterial dilatation due to low

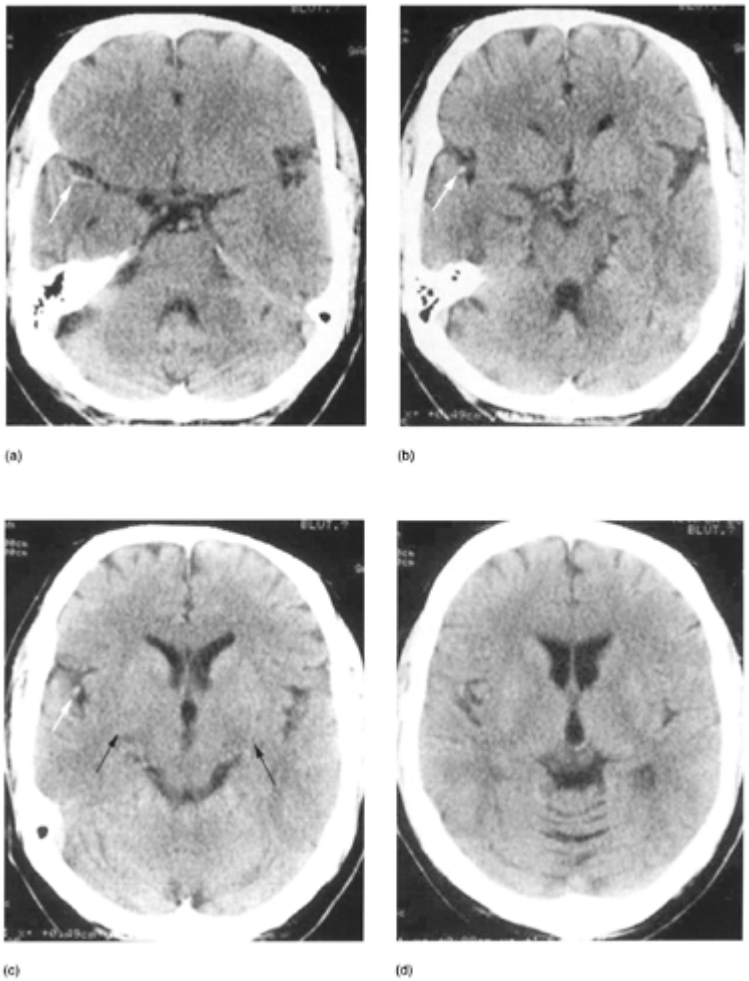

Figure 5.4 Unenhanced CT in a 54-year-old man with some weakness and numbness of his left hand for 2 hours.

(a-d) Four continuous sections of the CT show an occlusion of the trunk of the right middle cerebral artery and one of its branches (white arrows) indicated by hyperattenuating segments of the artery. Only very subtle hypoattenuation of the right lentiform nucleus can be appreciated (black arrow).

perfusion pressure[27] or passive arterial dilatation due to high venous pressure[28] causes this type of swelling. Tissue swelling without hypoattenuation indicates a severe perfusion deficit—or venous obstruction—but has a good prognosis if perfusion is enhanced by arterial or venous desobliteration. The recognition of brain tissue swelling should provoke a search for its cause in order to initiate the appropriate treatment. The chance- but not prevalenceadjusted agreement of six neuroradiologists on tissue swelling in 45 CT scans of acute stroke patients was γ=0.56–0.59[22] Because of the high variability of the CSF space, the detection of slight compression is unreliable. Swelling is more often observed in combination with hypoattenuating brain tissue.

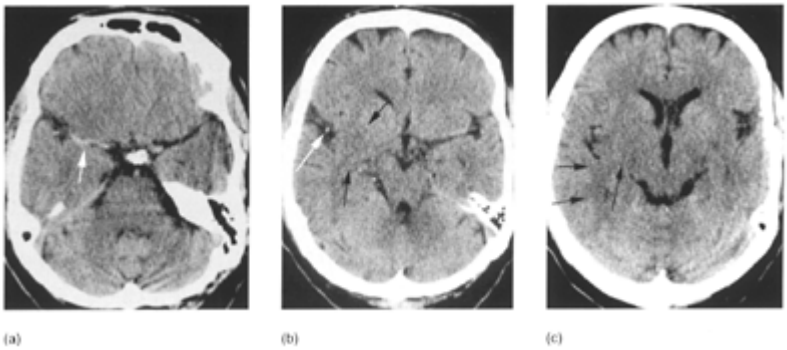

Figure 5.5 CT of the same patient as in Fig. 5.4 obtained 4 hours after severe clinical deterioration with hemiplegia and sopor.

(a) This section shows the complete occlusion of the middle cerebral artery trunk by a thrombus (arrow). Oblique section caused by fixed head rotation. (b) Occlusion of one middle cerebral artery branch (white arrow, 'dot sign') and hypoattenuation of lower right lentiform nucleus (black arrows). (c) Hypoattenuating brain tissue causes an 'obscuration of the lentiform nucleus' and 'loss of the insular ribbon' (black arrows).

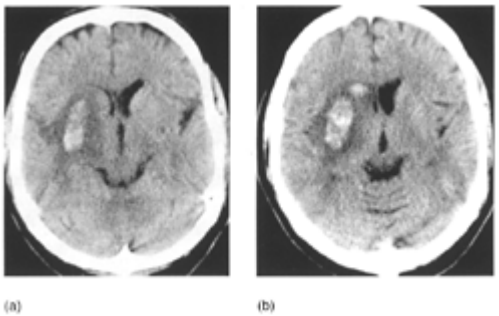

Figure 5.6 CT of the same patient as in Figs. 5.4 and 5.5 obtained 4 days after stroke onset and after local thrombolysis with 20 mg recombinant tissue plasminogen activator (rt-PA).

It shows marked hypoattenuating tissue of the right lentiform nucleus and caudate nucleus with hemorrhagic transformation and slight space-occupying effect.

CT DETECTION OF ISCHEMIC BRAIN EDEMA

CRITICAL LOW CBF CAUSES BRAIN TISSUE TO TAKE UP WATER: ISCHEMIC BRAIN EDEMA MEANS IRREVERSIBLE TISSUE INJURY

In patients with ischemic stroke, brain tissue swelling with hypoattenuation is best explained by ischemic edema. A CBF below 8–12 ml per 100 g per min cannot maintain the structural integrity of brain tissue for more than 30 min.[29,30] A sudden decrease in cerebral perfusion below this CBF threshold causes the gray matter to immediately take up water.[31–34] The amount of water accumulating during ischemia correlates with the duration of ischemia when mean CBF is reduced to 5.8 ±0.4 ml per 100 g per min.[35] Brain edema may resolve if ischemia lasts less than 15 min.[33] Consequently, detection of ischemic edema means detection of brain tissue with CBF below the threshold of structural integrity and with an immediate risk of

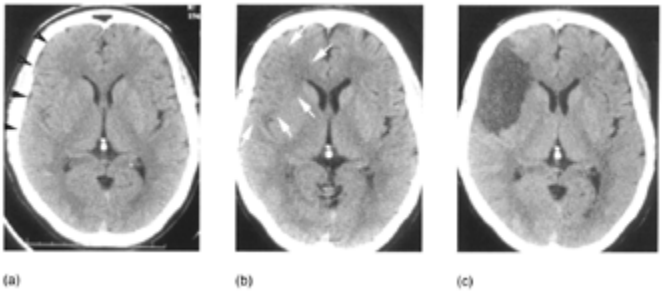

Figure 5.7 Development of ischemic infarct over time.

(a) CT obtained 3 hours and 40 min after stroke onset shows no hypoattenuating tissue, but effacement of CSF spaces in the right frontal and temporal middle cerebral artery territory (black arrowheads). (b) The CT obtained 22 hours after stroke onset shows an area of slightly hypoattenuating brain tissue (white arrows). (c) The infarct is well demarcated 3 days after stroke onset. The space-occupying effect is minimal, with slight compression of the right ventricle.

ischemic necrosis. Imaging of ischemic edema does then identify the ischemic brain tissue that is irreversibly damaged if the patient is symptomatic for more than 15 min.

DETECTION OF ISCHEMIC BRAIN EDEMA BY CT

CT can depict the volume of ischemic brain edema and measure the amount of water uptake. CT attenuation is linearly proportional to specific gravity and thus allows monitoring tissue water content.[11,36] An increase by 1% of tissue water content causes a decrease of X-ray attenuation by 2.6 HU in gels,[37] by 2.1 HU in experimental cryogenically induced brain edema,[11] and by 1.8 HU in ischemic brain edema of rats.[38] Co-registration of CT attenuation and CBF revealed that hypoattenuation develops only in areas of critically hypoperfused brain tissue.[18,39] A decline in cerebral blood volume (CBV) may add to the decrease in X-ray attenuation.

Using a CT window width of 80 HU, the minimal visible contrast is about at 4 HU, which corresponds with an increase in brain tissue water content of about 1.5%.[11,38] This suggests that the very first and potentially reversible stage of the developing ischemic edema cannot be seen on CT because the decline of attenuation has not caused enough contrast (see Fig. 5.7). In other words: a normal CT in a patient with stroke cannot exclude ischemic edema in a very early and potentially reversible stage. This insensitivity of CT for the very first stage of ischemic edema is related to the high specificity of CT for ischemic edema at its irreversible stage. Hypoattenuating brain parenchyma on CT after arterial occlusion thus indicates tissue that had suffered from severe ischemia under the critical level of structural integrity for at least 1 hour. Under clinical conditions, hypoattenuation may appear already 22 min after the onset of symptoms.[40] It is not yet been determined, however, whether hypoattenuation of ischemic brain tissue can disappear if the tissue is reperfused within less than 30–60 min and to what extent changes in CBV contribute to changes in CT attenuation.

INTER-OBSERVER AGREEMENT IN DETECTING EARLY ISCHEMIC BRAIN EDEMA: FLAWS OF THE KAPPA STATISTIC

The subtlety of early ischemic brain edema is a challenge that is not accepted by everybody.[41] Different groups tested the inter-observer reliability for the detection of 'early ischemic CT signs'. Almost all groups did not adjust their kappa for prevalence and many concluded that the assessment of early ischemic edema with CT is not reliable.[44] The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke trialists and others demonstrated that training in CT reading considerably affects the sensitivity to detect ischemic edema.[7,45] Attempts were made to improve the capability of CT in detecting ischemic edema by performing a density-difference analysis between both cerebral hemispheres, by varying window width and center level, and by using a quantitative score.[9,46,47]

DIAGNOSTIC ACCURACY OF CT IN DETECTING ISCHEMIC BRAIN EDEMA

The frequency of positive CT findings in acute stroke may also be diminished by the prejudice that CT is negative within the first 24–48 hours after stroke, which is still handed down in review articles[48] and books.[49] In contrast, many studies have described positive findings within the first 3–6 hours of stroke onset: Tomura et al. studied 25 patients with embolic cerebral infarction between 40 and 340 min after the onset of symptoms.[50] Twenty-three CT scans (92%) were positive with 'obscuration of the lentiform nucleus' (see Fig. 5.5c) caused by hypodensity.[50] Bozzao et al. observed parenchymal hypodensity in 25 of 36 patients (69%).[51] A 'loss of the insular ribbon' (see Fig. 5.5c) was reported in 23 of 27 (85%) patients.[52] Horowitz et al. reported on hypodensity and mass effect in 56% of 50 scans.[53] When comparing MR vs CT imaging in identical patients within 3 hours of symptom onset, CT was positive in 19 patients (53%) and MRI in 18 (50%) patients with hemispheric stroke.[54] We reported 17 positive CT scans (68%) performed in a series of 25 patients with MCA trunk occlusion during the first 2 hours. The incidence of positive CT findings increased to 89% in the third hour after symptom onset and to 100% thereafter.[24] In another series of patients with hemispheric stroke, the incidence of early CT signs of infarction was 82%.[55] In patients selected for thrombolytic therapy, 12 of 23 patients (52%) had a parenchymal hypodensity on the CT performed within 3 hours of stroke onset.[39] In a series of 100 consecutive patients with MCA infarction, CT detected hypodensity of the lentiform nucleus in 48% and of the insular cortex in 59% of the patients within 14 hours of stroke onset.[56] In a recent randomized trial on prourokinase in patients with MCA occlusions, the investigators detected signs of infarcts in 125 of 171 patients (73%) on CT within the first 6 hours.[57]

For the discussion of 'false-negative' CT in acute stroke, it is important to recognize that no reference standard exists to determine the accuracy of CT in assessing brain tissue swelling with and without edema. A normal CT without any hypoattenuating brain parenchyma in a patient with acute stroke may be a true negative and represent a disturbance of brain perfusion above the level that induces edema. Such a CT could be false negative if the hypoattenuation is too subtle or too small to be detected by CT. A negative CT in patients with acute ischemic stroke bears an important piece of information that is missed by many investigators: the lack of hypoattenuating tissue on early CT may mean that the brain tissue is not irreversibly injured. This was prospectively studied in 786 patients,[40] where CT predicted ischemic necrosis in 449 patients that was confirmed by follow-up CT in 433 patients (positive predictive value=96%, specificity=85%). The false-positive findings in 16 patients were explained in retrospect by image artifacts due to poor technique. A true normalization of prior hypoattenuating tissue was not observed.

DIAGNOSTIC IMPACT OF CT IN DETECTING ISCHEMIC BRAIN EDEMA

The diagnostic accuracy and clinical value of CT and MRI have rarely been properly compared. CT attenuation, T1-, and T2-relaxation times showed a linear relationship with the water content of a gelatin model. An increase in water content of 6%, however, resulted in a 19% increase in signal intensity of gel on the T2-weighted image, but in a 25% change in CT attenuation in the same specimens.[37] In an experiment with boiled eggs, Unger et al. demonstrated that T2 relaxation is not only affected by water content: egg hardening caused dramatic T2 shortening and modest T1 shortening, but had no effect on CT attenuation,[37] suggesting that the proportion of bound or structured water mainly affects T2 relaxation. It is still unclear, however, whether the effects of water structure play a role in the acute ischemic brain. Typical flaws of studies comparing CT with MRI were no or a poorly defined reference standard[58–61] and MRI performed considerably later than CT.[59,61] To our knowledge, only one group compared CT and MRI in a randomized order.[62] Not surprisingly, some studies found that MRI including diffusionweighted imaging (DWI) is more sensitive than CT,[58–61] whereas other studies did not show that MRI is superior to CT in detecting ischemic changes of cerebral parenchyma.[54,63]

Another approach to the diagnostic impact of CT is the interpretation of the extent of ischemic edema detected by CT. We showed that the extent of hypoattenuating brain tissue due to ischemic edema is associated with the neurologic score and with clinical outcome.[6,24,40,64,65] Fiorelli et al. concluded from their experience with emergency CT in acute ischemic stroke that it adds significantly to the prediction of clinical outcome made on clinical grounds.[66]

THERAPEUTIC IMPACT OF CT IN DETECTING ISCHEMIC BRAIN EDEMA

In acute cerebral ischemia, the only treatment that is proved to improve clinical outcome is intravenous thrombolysis with rt-PA applied within 3 hours of symptom onset or intra-arterial infusion of prourokinase in patients with MCA occlusion if applied within 6 hours of symptom onset.[57,67] Whereas the NINDS rt-PA Study Group used CT just to exclude patients with intracranial hemorrhage, the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) investigators excluded patients from the study who had a hypoattenuating area on CT exceeding one-third of the MCA territory. The first ECASS supported the hypothesis that patients with such large ischemic edema do not benefit from rt-PA treatment and have an increased risk for brain hematoma.[6,68] This hypothesis was confirmed by ECASS II.[69,70] Moreover, the ECASS II data showed, that acute stroke patients with normal CT have a less severe neurologic deficit and a more beneficial clinical course compared to patients with hypoattenuating brain tissue. This is illustrated in Fig. 5.8, showing the NIHSS over time in the ECASS I and II populations (1350 patients) in association with the findings on their baseline CT.

The hypothesis that the extent of hypoattenuating ischemic brain tissue is associated with poor prognosis and lack of benefit from tPA is supported by clinical evidence: patients with MCA trunk occlusions and hypoattenuation of more than one-half of the MCA territory had a mortality of 85%.[24] We, therefore, suggested using CT to identify patients with malignant ischemic brain edema early.[71,72] The quantitative grading of early CT findings in tPA-treated patients showed that the Alberta Stroke Programme Early CT Score (ASPECTS) predicted functional outcome and symptomatic intracerebral hemorrhage with high specificity and sensitivity.[47] In a recent analysis with re-evaluation of CT scans by a single observer, the risk for symptomatic hemorrhage was odds ratio (OR, 95% CI) =2.9 (0.3–32.4) in patients with hypodensity in >33% of the MCA territory and OR=1.5 (0.3–7.2) in patients with hypodensity in γ33% of the MCA compared to patients with normal early CT.[73] These data demonstrate a low statistical power because only

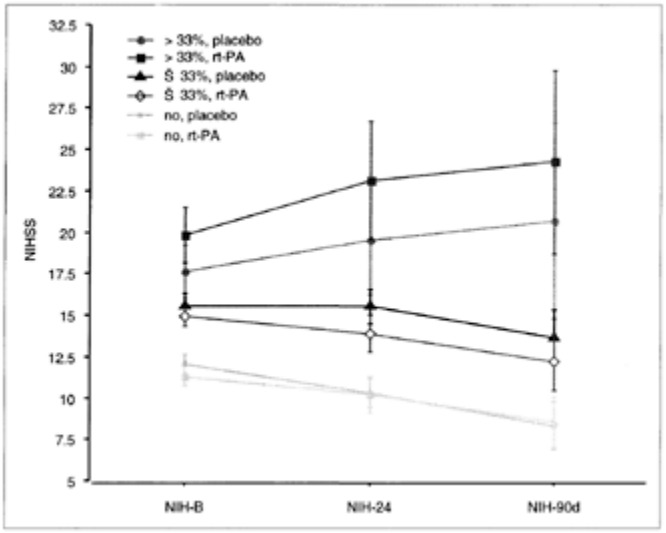

Figure 5.8 Extent of tissue hypoattenuation on baseline CT in ECASS 1 and 2 (1350 patients) and the response to rt-PA (recombinant tissue plasminogen activator) as measured by the NIHSS.

NIHSS, National Institute of Health Stroke Scale; NIH-B, NIHSS at baseline; NIH-4, NIHSS at 24 hours after stroke onset; NIH-90d, NIHSS at 3 months after stroke onset

few patients with hypodensity were identified. The CT reader in this study had a sensitivity of only 31% for early ischemic changes in contrast to a sensitivity of 75% in a comparable study.[47]

IMPACT ON PATIENT OUTCOME

Impact on patient outcome is the most important criterion for the usefulness of a diagnostic test, showing that it leads to a change in patient management that improves patient outcome.[3] ECASS I and II are the only studies with prospectively defined categories for the extent of ischemic edema on baseline CT. We will use here the combined dataset of both trials to study whether the response to rt-PA treatment was different in patients with normal CT compared to patients with small edema (ϒ33% of MCA territory) (see Fig. 5.4) and compared to patients with more extended edema (>33% of MCA territory) (Fig. 5.9). This dataset includes 1350 patients. According to the common assessment of three neuroradiologists, 688 patients had a normal CT at baseline, 618 patients had a small ischemic edema, and only 89 patients had an extended ischemic edema (such large edema was an exclusion criterion in ECASS I and II). Figure 5.8 shows that only patients with small ischemic edema had a benefit from rt-PA treatment. The OR for a beneficial outcome without functional disturbance (Rankin 0 and 1) at 3 months was 1.20 (95% CI, 0.89–1.63) for patients with normal CT, 1.47 (95% CI, 1.03–2.09) for patients with small ischemic edema, and 0.71 (95% CI, 0.21–2.41) for patients with large edema. This suggests that rt-PA treatment may enhance the chance for stroke patients by almost 50% to be undisabled after 3 months. In contrast, rt-PA treatment cannot significantly ameliorate the beneficial clinical course in patients with normal CT, and may deteriorate clinical outcome in patients with large ischemic edema. The last group was, however, too small to really prove the impact of this CT finding on patient outcome.

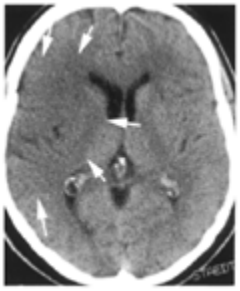

Figure 5.9 CT obtained within 6 hours of stroke onset shows hypoattenuating brain tissue of the entire middle cerebral artery territory (arrows).

In summary, CT has the capacity to identify different pathophysiological states that all results in the same clinical picture of an acute stroke syndrome: intracranial hemorrhage, ischemic edema, and ischemia without ischemic edema. In addition, arterial occlusion is detected in some patients. Because these CT findings represent different pathology, it is incorrect to address them all as 'early infarct signs.' Moreover, it makes no sense, to study and count certain 'CT signs,' like 'obscuration of the lentiform nucleus,' 'loss of the insular ribbon,' 'loss of gray-white matter distinction,' 'hypodensity,' because all these phenomena are caused by hypoattenuating gray matter due to ischemic edema.

THE ROLE OF CT IN PATIENTS TREATED WITH THROMBOLYTICS

Brain imaging with CT may be useful after the acute phase of stroke. It can detect the vascular territories with ischemic infarct, its extent, its space-occupying effect, any hemorrhagic transformation of ischemic tissue, and hemorrhage remote to ischemic tissue. The CT findings may explain changes in the clinical course of the patient and can early indicate the development of 'malignant ischemic brain edema' that requires decompressive surgery (Fig. 5.9).[24,71]

Hemorrhagic transformation (HT) of ischemic brain tissue occurs in treated and non-treated stroke patients with excess after thrombolytic therapy. It has different radiologic appearances, and may be detected on routine CT or when the patient deteriorates clinically. Hemorrhagic transformation is thus the main safety concern of thrombolytic therapy. The exact assessment of this risk requires a clear definition of HT in general and especially the definition of hemorrhages that may cause clinical deterioration. This concept should include a description of the assessment of HT, a hypothesis of the cause of HT, and considerations regarding the effects of blood on cerebral function under the conditions of ischemic edema.

Observations on the radiologic appearances of HT support the view that only dense hemorrhages (hematomas) that cause mass effect are clinically relevant. In patients with extended ischemic infarcts that cause compression of surrounding brain tissue, and sometimes shift of midline structures, the effect of blood within the ischemic tissue is hard to assess. Because HT has a higher incidence in large ischemic lesions, the combination is often observed. It was shown that HT is associated with tissue reperfusion.[74] Tissue reperfusion is, however, the precondition to keep cerebral infarcts small. If HT is a marker for arterial recanalization and reperfusion of ischemic brain tissue, it may be associated with clinical improvement. The association of HT with reperfusion may explain the observation that treatment with thrombolytics is beneficial despite the excess of HT.[74] The term 'symptomatic hemorrhage' is, therefore, at least questionable and misleading, if not very carefully defined.

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6.
Ultrasound in acute stroke: recent advances and future perspectives

Michael Hennerici and Stephen Meairs

INTRODUCTION

Noninvasive ultrasound techniques continue to play an integral role in the routine diagnostic work-up of stroke patients. Their use includes, among others, detection of extra- and intracranial sources of cerebral ischemia, elucidation of intracranial collateralization, transcranial Doppler (TCD) monitoring of microemboli, and assessment of hemodynamic reserve capacity.[1,2] New developments have significantly expanded the horizon of cerebrovascular ultrasound. In particular, diverse new applications using ultrasonographic contrast agents have provided new avenues for increasing diagnostic confidence and for visualizing perfusion deficits.

This chapter will briefly review the routine use of ultrasound for evaluation of acute stroke and then focus on recent advancements in terms of their current and potential diagnostic utility for identification of stroke etiology, for improving visualization of arterial disease, and for monitoring acute stroke patients. It will discuss new approaches to early ultrasonographic detection of brain infarction and current and future developments in the field of quantitative brain perfusion imaging. Lastly, as recent developments have expanded the field of neurosonology beyond the diagnostic realm, this chapter includes discussions on the possibility of using ultrasonographic thrombolysis for treatment of acute ischemic stroke and on exciting new concepts involving ultrasound-mediated gene therapy.

IDENTIFYING EXTRACRANIAL SOURCES OF STROKE

CAROTID ARTERY STENOSIS AND OCCLUSION

Doppler sonography is a rapid and reliable noninvasive technique for detecting extracranial arterial obstruction as a possible cause of acute ischemic stroke. According to the distribution of abnormal blood flow patterns within, proximal to, or distal to a narrowed arterial segment, this method provides information on the extent, site, and degree of lesions of more than 40% lumen narrowing. The sensitivity (92–100%) and specificity (93–100%) of various Doppler techniques have been shown to be similar to those of angiography.[3,4]

Low-frequency pulsed-wave (PW) Doppler devices can be used to assess distal extracranial lesions of the internal carotid artery, e.g. carotid dissections, fibromuscular dysplasia, or atypically located atherosclerosis. Adequate positioning of the probe in the submandibular region allows recording of flow velocity in the internal carotid artery (ICA) up to the base of the skull with a recording depth of 50–80 mm.

The degree of carotid obstruction can be estimated using the following guidelines:

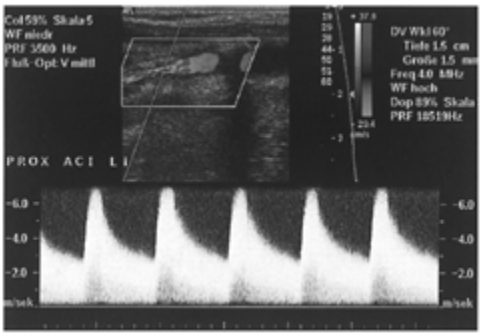

Figure 6.1 High-resolution B-mode image of a heterogeneous, symptomatic carotid artery stenosis.

The display is facilitated with color Doppler flow imaging, showing a high-grade stenosis with turbulent flow and maximal systolic velocity over 600 cm/s.

- *Mild stenosis* (40–60%) is characterized by a local increase of peak and mean flow velocities. Systolic peak velocities range above 120 cm/s (4-MHz probe).
- *Moderate stenosis* (60–80%) shows a distortion of normal pulsatile flow in addition to a local increase of peak and mean frequencies. Typically, systolic flow decelerations are found in the poststenotic segment. The systolic peak velocity ranges from 120 to 240 cm/s.
- *Severe stenosis* (more than 80%) produces markedly increased peak flow velocities exceeding 240 cm/s and occasionally reaching over 600 cm/s (Fig. 6.1). In addition, pre- and poststenotic blood flow velocity is significantly reduced compared with the contralateral unaffected carotid artery. Retrograde flow of the ophthalmic artery may occur.
- *Subtotal stenosis* (more than 95%) is characterized by variable, usually low frequencies, which decrease once a stenosis becomes pseudo-occlusive. This condition is difficult to separate from complete occlusion and may be misdiagnosed.
- *Occlusion* is characterized by the absence of signal along the cervical course of the ICA. In some cases, a low-velocity Doppler signal with predominantly reversed signal component and absent diastolic flow can be recorded at the origin of the ICA (‘stump flow’). Blood flow velocity in the common carotid artery is reduced, and frequently retrograde perfusion of the ophthalmic artery occurs.
- *Severe intracranial obstructions* within the carotid siphon or the middle cerebral artery (MCA) may lead to dampened spectra in the ipsilateral extracranial carotid artery. In addition, alterations of flow direction and signal frequency may occur in the ophthalmic artery, depending on the site and degree of the lesion.

The combination of B-mode imaging and PW Doppler sonography in duplex instruments has considerably improved the accuracy of the non-invasive diagnosis and grading of carotid stenosis. The degree of stenosis can be estimated from distinct parameters of the Doppler frequency spectrum. Instead of Doppler shift frequencies, equivalent flow velocity values can be used after correction of the Doppler insonation angle according to the flow direction in the vessel segment. In color Doppler flow imaging (CDFI) three sources of information are available for the classification of carotid stenosis: the Doppler frequency spectrum, measurement of the residual vessel lumen, and characteristic color flow patterns.[5] Using sequential longitudinal and transverse sections, both CDFI and power Doppler imaging[6] (PDI) allow reliable assessment of plaque configuration and relative obstruction by contrasting the intravascular surface.[7–12]

CAROTID ARTERY DISSECTION

Ultrasound is useful for diagnosis of carotid artery dissection, a cause of transient or permanent neurologic deficits, particularly in young patients. Internal carotid artery dissection usually occurs spontaneously and results in a typical syndrome of focal cerebral deficits, headache, neck pain, and ipsilateral Horner's syndrome.

Various patterns can be observed in carotid dissection. Color Doppler flow imaging can show marked flow reversal at the origin of the ICA in systole and absent or minimal blood flow in diastole corresponding to a high-resistance bidirectional Doppler signal.[13] B-mode scans can demonstrate a tapered lumen and occasionally a floating intimal flap.[14] Narrowing of the true lumen by the false lumen thrombus can be associated with a low-velocity Doppler waveform. The direction of flow in a patent false lumen can vary from being forward, reversed, or bidirectional. The flow dynamics in carotid dissections are complex and are primarily dependent upon the presence of thrombus within the false lumen, the entry and exit flaps if the false lumen is patent, the motion of the flap wall, and the extent of the dissection.[15] In some patients the only finding may be a retromandibular high-velocity signal associated with a distal stenosis of the cervical carotid artery.[16]

Follow-up examinations of carotid dissections demonstrate gradual normalization of the Doppler spectrum, indicating recanalization of the ICA within a few weeks to months in more than two-thirds of patients.[17] Carotid aneurysms can occur as complications of ICA dissections. Their follow-up with angiography and magnetic resonance angiography/magnetic resonance imaging (MRA/MRI) can be complemented with ultrasonography due to the development of broadband transducers with improved axial resolution and depth penetration.[18]

VERTEBRAL ARTERY STENOSIS AND OCCLUSION

Examination of the vertebral artery with ultrasound is limited to its origin from the subclavian artery, the proximal pretransverse segment, short intertransverse segments between the third and sixth cervical vertebrae, and to the atlas loop (Fig. 6.2). Although PW Doppler criteria for vertebral artery stenosis are similar to those used for diagnosis of carotid artery stenosis and have been defined by several duplex studies, classification and detection of vertebral artery stenosis or occlusion is more difficult than in the carotid arteries.[19–21] One reason for this difficulty is that variations in arterial caliber are frequent in vertebral arteries. Numerous collateral pathways of the vertebral system can permit orthograde flow to the basilar artery even in the face of vertebral occlusion. These features make examination of the vertebral artery at several locations mandatory. Color Doppler flow imaging allows noninvasive quantification of flow in the vertebral artery system in greater than 95% of all patients[22]and facilitates identification of the proximal segment and ostium, the predominant location of extracranial vertebral stenosis, as well as of the atlas loop.[23,24] Using this technique normal flow velocities of the vertebral artery origin (V0 segment), the pre- (V1 segment), and the intertransverse (V2 segment) have been defined.[25]

Correct interpretation of Doppler results from the vertebral artery requires knowledge of Doppler parameters from both the contralateral vertebral artery and from the carotid system. For example, an increase in the systolic or diastolic velocity profile of the proximal vertebral artery, although suggestive of stenosis, can also occur as a compensatory response to a variety of conditions of the contralateral vertebral artery such as hypoplasia, aplasia, stenosis, or occlusion, as well as to severe obstruction of the carotid system.

The predominant site of extracranial vertebral artery stenosis is the ostium of the subclavian artery. The atlas loop and intracranial V4 segment are involved less frequently, and stenoses in the intertransverse

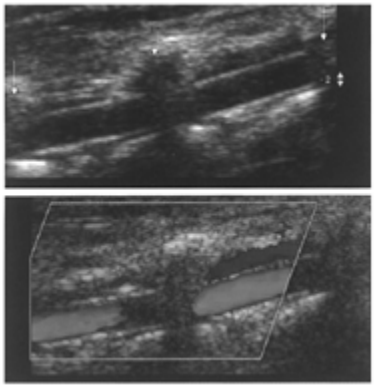

Figure 6.2 The upper image shows a high-resolution B-mode compound image of a vertebral artery as typically depicted between the cervical vertebrae (white arrows).

The lower image is complemented by color Doppler flow imaging.

segments are rare. A peak systolic frequency exceeding 4 kHz assessed by means of the integrated PW Doppler system indicates a relevant vertebral stenosis. Features of color-coded Doppler signals correspond to those of carotid stenosis. With increasing degree of luminal narrowing, decreased color saturation becomes more circumscribed and turbulence as well as poststenotic flow reversal are more severe. Hemodynamically significant obstruction of the intracranial vertebral artery produces a high-resistance Doppler waveform with a resistivity index exceeding 0.80.[24] However, the Doppler spectrum may be normal if flow to the ipsilateral posterior inferior cerebellar artery is preserved. In acute proximal vertebral artery occlusion, PW Doppler spectra cannot be recorded and color Doppler signals are absent in the pre- and intertransverse segments. However, demonstration of the vascular lumen differentiates this condition from vertebral hypoplasia, defined in pathoanatomical studies as a decrease in vascular lumen diameter below 2 mm.[26]

VERTEBRAL ARTERY DISSECTION

Vertebral artery dissection is one of the most important causes of brainstem strokes in young patients.[27,28] It presents with neck pain, occipital headache, and signs and symptoms of brainstem or cerebellar ischemia in about 90% of patients and commonly leaves a permanent deficit.[29–31] The role of ultrasound in diagnosis of vertebral artery dissection remains uncertain. In contradistinction to carotid artery dissection, there is no pathognomonic ultrasound finding for vertebral artery dissection if the lesion affects the V_2-V_4 segments. Examination of the atlas loop can show absent, low bidirectional or low poststenotic flow signals.[32] In dissections of the V_1 segment, the stenotic segment can be identified directly, while absent flow in the intertransverse segments should similarly raise the question of vertebral dissection (Fig. 6.3). Further findings can include a localized increase in the diameter of the artery with hemodynamic signs of stenosis or occlusion at the same level, decreased pulsatility, and the presence of intravascular echoes in the enlarged segment.[33,34] Occasionally, the specific finding of an intramural hematoma is found.[35]

Transcranial Doppler can be helpful in determining the length of dissection.[36]The combined use of extracranial and transcranial Doppler and duplex sonography increases the diagnostic yield to detect vertebral artery dissection. Consideration of any abnormal sonographic finding resulted in a yield of 86%, whereas reliance upon definite abnormal findings (absent flow signal, severely reduced flow velocities,

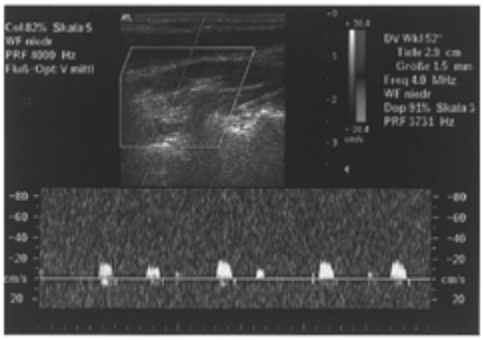

Figure 6.3 Vertebral artery dissection.

Note the low-flow, high-resistance signal.

absent diastolic flow, bidirectional flow, or stenosis signal) reduced the diagnostic yield to only 64%.[32] Similar results were obtained in another study in which ultrasound abnormalities (highresistance signal, occlusion, and bilateral retrograde flow) were found in 8 of 10 vertebral artery dissections.[37] Detection of abnormal flow patterns in the vertebral artery in cases of suspected dissection may guide further diagnostic imaging procedures and therapeutic measures. However, since unremarkable ultrasound findings do not exclude the diagnosis of vertebral dissection, further work-up in these cases is mandatory.

ROUTINE TRANSCRANIAL DOPPLER IN EVALUATION OF STROKE

Transcranial Doppler uses high-energy bidirectional pulsed Doppler, typically at a low frequency of 2 MHz, for intracranial vascular examination via transtemporal, transorbital, and transnuchal bone windows. Applications for TCD in stroke imaging include detection of intracranial stenosis and occlusion, evaluation of intracranial collateral circulations, detection of vasospasm in subarachnoid hemorrhage, and assessment of cerebral autoregulation. Transcranial Doppler monitoring techniques are available for detection of high-intensity transient signals suggestive of microembolism and for surveillance of intracranial hemodynamics during stroke therapy. The introduction of transcranial color Doppler flow imaging (TCDFI) has led to greater accuracy in vessel identification and reports on the merits of CDFI for detection of cerebral aneurysms, evaluation of arteriovenous malformations, and characterization of vessel morphology are now available.

Intracranial basal arteries are identified with TCD by flow direction, depth of the Doppler sample volume, and probe position. Since flow velocities of intracranial vessels are known to vary with age and sex,[38] hematocrit,[39] and endtidal CO_2 partial pressure, a standardized TCD examination procedure is mandatory.[40] Optimal performance and correct interpretation of TCD studies require knowledge of the clinical setting and of results from extracranial ultrasound examinations.

Transcranial color Doppler flow imaging facilitates identification of basal cerebral arteries.[41] Whereas conventional transcranial Doppler sonography assumes a 0° Doppler angle for the calculation of flow velocities, TCDFI allows correction for the Doppler insonation angle. The magnitude of the angle of insonation and the effect on flow velocity estimates in intracranial vessels have been determined through visually controlled measurements of the Doppler angle of insonation made by color flow imaging: anglecorrected peak systolic flow velocities were 3–30% higher compared with uncorrected velocity

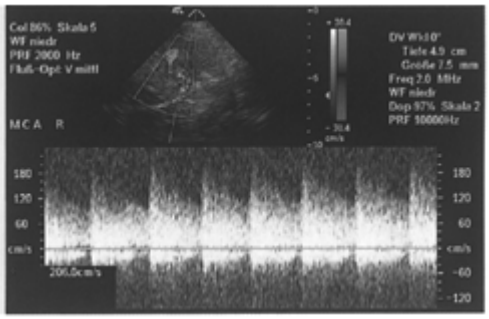

Figure 6.4 Middle-grade stenosis of the middle cerebral artery following amphetamine-induced vasculitis in a 19-year-old female patient.

Note the highly turbulent flow as evidenced by the mosaic pattern in color Doppler flow imaging and low-frequency components in the Doppler spectrum, which are due to severe irregularities in the surface structure of the arterial wall.

readings by conventional Doppler sonography.[42] Although TCDFI is generally considered to be the ultrasonic method of choice in evaluation of the intracranial circulation, there are no data on the failure rate of TCDFI in a large group of patients.

INTRACRANIAL STENOSIS AND OCCLUSION

Significant narrowing of intracranial arteries results in localized increases in mean and peak flow velocities, turbulence and reversed-flow phenomena, and reduction of pre- or poststenotic flow velocities.[43–45] Stenosis of greater than 50% lumen narrowing can be reliably detected in arterial segments with anatomically favorable insonation angles such as the M1 segment of the middle cerebral artery (MCA) (Fig. 6.4) and the P1 segment of the posterior cerebral artery (PCA).

A reliable diagnosis of occlusion in the M1 segment can only be made when unequivocal evidence of blood flow in the ipsilateral anterior cerebral artery (ACA) or PCA can be obtained, thus differentiating this condition from high ultrasound attenuation and poor echo window insonation. Further findings supporting MCA occlusion are dampened spectra in segments proximal to the occlusion, reversed-flow direction in distal MCA branches, and abnormally elevated ipsilateral ACA flow velocities.[46] In a series of 467 patients, the sensitivity for the detection of MCA occlusion by TCD was 79% with a specificity of 100%.[47]

Transcranial Doppler examinations of the vertebrobasilar arteries are less reliable than those of the anterior circulation. The junction of the basilar artery is difficult to define by TCD criteria alone, and investigation of the entire course of the basilar artery, usually limited by excessive insonation depth with poor signal-to-noise ratio,[48] can be achieved in only 30% of patients. As in the anterior circulation, partial obstructions are easier to detect than total occlusion. Using intra-arterial digital subtraction angiography as a standard reference, TCD has demonstrated sensitivities of 74–87% and specificities of 80–86% for detection of large-vessel occlusive disease of the intracranial vertebrobasilar system.[49,50] Best results, however, are obtained when TCD is used in combination with cerebral angiography[48]or MRA.[51]Unfortunately, detection of basilar artery occlusion is poor,[52]with a sensitivity of only 36%. This is of major clinical importance in evaluation of patients suspected of suffering from acute basilar artery thrombosis.

ASSESSMENT OF INTRACRANIAL COLLATERALIZATION

The presence of intracranial collateralization in patients with stenosis or occlusion of the extracranial carotid arteries can be investigated with conventional TCD. Findings compatible with collateral flow over the anterior communicating artery include retrograde flow in the ipsilateral ACA; increased peak and mean velocities in both ACA; increased velocities and low-frequency signals in the midline, indicating functional stenosis of the anterior communicating artery, and decreased MCA velocity during contralateral common cartoid artery (CCA) compression. Collateralization from the posterior circulation is suggested by increased velocities in the ipsilateral P1 segment of the PCA or in the basilar artery as well as by low-frequency signals in the posterior communicating artery. Leptomeningeal anastomosis, although more difficult to assess, may be associated with increased velocities in proximal and distal segments of the PCA and with retrograde flow signals in distal MCA branches. Transcranial Doppler can also detect retrograde flow in the ophthalmic artery, another avenue for collateralization.

Flow velocities in the MCA distal to significant stenosis and occlusion vary with regard to the efficacy of intracranial collateralization. Whereas reduced MCA velocities and pulsatility indexes have been found ipsilateral to symptomatic carotid occlusion,[53,54]normal peak and mean velocities indicating adequate collateralization have been reported for asymptomatic patients.[55]

ULTRASOUND CONTRAST AGENTS IN ISCHEMIC STROKE

The ability of intravenous contrast media to increase the echogenicity of flowing blood has been known for some time.[56] Only recently, however, has there been an increasing demand for using echo-enhancing agents in routine assessment of acute stroke. This is because contrast agents can be particularly helpful in transcranial ultrasound studies of patients with inadequate transtemporal bone windows. Moreover, they can be advantageous for quantification of internal carotid stenosis in the presence of calcification, and for differentiation between internal carotid occlusion and pseudoocclusion. Their use has expanded to include assessment of intracranial aneurysms and arteriovenous malformations, as well as investigation of the basilar and intracranial vertebral arteries.

Commercially available contrast agents consist of microbubbles with average diameters from 3 μm to 6 μm in concentrations typically on the order of 10^8 microbubbles/ml. The microbubbles are normally stabilized against dissolution by surfactants, phospholipids, or a surface layer of partially denatured albumin. Since current contrast agents can enhance the ultrasound signal by 10–30 dB,[57]they offer a unique opportunity to obtain anatomical and physiological information beyond that provided by current ultrasound imaging and Doppler systems.

The first generation of ultrasound contrast agents consisted of air-filled microbubbles. Examples of such agents are Albunex® (Molecular Biosystems Inc., San Diego, CA), which is produced by controlled sonication of a 5% human serum albumin solution, and Levovist® (Schering AG, Berlin, Germany), which is a galactose-based agent stabilized by 0.01% palmitic acid. Because of the low concentration of air gases in the systemic circulation, the air contained inside these agents quickly diffuses out of the microbubbles after injection into the body.[58] The type of gas inside the bubble determines the dwell time in the circulation,[59]and can also affect the backscattered signal in both linear and nonlinear regimes.[60] Second-generation ultrasonic agents consist of microbubbles containing less soluble gases, such as perfluorocarbons or sulphur hexafluoride.

Clinical studies with Levovist have shown it to be safe and effective in improving diagnostic confidence for patients with carotid artery stenosis. Contrast enhancement helps to reduce operator variability, improves ultrasound images, and can aid in distinguishing between pseudo and true occlusions, thus helping

to identify patients who will benefit most from surgery.[61] First reports on the use of ultrasonic contrast media to investigate carotid arteries demonstrated a significant improvement in characterization and quantification of severe internal carotid stenosis.[62] In further studies, Levovist considerably improved image quality in patients with highgrade carotid stenosis and allowed better visualization of the entire length of the intrastenotic residual flow lumen, suggesting that echo contrast media might play an important role in the diagnosis of internal carotid occlusion versus stenosis.[63] More recent data suggest that power Doppler imaging (PDI) without contrast agents may approach the diagnostic yield achieved with the combined approach for assessment of carotid artery pseudo-occlusion.[64] Since large clinical trials (NASCET and ECST) concluded that subtotal stenosis and pseudo-occlusion represent only a small risk for stroke similar to total occlusion, there is little relevance of sophisticated methodology for differentiating these conditions. Thus, contrast agents will at best only play a minor role in ultrasonographic evaluation of high-grade carotid stenosis.

In transcranial Doppler sonography, insonation through the transtemporal bone window is often impaired by an insufficient signal-to-noise ratio, especially in elderly patients. Echo-contrast agents have been shown to provide conclusive transcranial examinations in most patients with insufficient ultrasound penetration. Most studies have been performed with the galactose-based microbubble agent Levovist. Depending on the concentration of Levovist, the average maximal transcranial signal enhancement is approximately 12.0±5.4 dB for 300 mg/ml.[65] Albunex has likewise been shown to improve the quality of transcranial Doppler examinations through better visualization of the ICA, the MCA, and the circle of Willis,[66] although the relatively short duration of the contrast enhancement is a limiting factor.

Contrast agents have also been shown to enhance diagnoses when using TCDFI in patients with poor tissue penetration where imaging of vessels would otherwise be inadequate.[67] Other studies have confirmed these initial findings in patients whose basal arteries could not be assessed adequately with TCDFI. After administration of Levovist, over 85% of examinations of the MCA, the ACA, the P1 and P2 segments of the PCA, and the supraclinoid portion of the ICA siphon were satisfactory.[68] Moreover, use of intravenous contrast material often enables the entire circle of Willis to be evaluated from a single temporal bone acoustic window when using both PDI and CDFI.[69] Recently, contrast agents have been used to enable intracranial insonation through lateral and paramedian frontal bone windows, thus offering a new approach to study the circle of Willis, the venous midline sinuses, and the frontal parenchyma.[70] The technical success rate of three-dimensional transcranial PDI investigations has also been improved with contrast agents.[71]

There is good evidence that echo-contrast agents are valuable in transcranial Doppler examinations of patients with acute cerebrovascular disease. In an investigation of patients presenting with ischemic strokes and transient ischemic attacks who had insufficient temporal bone windows, 66% of contrast-enhanced transcranial CDFI studies were conclusive.[72] These findings have been confirmed by a similar study of acute stroke patients in which native transcranial investigations were inadequate.[73]

The quality of transtemporal precontrast scans is strongly predictive of the potential diagnostic benefit that is to be expected from application of an intravenous contrast agent. In patients whose intracranial structures are not visible in Bmode imaging and whose vessel segments are not depicted with CDFI, there is little chance that the use of a contrast agent will provide diagnostic confidence.[74] This has also been shown in patients with acute cerebral ischemia. Precontrast identification of any cerebral artery provided an overall accuracy of 97% in predicting a conclusive investigation with contrast agent, whereas in those without precontrast vessel identification, there were no conclusive studies.[72]

Examinations of the intracranial vertebral arteries and the basilar artery are also facilitated with echo-contrast agents. Insonation through the foramen magnum when using color-coded duplex sonography and

an echo-contrast agent can increase the depth at which vessels can be identified and improve the number of pathologic findings not seen in native scans by about 20%.[75] Moreover, echo-contrast enhancement of the vertebral and basilar arteries may significantly increase diagnostic confidence. As in the examination of the carotid arteries, however, the relative merits of using contrast-enhanced CDFI (CE-CDFI) and PDI for assessing the intracranial vertebrobasilar system remain unclear. One study comparing these two modalities concluded that contrast-enhanced transcranial color Doppler flow imaging and power Doppler sonography are equally effective in visualizing the vertebrobasilar system.[76] Conclusive studies on the role of contrast agents in investigation of the basilar artery are lacking.

ULTRASONOGRAPHIC MONITORING OF ACUTE STROKE

MONITORING OF THROMBOLYSIS

Recanalization time as determined *in vitro* is an important measure of thrombolysis when a clot is exposed to tissue plasminogen activator (t-PA). This is usually given as the time of complete clot dissolution with washout to the distal vasculature. In human stroke, complete recanalization correlates with clinical recovery as predicted from animal models. This process often begins many minutes before restoration of cerebral blood flow (CBF). Once recanalization starts, the clot softens and partially dissolves. This results in an improvement of residual flow that allows more t-PA to bind with fibrinogen sites. This process facilitates clot lysis and continually improves residual flow until the clot dissolves under the pressure of arterial blood pulsations.

Recanalization time may be an important clinical parameter of thrombolysis (Fig. 6.5). Whereas prolonged clot dissolution delays complete recanalization and may be associated with a longer duration of cerebral ischemia, a sudden early blood flow increase may cause immediate recovery. Late blood flow changes can disrupt the blood-brain barrier and lead to edema or hemorrhage. Alexandrov and co-workers have recently addressed these issues using real-time ultrasound monitoring of residual flow signals during thrombolysis with t-PA in patients with occlusion of the MCA or basilar artery.[77] In their study, recanalization was classified as sudden (abrupt appearance of a normal or stenotic lowresistance signal), stepwise (flow improvement over 1–29 min), or slow (30 min or longer). The results showed that recanalization began at a median of 17 min and was completed at 35 min after t-PA bolus, with a mean duration of recanalization of 23±16 min. Complete recanalization occurred considerably faster (median 10 min) than partial recanalization (median 30 min). Importantly, rapid arterial recanalization was associated with better short-term improvement, whereas slow flow improvement and dampened flow signals were less favorable prognostic signs. These findings, by providing valuable information on temporal patterns of recanalization, may assist in selection of patients for additional pharmacological or interventional treatment.

Detection of high intensity transient signals (HITS), i.e. microembolic signals (MES), by transcranial Doppler at the site of arterial obstruction can indicate clot dissolution, but should be carefully separated from artefacts. Clusters of MES may be detected distal to a high-grade M1 stenosis preceding spontaneous clinical recovery and minimal MCA flow signals followed by MES, increased velocities, and normal flow signals have been documented over a period of 2 min preceding complete recanalization.[78] Further studies are needed to establish the role of MES detection in the monitoring of thrombolytic therapy.

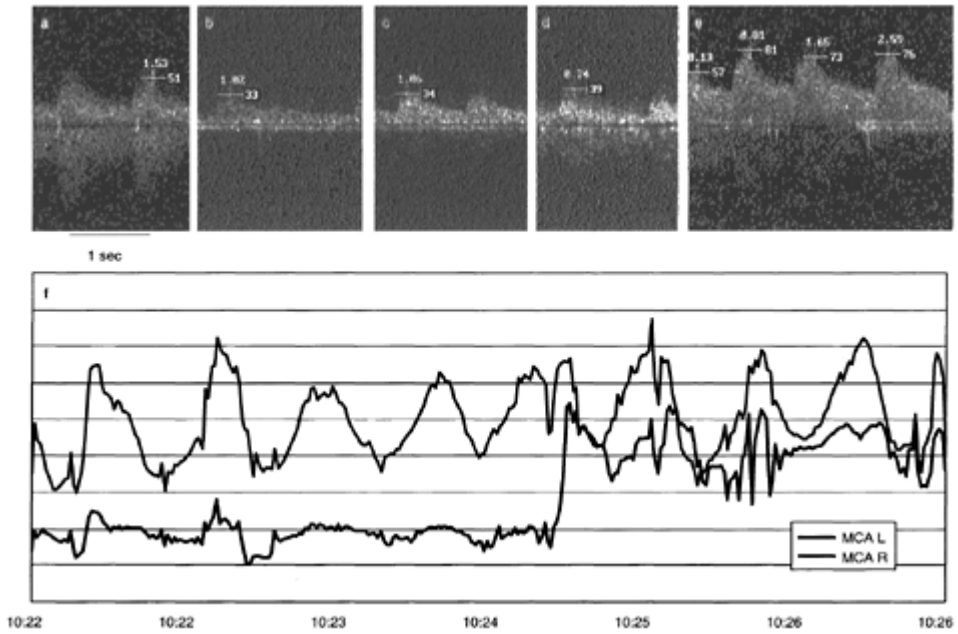

Figure 6.5 A 63-year-old male patient with sudden onset of right-sided sensorimotor hemiparesis and aphasia (at about 8:30).

(a) Transcranial Doppler (TCD) shows minimal signal in the left middle carotid artery (MCA) at time of tissue plasminogen activator (t-PA) bolus (10:18). (b) At 10 mins after bolus, further decrease of the cerebral blood flow velocity. (c) At 22 min, first improvement in signal intensity was noticed and marked as 'beginning' of recanalization. (d) At 26 min, signal changed to (e) normal waveform within <1 s. (f) Recanalization started at 26 mins after t-PA bolus, was completed within seconds, leading to complete recanalization of the distal M1 MCA segment.

ASSESSMENT OF FUNCTIONAL RECOVERY

The introduction of bilateral continuous TCD monitoring has resulted in the development of a variety of new sophisticated applications as supplementary tools to positron emission tomography (PET) and functional MRI (fMRI) studies. These include, among others, evaluation of functional recovery after stroke.

Recent studies have suggested that changes in cerebral perfusion during motor activity in stroke patients with early recovery of motor function may be monitored by TCD.[79,80] Increased flow velocities in both the contralateral and ipsilateral middle cerebral arteries during motor tasks have been demonstrated, suggesting that areas of the healthy hemisphere can be activated soon after a focal ischemic injury and contribute to the positive evolution of a functional deficit. This phenomenon of ipsilateral activation is not transient because it is evident months after stroke onset. In patients with Broca's aphasia following ischemic stroke, a similar increase in middle cerebral artery flow velocities has been detected after successful speech therapy, providing additional support for contralateral involvement in functional recovery after stroke.[81] The mechanisms for these interactions are not yet understood and need further multimodal investigation—fMRI, PET, ultrasound, etc.

ULTRASONOGRAPHIC BRAIN PERFUSION IMAGING IN STROKE

Since imaging of cerebral perfusion may allow detection of ischemic lesions earlier than computed tomography (CT) and distinguish the stroke subtype and severity of cerebral ischemia, there has been increasing interest in perfusion imaging for predicting recovery, differentiating stroke pathogenesis, and monitoring therapy. Validated proportional indicators of cerebral blood flow include Tc-HMPAO-SPECT, PET, xenon-CT and perfusion-weighted MRI. Although the application of these techniques has provided important insights into the pathophysiology of stroke and has prompted new approaches to stroke management, their use in the acute stroke setting is associated with a number of disadvantages. They may be time consuming, involve the use of radioactive tracers, be expensive, require transport to imaging facilities, or be intolerable for critically ill or restless patients. A noninvasive and readily available technique for bedside monitoring of cerebral perfusion in acute stroke patients is clearly needed. There is mounting evidence that this may be accomplished by application of new developments in ultrasound technology that exploit characteristics of contrast agents beyond those of simple echo enhancement.

STIMULATED ACOUSTIC EMISSION

Stimulated acoustic emission, also called contrast burst imaging, involves color or power Doppler imaging with the transmitting power set high enough to ensure contrast agent bubble disruption on the first pulse. Certain ultrasound contrast agents, such as those with thin polymer coatings (e.g., SHU 563A, Schering AG, Berlin), are durable linear scatterers at low acoustic pressures but undergo destruction, fusion, or splitting at higher acoustic pressures[82]that are within the range of diagnostic ultrasound, causing a transient high-amplitude broadband response.[83] Since ultrasound Doppler systems correlate the signals backscattered from a target within a number of successive pulses, the loss of signal correlation caused by the transient bubble collapse is interpreted by the machine as a random Doppler shift, resulting in a mosaic of colors at the location of the microbubbles, even without flow. This technique has been shown to be useful in detecting bleeding sites[84] and liver tumors.[85,86] The ability of stimulated acoustic emission to visualize brain perfusion has been recently demonstrated[82] (see Fig. 6.1). Current work is focusing on the ability of this technique to depict acute cerebral infarction.

CONTRAST HARMONIC IMAGING

Nonlinear oscillation of contrast agent microbubbles produces ultrasound signals with harmonic frequency components, the relative amplitudes of which are dependent upon the amplitude of the incident pressure, the type of contrast agent, and the size of the microbubbles.[60] Since harmonic components from microbubbles are several times larger than the harmonic signals scattered from biological tissues, they can be exploited to improve the contrast between microbubbles and tissue. Contrast harmonic imaging (CHI) is a recent ultrasound technology that uses transducers with broad bandwidths to transmit ultrasound at one frequency and receive signals at twice that frequency, thus enabling the detection of these microbubble harmonics.

The suitability of CHI for demonstration of tissue perfusion has been demonstrated in several studies. Noninvasive assessment of the intramyocardial coronary vasculature and measurement of coronary blood flow reserve have been successfully performed using second-harmonic contrast echocardiography.[87] Intermittent CHI, i.e. triggered imaging at pulse intervals in the range of several seconds, enables very low doses of intravenous contrast medium to produce transient but significantly better contrast enhancement. This has been demonstrated in humans and can be produced safely with minute quantities of intravenous perfluorocarbon.[88]

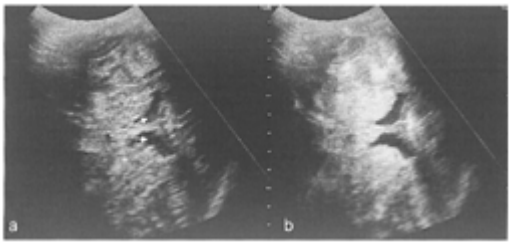

Figure 6.6 Excellent contrast enhancement of the brain following injection of Levovist is seen in (b) using pulse inversion contrast harmonic imaging.

The arrows depict the frontal horns of the lateral ventricles.

Several recent studies have applied CHI for visualization of intracranial brain parenchymal perfusion.[89–91] These investigations have provided good evidence for the capability of ultrasound to assess regional differences in brain echo-contrast enhancement. Moreover, first applications of CHI in stroke patients have demonstrated its potential to detect perfusion deficits.[92]

PULSE INVERSION CONTRAST HARMONIC IMAGING

Although conventional CHI can depict brain tissue perfusion, it has several technical limitations. To avoid overlap between the fundamental and second-harmonic frequencies, CHI employs narrow bandwidths. This leads to an inherent tradeoff in image resolution, thus accentuating the problem of insonation through the transtemporal bone window, which is associated with significant energy loss, signal reverberations, and aberrations. Pulse inversion contrast harmonic imaging (PICHI) is a new technique which minimizes the shortcomings of CHI. This method uses a two-pulse sequence with a 180° phase difference to cancel the effect of transmitted second harmonics on the received signal.[93] By preserving axial resolution and avoiding harmonic frequency overlaps, PICHI has opened up new possibilities for qualitative as well as quantitative evaluation of the cerebral circulation. First results with PICHI demonstrated excellent ultrasonographic visualization of adult brain tissue.[94] Exceptional depth penetration may allow simultaneous measurement of harmonic microbubble contrast enhancement in both ipsilateral and contralateral temporal lobes (Fig. 6.6), thus providing a basis for qualitative comparison of perfusion characteristics with a single bolus injection of contrast agent.

QUANTITATIVE MEASUREMENT OF CEREBRAL BLOOD FLOW

Comparison of echo-contrast washout curves has shown a significant decrease in signal intensity in investigations of similar brain structures at different insonation depths.[89] Because of this depth dependence of measured contrast enhancement, it is unlikely that a classical approach using indicator dilution modeling can provide a valid measurement of CBF in different regions of the brain.

A promising new method for determination of tissue blood flow with contrast harmonic imaging was reported several years ago.[95] This approach is based upon measurement of the reappearance rate of microbubbles following their destruction by ultrasound. Under steady-state conditions, measurement of the microbubble reappearance rate provides a measure of mean microbubble velocity, thus allowing blood flow

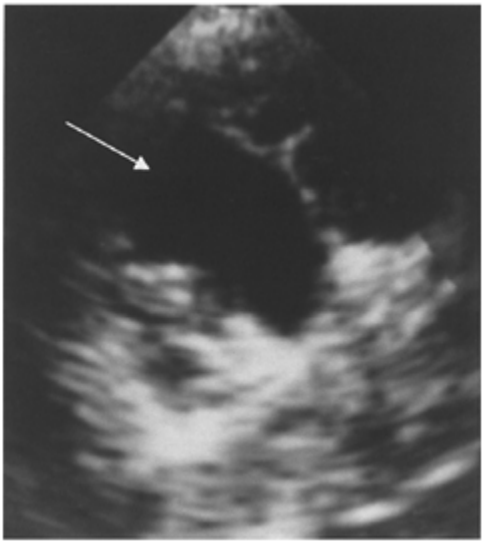

Figure 6.7 Visualization of demarcated middle carotid artery (MCA) infarction (white arrow) in the temporal lobe using power pulse inversion harmonic imaging.

to be calculated as a product of the reappearance rate and of the cross-sectional volume of the region of interest being measured according to the equation:

$$\gamma = A\,(1 - e^{-\beta t})$$

where γ is the measured acoustic intensity at a pulse interval t, A is the plateau of acoustic intensity, and γ is the rate constant that determines the rate of rise of acoustic intensity.

The technique using microbubble refill kinetics has been used to measure blood flow to various tissues, including the myocardium,[95] skeletal muscle[96] and kidney.[97] It has also been shown to be applicable for assessment of CBF in animal experiments.[98] Rim et al. have recently demonstrated that measurement of CBF can be obtained using real-time pulse inversion harmonic imaging in dog brains.[99] Real-time power pulse inversion harmonic imaging, a hybrid method using power Doppler and pulse inversion technology, is a promising new technique that may allow significant advances in both ultrasonographic visualization of brain infarctions (Fig. 6.7) and in assessment of CBF (Figs 6.8 a-d).

Although the approach of microbubble refill kinetics is appealing for measurement of CBF, several issues must be resolved before this technique can be successfully applied for quantitative assessment of brain perfusion in the clinical setting. Reliable methods for compensation of the effects of ultrasound attenuation and inho mogeneous ultrasound fields resulting from beam distortion through the transtemporal bone window[100]are lacking. Likewise, development of techniques for estimating errors due to distortion of the beam elevation, validation of steady-state conditions of microbubble delivery and elimination in the brain, and investigation of the role of inhomogeneous microbubble destruction resulting from variability of the mechanical index with focus, sector width, and imaging depth on uniform measurement of microbubble velocity are all necessary before the method of microbubble reappearance rate can be applied for quantitative assessment of brain perfusion.

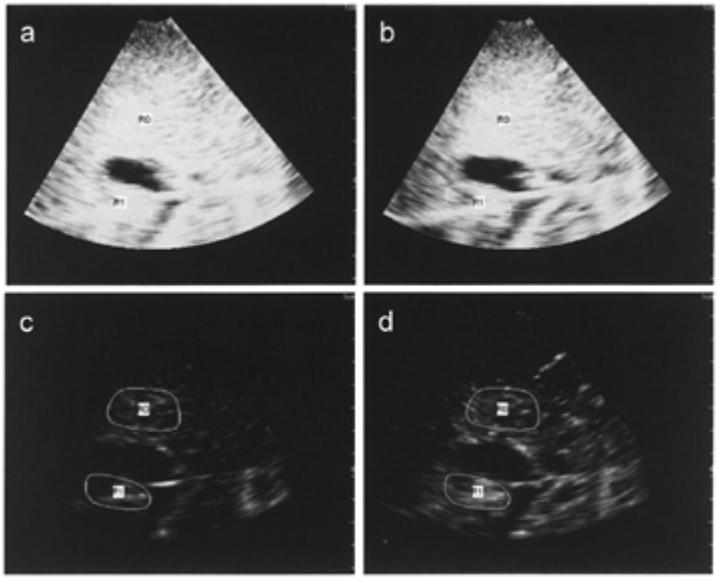

Figure 6.8 Real-time power pulse inversion contrast imaging of ipsilateral middle carotid artery (MCA) infarction with recanalization of the MCA.

The top images (a, b) show real-time destruction of the contrast agent Sonovue® using a high mechanical index of 1.3 (pulse interval 60 ms). The right image (b) demonstrates a discrete color desaturation following bubble destruction. In the lower images, a low mechanical index of 0.1 is used to observe contrast agent replenishment in real-time. The left image (c) was taken directly after bubble destruction (image b), while the right image (d) is approximately 5 s later. Two regions of interest have been set to evaluate bubble destruction and refill kinetics in both hemispheres.

ULTRASONOGRAPHIC THROMBOLYSIS

Deficiencies of current thrombolytic stroke therapy include slow and incomplete thrombolysis and frequent bleeding complications. Increasing evidence from in-vitro and animal studies indicates that application of ultrasound as an adjunct to thrombolytic therapy offers a unique approach to improve effectiveness and decrease bleeding complications. The potential for high-frequency ultrasound to dissolve intraarterial thrombi was first reported by Trubestein in 1976.[101] In these experiments, a 26.5-kHz ultrasound transducer was used to recanalize throm bosed iliofemoral arteries in dogs with minimal complications. In the next 25 years, further studies using catheter-based or transcutaneous ultrasound focused mainly on the ability of ultrasound to enhance the effect of fibrinolytic agents in recanalizing acutely thrombosed arteries.[102–108] More recently, animal studies have suggested that intravenously injected microbubbles may enhance the effects of ultrasound, and may even produce recanalization of acutely thrombosed arteries in the presence of ultrasound without the need for fibrinolytic agents.[109,110] Although invitro studies have observed microfragmentation of thrombi in the presence of microbubbles and ultrasound, the precise mechanism by which ultrasound and microbubbles induce thrombus dissolution remains unknown.

Recent in vitro studies have shown that very-low-frequency ultrasound transducers (33–71 kHz) can significantly potentiate the effect of tPA-mediated thrombolysis when delivered through the temporal bone.[111,112]. There is some evidence that TCD, even at diagnostic frequencies, can accelerate thrombolysis. In one study, dramatic recovery during t-PA therapy occurred in 20% of all patients when infusion was

continuously monitored with TCD.[113] Phase I clinical studies are currently under way to assess the value of both diagnostic and lowfrequency ultrasound for enhancing thrombolysis in acute ischemic stroke.

ULTRASOUND-MEDIATED GENE THERAPY

The promise of gene therapy in acute stroke lies in the potential to increase the brain's resistance to ischemic damage by upregulating genes known to improve cell survival. This may be accomplished by incorporating transfected genes into neurons already suffering from an ischemic insult or into those in which such an event is anticipated. A detailed review of recent advances in gene stroke therapy is presented in Chapter 21.

Although most therapeutic drugs are relatively low-molecular-weight compounds, gene-based therapeutic agents are much larger molecules. Therapeutic genes are macromolecules with several thousand base pairs and molecular weights over 1 million daltons. Although most conventional therapeutic agents are relatively stable in the blood, genetic materials are rapidly metabolized by serum esterases, and are therefore not stable to intravenous administration unless the genetic material is stabilized in some fashion.[114] Moreover, genes are usually too large to pass across the capillary fenestrations of blood vessels unless they are assisted by some mechanism. After genes reach the brain tissue, they must pass across cell membranes and enter the cell nucleus. This is not an easy step, since cells have designed efficient mechanisms for processing exogenous molecules. Once cells take up macromolecules, they are generally digested by lysosomes within the cells.[115] For successful development of clinical gene therapy, effective gene delivery is needed. Recent work suggests that ultrasound may play a central role in the development of new approaches for gene delivery in stroke patients.

Ultrasound may be a valuable tool in gene therapy due to its ability to enhance transgene expression. Simple exposure to ultrasound has been shown to enhance transgene expression in vascular cells by up to 10-fold after naked DNA transfection. Likewise, transfection studies performed using marker genes that do not exert a therapeutic effect, i.e. *p*-chloramphenicol acetyltransferase, γ-galactosidase and green fluorescent protein, demonstrated that ultrasound consistently increased gene expression in cell lines such as HeLa, NIH t-3, and COS-1 cells.[116] The enhancement of transfection occurred at levels of ultrasound of about 0.5 W/cm^2, and duration of exposure of only about 15 s and did not appreciably heat the cells or adversely affect their survival. Similar results on the effect of ultrasound on gene expression have been obtained in cell cultures during liposomal transfection experiments.[117] The mechanism by which ultrasound enhances transfection is mostly likely through cavitation,[118] which in turn increases microvascular permeability. This effect can be dramatically increased in the presence of ultrasound contrast agents.[119] As microbubbles are cavitated by ultrasound, local shock waves increase capillary permeability. This process increases transcapillary passage of macromolecules or nanospheres codelivered with the microbubbles.[120,121] Cavitation probably opens micropores in small blood vessel walls, making the vessels more passable to molecules and nanoparticles. Microvascular permeability caused by cavitation of microbubbles may therefore be exploited therapeutically to increase local delivery of therapeutic materials such as genes.

Not only can microbubbles be used to enhance the effects of ultrasound on gene expression but they may also be employed as carriers of gene therapeutic agents.[116,122]There are a number of ways to entrap different drugs with microbubbles. One technique is to incorporate them into the membrane or wall-forming materials that stabilize microbubbles. Charged drugs can be stabilized in or onto the surfaces of microbubbles by virtue of electrostatic interactions. In this way, cationic lipid-coated microbubbles can bind DNA. This is because DNA is a polyanion and binds avidly to cationic (positively charged) microbubbles.

Drugs can also be incorporated into the interior of microbubbles (gas-filled microspheres). Another way to entrap drugs in microbubbles is to create a layer of oil (e.g. triacetin) to stabilize the outer surface of the bubble. Hydrophobic drugs can then be incorporated into the oil layer. Regardless of the technique used to incorporate the drugs, they are released when ultrasound energy cavitates the microbubble. These methods for making drugcarrying microbubbles are most applicable to drugs that are highly active. This is the case for gene-based drugs, in which the amount of gene injected is usually on the order of micrograms or milligrams. Therefore, large volumes of bubbles are not required to deliver highly active drugs such as genes.

In summary, ultrasound may be used to enhance gene expression. In the presence of microbubbles, a synergistic effect is attained, and cavitation is a likely mechanism. Acoustically active materials that bind or entrap genetic materials have a potential role for gene delivery. These materials can be injected intravenously, and targeted gene delivery is attained within the tissue exposed to ultrasound. This new technology holds the promise of delivering genes more selectively than other methods and less invasively than direct injection. The ability to focus ultrasound and cause local cavitation with these new gene carriers may provide a powerful new tool for gene delivery in stroke patients.

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7.
General care in the acute phase

Peter Limpar and Daniel F Hanley

INTRODUCTION

Early intervention is a major goal in the strategy for acute ischemic stroke treatment. As with any other neurologic emergency, the treatment of patients with acute stroke is guided by important objectives:

- the preservation of life,
- the preservation of neurologic function
- the prevention of complications secondary to stroke which may cause death or delay successful rehabilitation.

Several general factors are important for all patients, such as airway and oxygenation, blood pressure and hemodynamics, temperature and metabolic homeostasis. Cerebral resuscitation refers to therapeutic interventions to reverse brain injury after an ischemic event. The time factor is important, especially during the first minutes and hours of stroke. The importance of rapid assessment and treatment has been emphasized by the National Institute of Neurological Disorders and Stroke (NINDS) study, where 52% of candidates to intravenous recombinant tissue plasminogen activator (IV rt-PA) treatment were excluded because of delay in presentation.[1]

General supportive care, evaluation, and treatment should proceed simultanously with neurologic evaluation and intervention when a patient is managed by an experienced stroke team.[2,3]

INITIAL EVALUATION OF STROKE PATIENTS AND INITIAL RESUSCITATION—THE FIRST HOURS

The treatment of stroke begins with the evaluation of the stability of the patient's vital signs. This dictates the extent of supportive care necessary to prevent acute complications. The examining physician should first assess the stroke patient as having a potentially lifethreatening illness, with emphasis on the ABC of resuscitation. The first minutes in evaluating a stroke patient should be devoted to assessing the adequacy of airway patency, ventilation, and circulation.[5] General measures are designed to optimize the chances of recovering the function of neurons rendered ischemic but not irreversibly damaged. Many general measures can be decided a priori, incorporated into a standing protocol, and implemented upon the arrival of patients with acute stroke. The first hours in stroke are devoted to medical stabilization, clinical assessment, and brain imaging; however, ultimate focus is on early arterial recanalization.[4]

AIRWAY, RESPIRATORY FUNCTION

Respiratory function is the first functional modality to be evaluated immediately in all stroke patients. A quick physical assessment of respiratory function includes observation of the quality and rate of the respiration. Tachypnea may indicate pneumonia, bronchospasm, congestive heart failure (CHF), or impending ventilatory failure. The use of accessory muscles of breathing indicates further respiratory compromise. The presence of paradoxical breathing indicates more severe ventilatory insufficiency. Auscultation of the lungs and the neck may reveal evidence of bronchospasm, pneumonia, CHF, or upper airway obstruction. In the awake patient, palatal movement as well as voluntary cough and swallowing may be assessed. In most cases of stroke, pulse oximetry is sufficient to assess the adequacy of oxygenation. The most common causes of hypoxia are partial airway obstruction, atelectasis, and aspiration pneumonia.

Deficits in airway protection arise from impaired oropharyngeal motility or sensation and loss of protective reflexes from ischemic or compressive brainstem dysfunction and/or decreases level of consciousness. It is important to remember that patients suspected of having cerebral infarction but who also have obvious airway compromise are more likely to have intracranial hemorrhage. Endotracheal intubation and mechanical ventilation are necessary in these patients. Although ventilatory drive is usually intact for the majority of stroke patients, notable exceptions are seen in stroke patients with medullary or massive hemispheric infarction. Ischemia in the posterior circulation can lead to well-defined abnormal ventilatory patterns and, ultimately, to apnea.[27] In certain types of medullary stroke, mild hypoventilation, which can be reversed when the patient is stimulated, but respiration may cease completely during sleep. In rare cases, hemispheric disease can cause Cheyne-Stokes breathing.[28]

Impaired airway protection secondary to a deficit in swallowing creates a high risk for aspiration of the stomach contents or oropharyngeal secretions which occurs many times prior to presentation.

Most stroke patients do not require aggressive airway maneuvers, but oxygen should be provided to maintain the oxygen saturation above 95%. Escalating requirements for FiO_2 (fraction of inspired oxygen) supplementation should be accompanied by chest X-ray evaluation for pneumonia. No data establish the benefit of supplemental oxygen.[10]

CIRCULATION

The patient should be assessed rapidly to determine the presence or absence of cardiovascular abnormalities. Circulatory function is stable during the initial hours after stroke for the majority of patients. However, a strong correlation exists between acute stroke and the occurrence of heart disease; thus, clinically significant heart disease at the time of admission may be present in these groups. Acute ischemic stroke can occur simultaneously with an acute myocardial infarction (AMI). Cardiac arrhythmias, including atrial fibrillation as well as CHF, can accompany stroke. Clinical cardiac examination —12-lead ECG, chest X-ray, and blood tests (including cardiac enzyme measurements)— should be performed. It should be remembered that deep vessel puncture, intramuscular injection, and other invasive interventions must be avoided in patients candidate to intravenous thrombolytic therapy.

Hypertension is a common finding at the time of initial stroke presentation, even among patients without prior elevation in the pressure. The presence of hypertension at presentation is likely multifactorial. Possible mechanisms include a compensatory increase of perfusion to ischemic brain areas or the presence of stress, anxiety, and a high catecholamine state. Most patients will have spontaneous and gradual reductions of blood pressure during the first hours to days after stroke. Unless the patient has had a subarachnoid hemorrhage from an aneurysm or other vascular anomaly, hypertension is not acutely detrimental when no signs of end-organ injury; i.e. angina, CHF and acute renal failure are not present. Even in patients with

parenchymal hemorrhage or hematoma, hypertension is well tolerated and has not been shown to influence further hemorrhage.

Patients admitted with acute stroke are frequently dehydrated. Fluid administration during the initial evaluation is recommended in the presence of evidence for dehydration by physical examination or from the results of laboratory studies.

Because blood pressure varies greatly from person to person, it is important to establish the routine blood pressure for all acute stroke patients. This personal 'normal level' establishes the individual baseline blood pressure around which treatment decisions can be made. A common and undesirable scenario is the hypertensive patient presenting with a neurologic deficit which worsens in response to the rapid lowering of the blood pressure. Indications and plans for treatment of hypertension are given in Chapter 8.

Hypotension (operationally defined as blood pressure less than 90/60), on the other hand, is more uniformly detrimental and should be treated aggressively. Low blood pressure is rarely detected in patients with acute ischemic stroke. The presence of hypotension suggests the possible presence of a serious complication such as severe dehydration (patient admitted several hours following cerebral infarction), myocardial ischemia or infarction, sepsis, or brainstem dysfunction from ischemia or compression. Volume expansion with normal saline is the first-line treatment. Pressors such as dopamine should be administered to patients who do not respond to volume expansion.

Cardiac monitoring should be continued during the first 24 hours to detect potentially lifethreatening arrhythmias.

NEUROLOGIC EVALUATION

Bedside assessment of neurologic function includes consciousness, language, vision and eye movements, body-spatial perception, sensory and motor function, cerebellar function, and neck stiffness. It is possible to evaluate these factors clinically in just a few minutes; more detailed assessment can be performed at a later time.

Standardized neurological scales, such as the National Institute of Health stroke scale (NIHSS) are useful for baseline diagnostics, follow-up, and as outcome measures.

The examination of the unconscious patient involves verbal, tactile, or painful stimulations, depending on the level of alertness, examination of brainstem function, an assessment for meningismus. In patients who are initially unconscious, the Glasgow coma scale is a simple and useful tool of assessment.

Most patients do not have depression in consciousness within 24 hours of onset of ischemic stroke in the cerebral hemispheres; if consciousness is impaired, a stroke-related seizure, hemorrhage, hypoxia, increased intracranial pressure (ICP), or brainstem involvement should be considered.

If seizures are suspected or if nonconvulsive status epilepticus is the likely cause of the patient's neurologic condition, an electroencephalogram (EEG) can be an important early diagnostic test. Blood tests for glucose and electrolyte imbalance should be completed to identify conditions that may require emergency management.

The emergency diagnostic evaluation of patients with acute stroke includes immediate neuroimaging. This is the single most important diagnostic step in the management of acute stroke. Computed tomography (CT) examination is often performed in a remote area outside the emergency department. Furthermore, acute stroke patients are frequently restless and uncooperative and may require slight sedation in order to achieve neuroimaging tests. Therefore, patients with severe stroke should be monitored and accompanied by a qualified practitioner when diagnostic procedures are performed.

Management of patients with acute confusional state or agitated delirium, most often seen in patients with right middle cerebral artery (MCA) territory infarction, may also require the use of short-acting sedative drugs. It is important to rule out somatic causes (such as pain, bladder distention, infection, drug and alcohol abuse, and metabolic abnormalities). No matter where the patient is transported to, it is important to remember that deterioration can occur. In some situations, patients may urgently need intensive therapy at the presentation. Patients with large strokes, increasing impairment, or loss of consciousness, and/or apnea, high ICP, patients with extensive vertebrobasilar territory infarction, seizure activity, or massive intracranial hemorrhage, severe hypoxemia, and hypercarbia will require immediate airway management and rapid admission to the intensive care unit (ICU).

MANAGEMENT DURING THE FIRST DAYS OF STROKE

The goals of early supportive care after admission to the hospital, as underlined in the AHA guidelines,[2] are to observe changes in the patient's condition that might prompt different medical or surgical interventions (monitoring), facilitate medical and surgical measures aimed at improving outcome after stroke, and institute measures to prevent subacute complications. Most common acute/subacute complications include dehydration, cardiac arrhythmia, myocardial ischemia, respiratory disturbances and pneumonia, urinary tract infections, deep vein thrombosis, suboptimal nutrition, and seizures.[6] Most patients are first treated with bed rest. An occasional patient may have worsening of neurologic signs upon standing, sitting, or elevating the head. Additionally, the physician should begin planning for chronic therapies to prevent recurrent stroke and begin efforts to restore neurologic functions through rehabilitation or other techniques.

MONITORING

The patient's vital signs—including blood pressure (BP), heart rate (HR), respiratory rate, temperature, and neurologic status—should be closely monitored for the first 24 hours.

Frequent neurologic monitoring has several benefits. First, changes in neurologic function may be indicators of a medical complication such as new-onset atrial fibrillation, cardiac failure, hypotension, or respiratory disorders resulting in hypoxia or hypercarbia. Secondly, neurologic complications and complications of therapeutic interventions are most rapidly identified and addressed by neurologic monitoring. Cardiorespiratory monitoring in stroke patients is useful for several reasons. First, cerebrovascular disease commonly coexists with coronary disease. Cardiac complications account for a large number of deaths in the acute phase.[7,9] In infratentorial strokes, especially, cardiovascular monitoring has great importance. In this type of stroke, the occurrence of cardiorespiratory complications is more frequent. Further, trends in vital signs may help to detect increasing ICP or shifts in the contents of the posterior fossa. In these situations, the classic Cushing response of bradycardia, hypertension, and irregular respirations may be observed. More commonly, increased heart rate and blood pressure are seen. Finally, monitoring helps the physician to support cerebral perfusion pressure and minimizes acute hypertensive cardiac or renal injury. Continuous electrocardiogram (ECG) and pulse oximetry monitoring is recommended in the specialized stroke unit. Intermittent blood pressure measurements are usually sufficient because the objective is to detect severe elevations or sustained declines in pressure.

If a central line is available, central venous pressure (CVP) measurements can be performed, which may provide some indirect information on right ventricular filling especially as a response to volume changes.

Although continuous pulse oximetry assesses the adequacy of oxygenation, it does not indicate changes in ventilation (hypercarbia due to impaired ventilation). If, however, the patient appears to be in respiratory

difficulty or has an oxygen saturation of less than 90%, arterial blood gases should be measured. The patient should be monitored for nocturnal apnea. Chest X-ray should be performed if auscultation of the lungs reveals abnormal findings for evidence of pneumonia, atelectasis, effusions, and CHF.

Bedside trancranial doppler (TCD) has been proposed to evaluate patients with acute cerebral infarction and to monitor the effect of therapeutic interventions such as vessel opening.[11]

Several additional diagnostic studies are performed during the first hours or first days following stroke, including brain imaging and cardiac diagnostic tests. These studies are clinically important and facilitate decisions regarding changes in medical (anticoagulation, transfer to the ICU) or surgical management (neurosurgical intervention). Patients should be adequately prepared. Each patient should receive information about the procedure: in some cases medication for anxiety is necessary; however, risks (excessive sedation, respiratory depression, and aspiration) and benefits of such a medication should be balanced and the patient adequately observed during the transfer and procedure.

CARDIOVASCULARTHERAPY

Because stroke patients often have underlying cardiovascular disease, they are prone to blood pressure instability, myocardial ischemia, and left ventricular dysfunction. Cardiovascular complications account for 10–20% of the deaths following stroke.[7,9]

The crucial goal of cardiovascular therapy in stroke patients is to provide circulatory support for sufficient metabolic substrate to the threatened central nervous system (CNS) without adversely affecting cardiac function. Cardiovascular therapy can increase CNS swelling and result in secondary injury. Therefore, while maintaining oxygen delivery to the myocardium, care must be taken not to compromise intracerebral hemodynamics. For example, vasodilators may increase ICP. Alternatively, increasing cerebral perfusion pressure (CPP) by elevated mean arterial pressure (MAP) might be needed to protect cerebral perfusion, especially if elevated ICP is suspected.

BLOOD PRESSURE MANAGEMENT

Management of blood pressure is discussed in Chapter 8.

ELECTROCARDIOGRAPHIC CHANGES

Neurogenic ECG changes

The CNS plays an essential role in the regulation of cardiac function. There is strong evidence that acute brain injuries, mainly those of hemorrhagic origin, may induce repolarization abnormalities and prolongation of the QT interval and several types of arrhythmias. Several reports have described numerous different electrocardiographic abnormalities associated with acute neurologic illness.[12–14] In some cases these changes have been related to sudden death. The imbalance between the sympathetic and parasympathetic nervous systems seems to be an important factor. Prognostic relevance of the sympathetic activation has not yet been well established. With the exception of prolonged QT intervals and persistent U-waves, most of these changes usually resolve within 72 hours. No specific treatment has been shown to be effective in humans. All patients presenting with these changes should be evaluated initially for myocardial ischemia; thus, neurogenic changes are a diagnosis of last resort.

ARRHYTHMIAS

Established or new-onset atrial fibrillation accounts for about 16% of ischemic stroke.[15,17] Other supraventricular arrhythmias associated with cardioembolic stroke include sinoatrial disease and atrial flutter.

Poststroke atrial fibrillation is infrequent, occurs early, and is often transient.[13] It is noteworthy that cardiac arrhythmias (much like other ECG changes and high blood pressure) decrease greatly by the third day of the stroke onset. Abrupt arrhythmia can precipitate an embolic event or compromise cardiac output and coronary perfusion. Tachycardia increases myocardial oxygen demand and induces ischemia in susceptible patients. Rapid ventricular rates might also compromise the heart's ability to deliver an adequate cardiac output: therefore, the ventricular rate should be controlled.

For persistent atrial fibrillation and flutter, anticoagulant therapy should be considered. There are other cardiac conditions associated with cardioembolic stroke which require introduction or adjustment of anticoagulation, including valvular heart disease and prosthetic cardiac valves, MI, patent foramen ovale, atrial septal aneurysms, mitral annular calcification, and cardiac tumors. Non-emergency diagnostics and management of cardioembolic stroke and antico agulant therapy are discussed elsewhere (see Chapters 10 and 16).

ANTIARRHYTHMIC MEDICATIONS

The goal of antiarrhythmic medications is to reestablish cardiac homeostasis without increased blood pressure instability. The urgency of therapy is dictated by the ventricular response rate and the patient's hemodynamic tolerance of the arrhythmia. Adenosine and beta-blockers such as esmolol, propranolol, metoprolol, and labetalol are often used as first-line drugs due to their rapid onset and relative safety. Some calcium channel blockers such as verapamil and diltiazem are also used to control ventricular rate, particularly for supraventricular tachycardias. Amiodarone is sometimes used for this indication. Beta-blockers and calcium entry blockers are used as antianginal therapy as well. Beta-blockers also have the benefit of improving intracranial compliance and do not cause cerebral vascular relaxation, which can lead to ICP elevation.

Most of these drugs have a negative inotropic effect and some of them vasodilatatory properties; thus, they can result in low cardiac output or hypotension. Particular caution is necessary in patients with altered left ventricular function. Adenosine generally does not induce hypotension when used for controlling supraventricular tachycardia, although a prolonged pause and short-lived bradycardia can be observed. Patients with bronchospastic disease experience exacerbation of their symptoms when receiving a betablocker (relative contraindication).

Digoxin, given as intravenous (IV) loading and oral maintenance doses, can be used to slow atrioventricular nodal conduction and to assist in rate control. It can be effective in preventing recurrent paroxysmal supraventricular tachycardia. Digoxin possesses mild to moderate inotropic activity, increasing cardiac output by 10–20% in otherwise stable chronic heart failure patients. Its onset is not immediate nor is it easily titratable. Undocumented previous digoxin administration, hypokalemia, and onset of renal failure increase the risk of digoxin toxicity.

If hypertension—tachycardia is thought to occur as a result of the Cushing reflex, then attention should be directed towards primarily decreasing ICP. By contrast, manipulation of cardiac tonus without addressing the underlying cause may result in critical CPP reduction.

Finally, because of lack of clinical data, the routine use of a prophylactic strategy to suppress sympathetic activation such as beta-blockers is not recommended[18,19] (their use as primary stroke prevention is justified,

and patients who are already on beta-blockers should be left with this treatment unless severe cardiac conduction failure occurs).

Antithrombotic therapy for acute atrial fibrillation associated stroke is a complex issue, balancing the benefit of reduction in early recurrent embolism against the risk of potentiating secondary brain hemorrhage. The situation may be challenging in the presence of intracranial bleeding, previous antithrombotic and thrombolytic therapy, or contraindication to anticoagulants. Given the lack of adequate clinical data in this area, the range of acceptable management is wide. This issue is discussed in Chapters 10 and 16.

ACUTE MYOCARDIAL ISCHEMIA, ACUTE CORONARY SYNDROME

The appearance of heart failure or new-onset arrhythmia may indicate development of acute myocardial ischemia or AMI. Coincident MI and stroke is not exceptional in patients admitted for stroke. It is noteworthy that 10% of cardioembolic strokes result from AMI. The source is most probably the left ventricular thrombi, which develop between 1 and 10 days after AMI.[15–17]

Careful physical examination, ECG monitoring, cardiac enzyme monitoring, and nonivasive diagnostic techniques for coronary artery disease (CAD) such as echocardiography provide useful data to differentiate neurogenic ECG changes from cardiac ischemic disease.

Treatment of new-onset myocardial ischemia requires improvement in the myocardial oxygen consumption/supply balance with nitrates, betaadrenergic blockers, and calcium channel blockers, and appropriate emergency consultation to achieve revascularization. Management of patients who require surgical revascularization may represent a difficult case when acute stroke is associated with significant stenosis in the cerebral vessels (endarterectomy before bypass surgery).

ACUTE CARDIAC FAILURE

Heart failure is not commonly present during the first hours after onset of stroke and may be more common in patients with new-onset atrial fibrillation.[6–8] Increasing MAP might decrease cardiac output if left ventricular dysfunction exists. Other causes precipitating CHF include excessive fluid administration, negative inotropic drugs, and myocardial ischemia.

If heart failure is identified, treatment is immediate, although rapid contraction of intravascular volume is to be avoided because it may lower blood pressure and cerebral blood flow. Optimizing fluid administration and using diuretics as necessary, controlling ventricular rate and discontinuing not-needed negative inotropic drugs comprise the first step. The classic therapy for CHF includes diuretics, digitalis, vasodilators, and contractility enhancers (such as phosphodiesterase inhibitors and dobutamine). Hypotension (even relative) must be avoided; therefore attention must be paid if using diuretics, vasodilators, or phosphodiesterase inhibitors. In the case of acute cardiogenic pulmonary edema, respiratory support using continuous positive airway pressure (CPAP) is an effective option if the situation does not necessitate intubation and mechanical ventilation.

RESPIRATORY CARE OF THE ACUTE STROKE PATIENT

Arterial hypoxemia commonly occurs over the clinical treatment course in patients with CNS injury. Hypoxemia is especially associated with a poor neurologic outcome after head injury. Although there is no study demonstrating this type of direct relationship in stroke, prompt recognition and treatment of respiratory disorders appears to be important in the management of stroke patients. The physician must

recognize preexisting lung disease, as well as obesity and cigarette smoking, as important predictors of impaired pulmonary function.

Most commonly, respiratory insufficiency is caused by atelectasis and pneumonia due to impaired airway protection and poor secretion clearance.[6,8,35]

Alveolar collapse, or atelectasis, commonly occurs in dependent regions of the lung. Atelectasis is particularly problematic in supine patients whose cough and secretion clearance is impaired, in patients who may not reposition themselves in bed spontaneously due to motor deficit, or in patients whose lung expansion is limited by obesity.

Pneumonia accounts for 15–29% of the deaths following stroke,[7,26]most of which result from bacterial infections and are secondary to aspiration. The pneumonia is likely to be communityacquired in patients for whom the infiltrate becomes detectable radiographically during the first 24–48 hours. The diagnosis of aspiration pneumonia is made when a patient at risk for aspiration has radiographic evidence of an infiltrate in a characteristic-dependent bronchopulmonary segment. Any condition that increases the volume or bacterial burden of oropharyngeal secretions in a person with impaired defense mechanism may lead to aspiration pneumonia. Factors such as dysphagia, oral abscess, sinusitis, and concurrent antibiotics increase the risk of oropharyngeal colonization with pathogenic organisms. Patients with overt dysphagia and abnormal gag reflex, especially elderly patients, are at increased risk for oropharyngeal aspiration. In patients with stroke, the prevalence of swallowing dysfunction ranges from 40 to 70%.[31–33] Even small-vessel strokes can be associated with significant aspiration. Many of these patients have silent aspiration. Among patients who had a stroke, pneumonia is 7–20 times as likely to develop in those in whom aspiration can be confirmed than in those who do not aspirate [35,36] There is a strong correlation between the volume of the aspirate and the development of pneumonia. Several factors, including premorbid pulmonary function, mobility, oral hygiene, and frequency of aspiration, contribute to the development of aspiration pneumonia [33,35,36] Additional risk factors include multiple stroke, bilateral cranial nerve signs, dysphonia, brainstem stroke, or subcortical stroke.

Stroke patients may also suffer from chronic pulmonary conditions such as chronic obstructive pulmonary disease (COPD) or asthma. They may have a concurrent increase in symptoms. Studies of patients with stroke indicate impairments in response to changes in airway resistance as well as impairments of ventilation during sleep. Within several days of the onset of acute cerebral infarction, deep vein thrombosis may develop and a high risk for acute pulmonary embolism results. Up to 25% of early deaths following stroke are attributed to pulmonary embolism (the higher rate suggests a high mortality of PE when it occurs); however, fatal emboli are unusual in the first week.[25,26]

AIRWAY

A patient with an ischemic stroke usually has a stable airway. Even the patient with a very large hemispheric infarct usually will not have airway compromise. Exceptions to this rule include patients with strokes of the brainstem and patients with infarction complicated by status epilepticus. Additionally, patients with intracerebral hemorrhage (ICH) more frequently have airway compromise. These conditions may require early intubation and mechanical ventilation. Brainstem infarction can lead to central, or more frequently, obstructive and mixed sleep apnea. In the alert patient, noctural continuous positive airway pressure or bilevel positive airway pressure may be effective in most cases.

GAS EXCHANGE

Hypoxemic patients whose $P(A\text{-}a)O_2$ is increased require therapy for the underlying cause as well as supplemental O_2. Initially, hypoxemia usually responds to increasing the FiO_2.

Administration of oxygen

Using nasal prongs and a Venturi mask can deliver an FiO_2 of 24–44%. The FiO_2 varies, depending on the patient's inspiratory flow rate, with lower-flow FiO_2 occurring during high in spiratory flow rates.

Face masks

Open face masks provide a higher flow of humidified, premixed air and O_2 at an FiO_2 of up to 0.5. Non-rebreather masks with reservoir bag can provide an even higher FiO_2. Tightly fitting face masks (if the patient is perfectly able to control his airway) or nasal masks (if the patient is able to keep the mouth closed) and CPAP can be used to increase concentrations of O_2 for patients whose hypoxemia is caused by shunting, such as patients with severe pneumonia. Studies in intubated patients suggest that PEEP (positive end-expiratory pressure) increases up to 12 mmHg does not significantly influence ICP.[20]

Aspiration, intubation

The treatment of massive atelectasis with acute hypoxia may require aggressive interventions such as fiberoptic aspiration. Elective endotracheal intubation is necessary when a high FiO_2 is required; thus, intubation is best planned when FiO_2 requirements are rapidly increasing.

Secretion clearance, chest physiotherapy

Various techniques for augmenting the secretion and cough clearance mechanisms of the lungs—such as chest percussion, postural drainage, and more recent techniques of the active cycle of breathing—can be used to prevent respiratory compromise. Incentive spirometry, periodic face mask administration such as PEEP, and CPAP are used in some institutions; none of these techniques has been specifically evaluated for systematic prevention of atelectasis in stroke patients.

Positioning

Frequent repositioning of patients with high risk of atelectasis may also prevent alveolar collapse. Nurses look at patient positioning as a treatment to improve comfort and prevent pressure sores, chest infections, and deep venous thrombosis. Upright positioning of patients who developed atelectasis and turning them from side to side can greatly improve the PaO2.[22,23] However, a review of the nursing literature on the effects of patient positioning on arterial oxygen saturation found that there were differences in practise regarding how best to position patients in order to aid their breathing.[21,24]

Oral care

To decrease the bacterial burden of oropharyngeal secretions in patients with impaired cough, oral care includes frequent suction, and multiple daily tooth brushing and mouth-washing. Cleaning the tongue can also be helpful.

VENTILATORY FUNCTION

Hypercarbia and acidosis are known to be deleterious in patients with acute brain injury. Therefore, in addition to adequate oxygenation, ventilatory function should be frequently assessed and, when impaired, actively supported. In the presence of a sudden alteration of the ventilation pattern, a new neurologic event (elevated ICP or brain stem infarct) or cardiorespiratory emergency (cardiac failure, pulmonary embolism, or bronchospasm) must be ruled out.

SPECIFIC THERAPY

Pneumonia

When the presence of pneumonia is identified on the chest radiograph, cultures and serological testing for viral agents, *Mycoplasma* spp., or *Legionella* spp. should be obtained. Broad-spectrum antibiotic therapy is administered until a specific etiologic diagnosis is established and antibiotic sensitivities are determined. Antibiotic therapy is unequivocally indicated in patients demonstrating aspiration pneumonia. Antibiotic agents with activity against Gram-negative organisms, such as third-generation cephalosporins and fluoroquinolones are usually required. Antibiotic agents with specific anaerobic activity are not routinely warranted but may be indicated in patients with severe periodontal disease, putrid sputum, or lung abcess.[36,37]

Antibioprophylaxy and aspiration pneumonia.

Although some clinical data show a decreased incidence of pneumonia in comatose stroke patients with prophylactic antibiotics administration, oropharyngeal or intestinal decontamination, randomized studies have not established the benefit of these prophylactic strategies.[38] We do not believe they are justified.

Assessing the risk of oropharyngeal aspiration.

Numerous studies suggest that assessment of the cough and gag reflexes is an unreliable means of identifying patients at risk for aspiration. A comprehensive swallowing evaluation, supplemented by either a videofluoroscopic swallowing study or a fiberoptic endoscopic evaluation remains the optimal assessment of aspiration.[29,30,34] A speechlanguage pathologist or other professional with assessment experience can perform this evaluation at the bedside.

It is important to note that videofluoroscopy has important limitations: it is labor-intensive, does not mimic normal feeding, may promote anxiety and exposes patients to radiation. Furthermore, it is not universally available or suitable for all patients (e.g. many patients cannot be transported to a radiology department and positioned as required). Thus, the value of routine screening with videofluoroscopy to

detect aspiration and to predict risk for pneumonia is questioned by many authors.[29] In fact, a significant proportion of swallowing problems resolve over the first 2 weeks.

In patients found to be at risk for aspiration, further behavioral, dietary, and medical management to reduce the risk can be initiated. Initially, prohibiting oral feeding is the simplest maneuver to consider. In patients with mild swallowing dysfunction, but preserved reflex and voluntary swallow, a soft diet should be introduced, and the patient should be taught compensatory feeding strategies. One should avoid placing patients unnecessarily 'nil by mouth' with prolonged intravenous hydration. Soft tube feeding is usually recommended in patients who have significant aspiration risk by clinical and/or radiological evaluation. Feeding tubes offer no protection from colonized oral secretions, which are a serious threat to patients with dysphagia. Numerous problems are associated with using a nasoenteric tube, including discomfort, excessive gagging, esophagitis, misplacement, displacement, or clogging of the tubes, and poor cosmesis. Thus, swallowing should be reevaluated periodically. Patients who are likely to recover their ability to swallow within a few weeks are not candidates for gastrostomy tubes. The incidence of aspiration pneumonia seems to be similar with the two feeding methods (nasoenteric tube and gastrostomy tube).[36]

Pulmonary embolism

When pulmonary embolism is identified, critical care consultation should be obtained immediately and appropriate therapy should be administered without delay: this includes oxygen, volume augmentation, and anticoagulation or thrombolytics. Frequently, patients cannot be treated with either thrombolytics or full-dose anticoagulation and, in such patients, a Greenfield filter can be placed in the inferior vena cava.

Obstructive disease

Patients with COPD and asthma may be treated with theophylline, steroids, beta$_2$-adrenergic agonists, and anticholinergic agents. Aerosol forms of the latter drugs is preferred because systemic effects such as tachycardia, arrhythmia, and tremors can be minimized. Theophylline is less useful in the emergency setting because of its limited bronchodilating properties and its potential for CNS toxicity (such as seizures).

FLUID MANAGEMENT

Dehydration is commonly present in patients admitted with acute stroke. Even patients who initially are hydrated adequately may become dehydrated over the first 24–48 hours when thirst, appetite, and the capability for oral ingestion are compromised. Some patients may have received excessive diuretic therapy. Appropriate volume replacement improves cardiac output and cerebral perfusion in many patients with acute stroke.

For the first 12–24 hours, oral fluid intake is usually delayed, except in those patients who had early assessment of swallowing (patients without dysphagia, impairment of cough). Until the patient resumes a normal dietary intake or nutritional support is instituted, routine maintenance intravenous fluids such as isotonic saline are generally given, unless intravascular volume deficits dictate the need to use colloid-containing fluids with better intravascular retention such as plasma extracts or synthetic colloids.

After this period, oral administration of fluids or fluids given via a gastric feeding tube are safe, cost-effective, and associated with infrequent complications regarding osmolality and volume.

Optimizing fluid administration while avoiding overload and protecting cerebral perfusion can be difficult in hemodynamically fragile patients. Hypertension can be associated with normal, low, or high intravascular volume.

Daily examination should be performed for, BP, HR, jugular venous distention, respiratory rate, cardiac and pulmonary auscultation, skin turgor, weight, and fluid balance.

However, assessment of cardiac and hemodynamic function can be misleading when relying on bedside examination techniques alone. Laboratory data, chest X-ray, and CVP monitoring may provide indirect information regarding intravascular volume. Most patients do not require a central line, unless intravenous volume administration is necessary with no peripheral venous access or venotoxic drug administration is planned. The risk of complication associated with central insertion is high when thrombolytic therapy has been recently administered.

Other noninvasive cardiac assessment tools such as bedside transthoracic echocardiography are useful and can provide indirect information regarding intravascular volume status and direct information regarding contractility.

INTRAVENOUS FLUID MANAGEMENT

In patients without signs of increased ICP but with signs by the initial CT scan of a very large cerebral infarction, intravenous fluids are often administered sparingly in an attempt to attenuate the cerebral edema, which will probably complicate such an infarct during the next 24–96 hours. Fluid restriction minimally affects cerebral edema and, if overzealously pursued, can lead to hemodynamic instability. The available data suggest that volume replacement and expansion will have no effect on cerebral edema as long as serum osmolality is maintained. True volume overload is detrimental (by significantly increasing cerebral and/or left ventricular hydrostatic pressures).

Serum osmolality should be maintained within the normal range or slightly increased. Thus, the osmolality of the selected fluid is the single most important variable. Isotonic solutions are widely used to maintain and/or restore intravascular volume. These include normal saline, some other balanced salt solution, or an isotonic colloid (plasma, albumin, hetastarch). Hetastarch must be used with caution due to depletion of factor VIII and possible coagulation difficulties encountered with volumes of more than 1000 ml.

It should be remembered that lactated Ringer's solution is not perfectly iso-osmotic. Only small volumes of this solution should be administered, particularly to patients whose baseline osmolality has been increased (dehydration, mannitol, hypertonic saline).

By contrast, reduction of colloid oncotic pressure with maintenance of serum osmolality exerts little influence on brain water content and ICP.[39] Hypervolemic hemodilution has been advocated as a method for increasing cerebral blood flow. Clinical trials have failed to realize the putative rheologic benefits of this therapy. We do not recommend hemodilution for stroke patients.

Although it has not been possible to demonstrate that the administration of glucose in humans is detrimental, it is prudent to withhold intravenous glucose-containing solutions in stroke patients, except for diabetic patients where strict blood glucose control may produce hypoglycemia.

The routine use of mannitol in patients with acute stroke is not supported by any evidence from randomized controlled clinical trials.[40]

PREVENTION AND TREATMENT OF SUBACUTE COMPLICATIONS

NEUROLOGIC DETERIORATION

Approximately 25% of patients worsen during the first 24–48 hours after admission to the hospital.[7,8] It is often difficult to predict deterioration: therefore, all patients should be considered at risk for neurologic worsening. Urgent CT of the brain is often beneficial in defining unanticipated new mass effect.

The most important acute neurologic complications of stroke are:

1. cerebral edema and increased ICP, which can lead to herniation or brainstem compression
2. seizures
3. hemorrhagic conversion and secondary bleeding.

Less frequently, metabolic disorders (such as hyponatremia, hyper- or hypoglycemia), respiratory failure (hypoxia and/or hypercarbia), sedative drugs (benzodiazepines, antidepressants, antiepileptic drugs) contribute to the impairment of consciousness. Immediate supportive treatment may reverse these conditions.

Recurrent stroke occurs frequently.[6,7,8,58] The immediate period after a stroke carries the greatest risk for early recurrence.

ELEVATED ICP

Deaths during the first week after stroke are commonly caused by brain edema and an elevated ICP, which are largely complications of major intracranial artery occlusion and large multilobar infarctions. Only 10–20% of patients develop edema that produces clinical deterioration and warrant medical or surgical intervention. Initial symptoms from swelling occur at 3 through 5 days after stroke. They are usually not a problem within 24 hours of the ictus, except among persons with large cerebellar infarctions. Increased ICP can also result from acute hydrocephalus secondary to obstruction of cerebrospinal fluid (CSF) pathways by large cerebellar infarctions.

Development of signs such as decline in level of consciousness, new focal neurologic deficit or progression of the focal neurologic deficit, enlargement of the pupil ipsilateral to the affected hemisphere, corticospinal signs (such as weakness and hyperreflexia) on the side that was not initially affected by the stroke, new cranial nerve involvement, abnormal respiratory patterns, and sudden cardiovascular instability should prompt a thorough medical evaluation and urgent CT of the brain. Management of abrupt deterioration requires an ICU environment.

TREATMENT OF SEIZURES

About 10% of all stroke patients experience seizures from stroke onset until several years later.[41,42,44] Seizures after stroke are classified as early or late onset. In a large prospective multicenter study, 50–60% of the seizures occurred on the first day.[41] General tonic-clonic seizures are the most common. Given that most poststroke seizures are caused by a focal lesion, poststroke seizures are typically focal at onset.[45] Occasionally, seizure is caused by hyponatremia, hypocalcemia, or other dysmetabolic states; therefore, electrolyte levels and serum glucose must be tested. Drug toxicity must be ruled out. Cortical location is

among the most reliable risk factors for poststroke seizures. The only clinical predictor for seizures after ischemic stroke is the severity of the initial neurologic deficit.

Seizure can be associated with recurrent stroke and new intracranial bleeding; thus, an imaging study should be performed soon after the seizure stops and the patient is stable.

The treatment of poststroke seizures is no different from the approach to treatment of acuteonset seizures due to other cerebral lesions. Poststroke seizures usually respond well to a single antiepileptic drug.

Patients with solely cerebellar or deep subcortical lesions are at very low risk for seizures and need not be treated.

The choice of an anticonvulsant medication depends on the type and frequency of seizures, the route available for administration of medication, and any contraindication for the use of a specific drug. No controlled trials evaluating only poststroke seizures have been conducted to assess specific agents.

Patients with nonrepetitive generalized tonicclonic seizures can be treated with intravenous phenytoin, clonazepam, and diazepam. Both BP and HR should be monitored. Fosphenytoin sodium is a useful option in stroke patients because it causes less cardiotoxity than phenytoin.

In the absence of absolute predictors of post-stroke epilepsy, most physicians empirically place patients on prophylactic anticonvulsants such as phenytoin, clonazepam, valproic acid, felbamate, and carbamazepine depending on seizure type and medical history. The newer antiepileptic drugs (gabapentin, topiramate, and levetiracetam) are being touted as first-line agents for the elderly because of their effectiveness and favorable side-effect profiles.

For all antiepileptic drugs, the chief relevant dose-limiting adverse effect is sedation, particularly in the elderly stroke patient. Drug interactions are an important consideration as well (e.g. phenytoin with warfarin), since most stroke patients take multiple medications.

In a large series of patients with poststroke seizures, 9% had status epilepticus.[43]

There are no data about the value of prophylactic administration of anticonvulsants after stroke. Until such data become available, stroke patients who are seizure-free should not receive anticonvulsants after stroke.

ENDOCRINE DISORDERS

Severe electrolyte disturbances are rare in acute ischemic stroke.[53] Hyperglycemia or impaired glucose tolerance in the acute phase of stroke is a frequent finding.[53] Many patients with acute hyperglycemia do not have a prior history of diabetes. Hyperglycemia can be a response to a serious brain injury. Whether hyperglycemia in nondiabetic stroke patients is caused by stress is controversial. No data exist about the efficacy of treating an elevated blood glucose in improving the outcome of a stroke patient. Until there are more data to guide treatment, management of an elevated glucose in stroke patients should be similar to that of other persons with an elevated blood glucose. Prolonged hypoglycemia has adverse effects on injured brain tissue and should be avoided.

Syndrome of inappropriate antidiuretic hormone (SIADH) secretion may occur in a small proportion of patients: most cases are asymptomatic and require no treatment.

NUTRITIONAL SUPPORT

Since the early 1980s, the importance of nutritional support in patients with severe neurologic injury has been appreciated. Delays in the initiation of nutritional support can cause muscle atrophy, respiratory muscle weakness, and gastrointestinal atrophy. Most of the studies on nutrition and neurologic injury have

focused on head trauma, but recent studies are also reporting the same nutritional and metabolic requirement in patients with acute ischemic injury.

Decisions about feeding are among the most difficult to face those managing stroke patients. About one-fifth of patients with acute stroke are malnourished on admission to hospital. Moreover, a patient's nutritional status often deteriorates thereafter because of increased metabolic demands, which cannot be met due to feeding difficulties.[46,47] In a recent study, 32% of 162 patients admitted for stroke rehabilitation were undernourished.[48] Causes of poor nutritional intake include reduced conscious level, an unsafe swallow, arm or facial weakness, and poor mobility. Malnutrition is universally associated with poorer survival and functional outcomes.

Although many patients can safely handle protein and calorie deprivation for several days, nutritional support should not be delayed in patients who are not expected to tolerate oral intake for a prolonged period. Enteral feeding is preferred because it is easier, safer, and less expensive. Modalities of the nutritional assessment and the choice of enteral formulas should be determined by assessing body mass, nutritional state, and specific caloric needs. The collaboration of a nutritionist is helpful to establish such a plan. Attention should paid to meeting fluid requirements if patients are not on enteral feeding or intravenous fluid regimens. Intravenous hyperalimentation is rarely indicated.

Many patients with acute stroke will tolerate oral alimentation a couple of days following the ictus, especially when adequate behavioral, dietary, and medical management to reduce the risk of aspiration is initiated. However, eating difficulties are found in 80% of stroke patients admitted for rehabilitation.[48] Thus, the role of active management cannot be understated.

Although these measures probably improve nutritional parameters, it is unclear whether they improve patient's outcome. Also, the optimal timing, type, and method of enteral feeding is uncertain. Large randomized trials are now in progress to identify the optimum feeding policies for stroke patients.

DEEP VENOUS THROMBOSIS

Patients with acute stroke and impaired mobility are at high risk for deep vein thrombosis (DVT) and acute pulmonary embolism, especially when no acute antithrombotic therapy is administered. Estimated frequency of DVT in stroke patients ranges from 20 to 75%.[57,60] Most of the thrombi occur in the paretic limb. Therefore, daily attention should be given to the examination of the legs. Early mobilization helps lower the risk of DVT.

Prophylactic subcutaneous low-dose unfractionated heparin (LDUH), or low-molecular-weight heparin (LMWH), and the heparinoid danaparoid, have been shown to be protective against deep vein thrombosis in several studies.[57,59] More recent trials have confirmed these results, and demonstrated a slight decrease of fatal and nonfatal pulmonary embolism.[57,58,62] Preliminary data also suggest that treatment with low-dose heparin combined with aspirin is not associated with an excess risk of intracranial hemorrhage.[58] Aspirin alone was ineffective in reducing fatal or nonfatal PE in these studies. From these studies many physicians recommend the routine use of LDUH, LMWH, or danaparoid, except when absolutely contraindicated. It is unclear at what time treatment should be started and how long it should be maintained. Platelet count should be performed periodically. More clinical data are required in order to establish recommendations on this subject.

A combination of intermittent pneumatic compression boots or elastic (graduated compression) stockings, early mobilization, and adequate hydration is considered good practice in patients with ischemic stroke.[61] Symptomatic venous thromboembolism complicating stroke should be managed according to established guidelines.

GASTROINTESTINAL COMPLICATIONS

The reported incidence of serious gastrointestinal hemorrhage after acute stroke is low (<5%).[54,55] There is no evidence for increased risk in patients on antithrombotic therapy (however, this rate increases in patients treated by acute thrombolytic therapy, and the routine early use of aspirin may induce changes in the occurrence of gastrointestinal hemorrhage).[56] Thus, the routine use of prophylaxis of gastrointestinal hemorrhage is not recommended by most authors at this point. It is unclear whether certain subsets of patients, such as patients with prolonged use of a gastric feeding tube, could benefit from such a preventive treatment.

INFECTION RISK AND FEVER

Patients with acute stroke frequently have elevations in temperature.[50] Fever and acute focal neurologic dysfunction should alert the treating physician to the possibility of infection, particularly encephalitis. The primary infections noted in patients with acute stroke are pulmonary and urinary infections. The most common cause of hospital-acquired urinary tract infection is indwelling catheters. Fever in the first 48 hours is commonly due to atelectasis and signals the need for aggressive chest physiotherapy. Intravenous lines are removed within 48 hours in patients without complications. If possible, urinary catheters should be avoided and limited to the first several days of hospitalization. The use of condom catheters is preferable. Although, infrequent, fever may be of central origin; it should lead to blood, sputum, and urine cultures, and a careful physical examination. Treatment of radiographically evident pneumonia has been outlined previously. In some cases, deep vein thrombosis or pulmonary embolism result in unexplained hyperthermia.

There is growing evidence that fever or even mild hyperthermia is deleterious after an acute ischemic injury.[49,50] For patients with cerebral infarction and fever, with or without infection, normothermia should be maintained with antipyretics or cooling blankets.[51,52] Physical methods such as cooling blankets have been used with conscious stroke patients; however, this usually requires neurointensive care and pharmacologic treatment of shivering.[51] It is unclear whether a small temperature decrease achieved by pharmacologic means improves outcome.

MISCELLANEOUS ISSUES

Many stroke patients are incontinent, are unable to manage their excretory function, and/or to express their needs for contenence.[63] Indwelling catheters should be a last resort.

Renal function should be monitored. Age, pre-existent impaired renal function, pre-existent drug therapies, dehydration, urinary retention, the use of contrast agents, and nephrotoxic therapies such as aminoglycosides may account for most problems in this area. Appropriate imaging protocols, optimal hydration, frequent examination of the bladder, and careful drug administration can minimize the occurrence of renal failure.

Complications related to immobility occur already during the hyperacute phase. As a general rule, preventive strategies should begin as soon as possible after the stroke. In some difficult situations of intractable acute confusional state or agitated delirium, antipsychotic therapy can be considered.

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8.
Management of blood pressure in acute stroke

Philip Bath

DEFINITIONS

HYPERTENSION

Essential hypertension is defined by the World Health Organization as a systolic blood pressure >140 mmHg and, as such, includes around 40% of populations (depending on age) in the western world.[1] However, more than three-quarters of patients presenting with acute stroke have a blood pressure which exceeds this (Table 8.1); hence, this cutoff can be considered non-discriminatory and too low. A recent survey of stroke-interested physicians suggested a boundary of 200/110 mmHg in acute stroke,[2] a figure which would include less than 10% of patients (Table 8.1) and is therefore too high to be useful. Since the risk of a poor outcome after stroke starts to rise at blood pressure levels above 180/100 mmHg (see below[3–5]), this may be an appropriate and clinically useful working definition.

HYPOTENSION

Less attention has been paid to the issue of low blood pressure in acute stroke. Taking the pragmatic view used for defining hypertension above, a poor outcome after stroke appears to be associated with admission blood pressure levels below 120/80 mmHg, although this is present in less than 5% of patients (see Table 8.1).

INCIDENCE AND NATURAL HISTORY OF BLOOD PRESSURE IN ACUTE STROKE

HYPERTENSION

Blood pressure is elevated in 70–94% of patients with acute stroke,[4–7] depending on the definition used and population studied. Rapid falls in blood pressure occur over the first hours[8] and normotension is achieved in two-thirds of individuals over the first week.[6,9,10] In spite of this downward trend during the acute and subacute phase of stroke, great variations can occur from moment to moment (Fig. 8.1). As with most aspects related to blood pressure, the magnitude of decline is proportional to the initial level.[11] Persisting hypertension should be treated, e.g. with a diuretic or angiotensin-converting enzyme (ACE) inhibitor,[12–14]

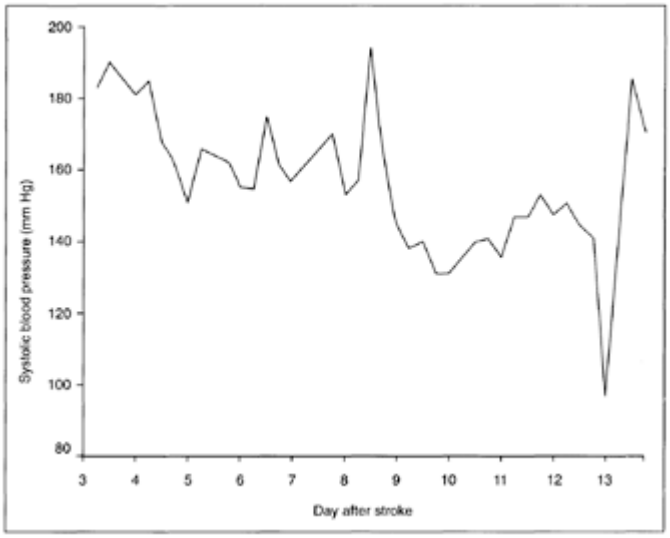

Figure 8.1 Incidence of blood pressure in acute stroke.

for the purposes of secondary stroke prevention; drug therapy should not be initiated or restarted for at least a week when stable levels are achieved.

Table 8.1 Frequency of systolic blood pressure at enrollment into acute stroke trials

Systolic blood pressure (mmHg)	International Stroke Trial[4] (%) (*n*=17 398)	Blood Pressure in Acute Stroke Collaboration[5] (%) (*n*=3470)
<120	4.2	4.7
120–139	14.2	17.5
140–159	27.9	29.4
160–179	26.1	25.9
180–199	16.9	14.7
>200	10.7	7.8

HYPOTENSION

A low blood pressure (systolic blood pressure <120 mmHg) is present in less than 5% of patients.[4,5] Although its natural history is not known, this is most likely to be determined by the underlying cause (see next section).

CAUSES OF HYPERTENSION AND HYPOTENSION IN ACUTE STROKE

Many factors are associated with hypertension, in particular stroke type (primary intracerebral hemorrhage, PICH) and a prior history of hypertension (Table 8.2).[15] Some factors are likely to be causative—such as activation of neurohormonal systems (corticotropic, sympathetic, renin- angiotensin) or reduced vascular

nitric oxide synthesis—and therefore offer potential and selective targets for treatment. Blood pressure control is modulated by a number of brain centers and it has been proposed that damage to one or more of these, especially the right insular cortex, might alter blood pressure;[16] more recent data suggest that this is not the case.[17]

Hypotension most commonly seems to be associated with the presence of concurrent conditions which themselves cause low blood pressure, especially heart disease or infection (Table 8.2).

BLOOD PRESSURE AND OUTCOME AFTER ACUTE STROKE

HYPERTENSION

Many studies,[3,18–22] but not all,[23–25] have shown that hypertension during the acute phase of ischemic or hemorrhagic stroke is associated with a poor outcome. Analysis of two large datasets, together involving almost 21 000 patients with acute ischemic stroke, reveals that a curvilinear relationship exists such that blood pressure above 180/100 mmHg is associated with a worse outcome assessed either as early

Table 8.2 Associations and possible causes of hypertension and hypotension in acute stroke

Hypertension
Age[11]
Race—black[89]
Primary intracerebral hemorrhage[89]
Previous hypertension[11,15,90]
Damage to vasomotor modulatory centers, e.g. insular cortex[16]
Stress of hospitalization (‘white coat hypertension’)
Activation of corticotropic (ACTH, cortisol) system[91–94]
Activation of sympathetic nervous system[91]
Activation of renin-angiotensin system
Low plasma nitric oxide levels[95]
Increased cardiac output[36]
Secondary to raised intracranial pressure (Cushing reflex)
Hypotension
Large cortical stroke (total anterior circulation syndromes)[4]
Heart disease (myocardial infarction, heart failure)[4,11]
Infection (septicemia, respiratory tract, urinary tract)

death, or late death, or dependency.[3–5] This link is independent of standard prognostic factors, including age, gender, stroke severity, stroke position (cortical vs lacunar), time to randomization, level of consciousness, and atrial fibrillation.[4]

These disparate findings have at least two explanations. First, the three neutral studies were all small and are likely to have suffered from a type 2 error (false-negative result). Secondly, studies employing both casual and beat-to-beat or 24-hour blood pressure readings have found that the first are relatively insensitive to the blood pressure-outcome relationship,[20,22] presumably because they suffer from considerable variation. The latter explanation would be particularly relevant to small studies.

Little research has been preformed on why a high blood pressure causes a worse outcome, but a number of putative explanations have been proposed (Table 8.3).[26] Of these, the most obvious is the relationship between hypertension and early recurrent stroke after cerebral infarction,[27] which mirrors the relationship between blood pressure and both first and recurrent stroke.[28,29]

Table 8.3 Mechanisms which may link blood pressure with outcome

Hypertension
Ischemic stroke
Recurrent ischemia[4,27]
Hemorrhagic transformation[26]
Cerebral edema[4,26]
Hemorrhagic stroke
Recurrent bleeding[31]
Hypotension
Recurrent ischemia[4]
Heart disease (myocardial infarction, heart failure)[4]
Infection (septicemia, respiratory tract, urinary tract)

Hypertension may also promote cerebral edema in patients with ischemic stroke,[4] and rebleeding in intracerebral hemorrhage.[30,31]

HYPOTENSION

Few studies have reported a link between hypotension and a poor outcome after ischemic stroke for two reasons: first, the proportion of patients with blood pressure below 120/80 is small, meaning that studies must be large; and, secondly, most investigators have assumed a pseudo-linear relationship based on the concept that outcome improves with lower blood pressure. Where investigators have allowed for three states (hypertension, normotension, and hypotension) it has become clear that hypotension is also associated with a poor outcome.[32] This is most apparent in data from the International Stroke Trial[4] and 'Blood Pressure in Acute Stroke Collaboration',[5] which suggest that outcome is worst in patients with systolic blood pressure <120 mmHg and/or diastolic blood pressure <70 mmHg.[3–5] The relationship between hypotension and outcome in primary intracerebral hemorrhage is unknown.

OTHER HEMODYNAMIC MEASURES

Functional outcome after stroke is not just related to absolute blood pressure levels but also to other hemodynamic measures, including beatto-beat blood pressure, blood pressure variability, pulsatility index, and heart rate.[22,33]

RELATIONSHIP BETWEEN BLOOD PRESSURE AND CEREBRAL PERFUSION

Cerebral perfusion is normally determined by local brain metabolic demands and is independent of systemic blood pressure except at very low or high levels, so-called cerebral autoregulation. Chronic hypertension is associated with a right shift of the perfusion/pressure curve so that perfusion is maintained at higher blood

pressures.[34] Following acute ischemic stroke or PICH, autoregulation is lost and perfusion becomes, all other things being equal, pressure-dependent.[35] This dysautoregulation usually settles over a period of a few weeks.[35]

In view of the above, it is commonly held that raising blood pressure will improve perfusion, and therefore potentially improve outcome, and lowering blood pressure will reduce it, thereby possibly worsening outcome. Unfortunately, this view is simplistic and takes no account of many factors, including the pathophysiological response to raising blood pressure, the magnitude and rate of blood pressure change, pial blood flow, and the agent being used. Co-morbid factors which alter hemodynamic function are also likely to be important, including cardiac output, atrial fibrillation, diabetes mellitus, and pyrexia.[26,36]

Evidence is also accruing that it is possible to lower blood pressure without compromising cerebral blood flow following acute ischemic or hemorrhagic stroke.[37–39]

MEASUREMENT OF BLOOD PRESSURE

Blood pressure is one of the most common physiological measures in clinical medicine and yet it is also one which is performed very poorly. Review of existing trials of vasoactive drugs in acute stroke reveals that little if no thought was given to the measurement of blood pressure, and that study reports rarely provide any information.[40] It is vital that current and future studies rectify this point through careful design and reporting. Important considerations need to be given to the following information:

- *Measurer:* who (nurse, doctor, technician), training, assessment, retraining and reassessment (and their interval).
- *Patient:* position (supine, sitting, standing), time of day, environment (ward, outpatient clinic).
- *Blood pressure equipment:* manufacturer, model, type (mercury, oscillometric), use (manual, semiautomatic).

EXPERIMENTAL STUDIES

ALTERING BLOOD PRESSURE

Inducing arterial hypertension in experimental animals may, in some situations, worsen cerebral edema associated with focal ischemia.[41,42]

CANDIDATE DRUGS

Several drugs which are candidates for treating stroke are vasoactive and have been tested in experimental models of ischemia. Nitric oxide donors (including sodium nitroprusside) reduce infarct lesion size although dramatic falls in blood pressure must be avoided, either by giving a pressor agent in parallel or by using low doses.[43–45] Similarly, some of these agents, as well as other vasoactive drugs such as propentofylline, maintain or improve cerebral blood flow in spite of their hypotensive effects.[44,46,47] In contrast, a systematic review of nimodipine in experimental stroke found no evidence of benefit,[48] mirroring the results of clinical studies.[49]

ARGUMENTS FOR RAISING BLOOD PRESSURE

Lost autoregulation and the possibility that raising blood pressure will improve perfusion, and thus outcome, is the main argument for this approach. Four case series, involving a total of 49 patients, have reported that elevating blood pressure—with noradrenaline (norepinephrine), metaraminol, levarterenol, or phenylephrine—can be beneficial.[50–53] Vasopressor therapy was also reported to be effective in reversing hemiplegia complicating cerebral arteriography in two patients.[54] Unfortunately, no published data from randomized controlled trials (RCTs) exists on the efficacy of raising blood pressure in acute ischemic stroke or PICH.[40,55] Indirect support for this approach comes from the observation that 'triple H' therapy, which includes inducing hypertension,[56] may be beneficial in patients with subarachnoid hemorrhage, although the overall effectiveness of this approach in this form of stroke has yet to be confirmed.[57] However, trials in acute ischemic stroke where hypervolemic hemodilution was induced (and where blood pressure is likely to have increased) did not find benefit for this intervention.[58]

ARGUMENTS AGAINST RAISING BLOOD PRESSURE

Severe hypertension is associated with forced vasodilation, cerebral edema, capillary vasoconstriction, and ultimately in hypoperfusion, thereby presenting clinically as infarct extension or reinfarction. This sequence of pathophysiological events is found in hypertensive encephalopathy and could occur if blood pressure is elevated during acute ischemic stroke. Hypertension could also promote bleeding, manifest as hemorrhagic transformation in ischemic stroke, and rebleeding or hematoma enlargement in patients with PICH.[30,31]

Acute stroke is associated with a raised cardiac output[36]and the propensity for cardiac dysrhythmias. Inotropes will exacerbate these, and thence the risk of myocardial ischemia and heart failure.

Two agents which raise blood pressure, although this was not their intended effect, have been assessed in RCTs in acute ischemic stroke and had unfavorable effects on outcome. Diaspirin cross-linked hemoglobin (DCLHb), a hemoglobin-based oxygen carrier, raised blood pressure and increased early death.[59] Similarly, the development of aptiganel, an NMDA antagonist which raises blood pressure,[60] has ceased in stroke; the exact reasons are unclear since phase III data have yet to be published.

Pressor agents such as phenylephrine, ephedrine, and phenylpropanolamine are sympathomimetic amines and therefore promote vasoconstriction (the mechanism by which they elevate blood pressure) and platelet aggregation. Neither property would seem beneficial in acute ischemic stroke, since both could cause reinfarction, and yet this class of drugs have been used to elevate blood pressure in stroke patients.[50–53] Nevertheless, they may cause stroke (subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke and transient ischemic attack) as has already been shown in fit subjects when used as appetite suppressants or decongestants.[61,62]

ARGUMENTS FOR LOWERING BLOOD PRESSURE

Hypertension at admission is an independent prognostic factor for death or a poor functional outcome, as detailed above. Furthermore, hypertensive patients with acute ischemic stroke are at increased risk of suffering early recurrence and cerebral edema according to observational data from the International Stroke Trial.[4,27] Several case series, describing either ischemic stroke (481 patients) or primary intracerebral hemorrhage (254 patients) suggest that lowering blood pressure (with a large variety of agents) may be beneficial.[19,63,64] Indirect evidence comes from the NINDS trial of alteplase,[65] where blood pressure was lowered in some patients either before, during, or immediately after thrombolysis, as thought clinically

relevant. However, it remains unclear what effect this strategy might have had on the positive findings of this trial.[66,67]

No large RCTs have assessed the safety and efficacy of lowering blood pressure[40,55] and there are only a handful of phase II trials which have tested, or are testing, the effect of vasodepressors (Table 8.4).[37,40,68]

ARGUMENTS AGAINST LOWERING BLOOD PRESSURE

Since cerebral autoregulation is lost during acute stroke and perfusion becomes, at least in part, pressure dependent, lowering blood pressure might be expected to worsen outcome (see above). Case series, involving 8 patients, have suggested that blood pressure reduction is associated with a worsening in outcome.[69,70] However, the strongest arguments against lowering blood pressure come from some trials in acute stroke involving vasoactive drugs, in particular calcium antagonists and beta-receptor antagonists (see next section).

Table 8.4 Drugs for elevating and lowering blood pressure in acute stroke

Drug	Potential detrimental effects	Effect on outcome
Lower BP		
Alpha blockers		Not known
Angiotensin II receptor antagonists (candesartan, losartan)		Two ongoing studies[78,96]
Angiotensin-converting enzyme inhibitor (captopril, perindopril)	Maintain global CBF[37]	
Beta-receptor antagonists (atenolol, propranolol)	Negative inotropes	Neutral/worse[72]
Calcium channel blockers (nimodipine, lifarizine)	May reduce regional CBF.[85] Significant BP lowering associated with a worse outcome after ischemic stroke[73–75,97]	Neutral/worse[49]
Diuretics	Can cause hemoconcentration and dehydration	Not known
Nitric oxide (glyceryl trinitrate, sodium nitroprusside)	Maintains regional CBF.[38] Donors may, or may not, have antiplatelet effects.[38,68] Used in alteplase trials.[65,66,98]	Not known
Dextrorphan	Induces adverse central events, e.g. stupor, apnoea[99]	
Trafermin	Leucocytosis	Neutral[100]
Raise BP		
Corticosteroids	Complicated by hyperglycemia, infection, gastrointestinal bleeding[101]	Neutral[101]
Hemodilution	Used in SAH[57]	Neutral[58]
Sympathomimetics (levarterenol, metaraminol, noradrenaline (norepinephrine), phenylephrine)	Inotropes can induce cardiac ischemia and dysrhythmias. Activate platelets. Vasoconstrictors might worsen cerebral perfusion	No trials

BP, blood pressure; CBF, cerebral blood flow; SAH, subarachnoid hemorrhage.

WHICH DRUGS SHOULD WE USE TO ALTER BLOOD PRESSURE

RAISING BLOOD PRESSURE

Pressor agents which could in principle be used for raising blood pressure include, amongst others, sympathomimetics, angiotensin, endothelin, and nitric oxide synthase inhibitors (Table 8.4). These drugs are either positive inotropes, vasoconstrictors, or both. Whether they should be used to raise blood pressure in ischemic stroke is, however, questionable for several reasons. First, they will tend to promote cardiac ischemia, an important cause of death after stroke, in a population who are already likely to have clinical or occult ischemic heart disease. Secondly, positive chronotropic agents will tend to facilitate cardiac dysrhythmias. Thirdly, vasoconstrictors with cerebral activity may reduce perfusion. Lastly, many sympathomimetics promote platelet activation. If blood pressure must be raised, it may make most sense to use chrononeutral vasodilating inotropic agents such as dobutamine, dopexamine, or low-dose dopamine, although even these are not totally immune from the above problems. We are currently performing a phase II trial with dobutamine in acute ischemic stroke.[40]

LOWERING BLOOD PRESSURE

No significant differences exist between antihypertensive drug classes in the primary prevention of stroke and myocardial infarction.[71] In contrast, it appears that all classes are not equal in acute stroke. Both calcium channel blockers and beta-receptor antagonists have been tested, although not for their hypotensive properties, and been associated with a worse outcome (see Table 8.4).[72–75] The INWEST trial found that outcome was worst in those patients treated at a higher dose of nimodipine and who had a 20% or greater fall in blood pressure.[74,76]

Limited data suggest that ACE inhibitors and nitric oxide donors can lower blood pressure without compromising cerebral blood flow.[37,38,68] Interestingly, these results do not fit in with a theoretical argument that cerebral vasodilators (nitric oxide donors but not ACE inhibitors) should not be given since they may compromise cerebral perfusion by increasing intracranial pressure.[77] Furthermore, it can be argued that cerebroactive drugs might be especially useful if they improved penumbral perfusion.

No published data exist for alpha-adrenergic receptor antagonists, angiotensin receptor antagonists,[78] diuretics, or centrally acting drugs such as methyldopa or moxonidine. Many antihypertensive agents are probably unsuitable for use in PICH since they have antiplatelet properties, e.g. calcium channel blockers and sodium nitroprusside.[38]

CONTINUING OR STOPPING PRE-STROKE ANTIHYPERTENSIVE MEDICATION?

Around 50% of patients with acute stroke are admitted on antihypertensive medication and the question arises as to what should be done with this. In a recent survey, almost three-quarters of responders reported that they continued such medication with the other one-quarter stopping it.[2] This variation is also reflected by practice in clinical studies where some patients continue medication,[79] while others stop it.[37,68] No completed trials have yet addressed whether outcome is altered by stopping or continuing antihypertensive drugs,[80] although the ENOS trial has factored this question into its design.[81,82]

WITHDRAWING ANTIHYPERTENSIVE THERAPY DURING THE SUBACUTE PHASE

Only one trial has assessed the effect of withdrawing antihypertensive therapy once it has been initiated following stroke onset.[83] Nifedipine, clonidine, furosemide, and/or acetazolamide were given to 112 hypertensive patients with acute ischemic stroke. They were then randomized to continue or stop this medication after 3 days. No difference in functional outcome or death were observed at 1 month[83] although the trial was underpowered to answer this question. However, the relevance of this question has largely disappeared since it is now known that lowering blood pressure in the chronic phase after ischemic and hemorrhagic stroke is an important form of secondary prevention.[12–14]

RANDOMIZED CONTROLLED TRIALS

In comparison with other areas of acute stroke management, the question of how to manage blood pressure has attracted little interest. Nevertheless, several RCTs have been completed, and others are underway or planned (Table 8.5). Some of these studies are large enough to provide information on the effect of altering blood pressure on outcome and should inform future practice. However, these trials have largely focussed on lowering blood pressure, leaving one issue underresearched—namely, whether blood pressure should ever be elevated, especially if it is low.

EFFECTS OF CHANGING BLOOD PRESSURE ON SURROGATE MEASURES OF OUTCOME AND EFFICACY

It is evident that any trials of vasoactive drugs in acute stroke should be paralleled by studies assessing the effect of these agents on regional cerebral perfusion, assessed using semiquantitative techniques such as position emission tomography (PET), single-photon emission computed tomography (SPECT), perfusion magnetic resonance (MR), or xenon computed tomography (CT). Few studies have been performed to date[84] but perindopril (an ACE inhibitor) and sodium nitroprusside (a nitric oxide donor), given at doses which reduce blood pressure by 10%, do not appear to reduce perfusion in ischemic stroke.[37,38] In contrast, calcium channel blockers may worsen cerebral blood flow in parallel with their hypotensive effect.[85] No assessment of the effect of pressor agents on cerebral perfusion have been reported in acute stroke.[84]

Since almost all vasoactive drugs have collateral effects (see Table 8.3), it is also vital that these are also assessed in future studies. Of particular importance is hemostasis, since drugs with antiplatelet activity (e.g. sodium nitroprusside[38]) should not be used in PICH, whereas those which activate platelets (e.g. sympathomimetics) should be used cautiously, if at all, in any type of stroke.

GUIDELINES

Until definitive trial (level 1) data become available, guidelines built on expert opinion and the limited results of case series and observational studies should inform clinical practice. Nevertheless, these are, as a group, inconsistent with each other, as shown in Table 8.6.

CONCLUSIONS

If the past few years have seen the treatment of acute stroke focus on thrombolysis and neuroprotection, a future emphasis will be on the management of physiological variables, especially blood pressure. Repeated

calls have been made for large trials in this area and yet these are now only just starting. The design of such trials is complex since blood pressure could be raised or lowered on the basis of opposing pathophysiological arguments. Parallel studies will need to assess collateral effects of vasoactive drugs, especially on cerebral perfusion and hemostasis. While such trials are underway, blood pressure should be managed according to published guidelines.

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Table 8.5 Completed, ongoing, and planned trials assessing the effect of altering blood pressure in acute or subacute stroke

Intervention, treatment period, trial acronym	Patients/ centers	Stroke type, time window	BP inclusion (mmHg)	Prior antihypertensive hypertensive medication	Aim, outcome	Status
Candesartan 7 days (or longer if BP remains high), ACCESS	500/60–70	Ischemic,	SBP>200 and/ or DBP>110	?	Lower BP, MRS at 12 months	Ongoing[78,108]
Dobutamine (intravenous) 2 hours	24/1	Ischemic, <96 hours	100<SBP<180 60<DBP<110	Stop	Raise BP, BP at 2 hours	Ongoing[40]
Glyceryl trinitrate (transdermal) 12 days	37/1	Ischemic, PICK <120 hours	Any	Stop	Lower BP, BP at day 1	Completed[68]
Glyceryl trinitrate (transdermal) 10 days	90/1	Ischemic, PICH <72 hours	Any	Stop	Lower BP, BP at 7 days	Completed[40]
Glyceryl trinitrate (transdermal) 7 days, ENOS	5000/100+	Ischemic, PICH <48 hours	140<SBP<220	Randomize to stop or continue	Lower BP, MRS>2 at 3 months	Ongoing[81,82]
Losartan (?) (?)	24/1	Ischemic 36–168 hours	DBP>90	?	Lower BP, Cerebral perfusion, renal function	Completed[96]
Perindopril (oral)	24/1	Ischemic 48–168 hours	170<SBP<250 95<DBP<120	Stop	Lower BP, Global cerebral blood flow	Completed[37]

BP, blood pressure; DBP, diastolic blood pressure; MRS, modified Rankin score; PICH, primary intracerebral hemorrhage; SBP, systolic blood pressure.

Table 8.6 Published guidelines for the management of blood pressure in acute ischemic stroke

Patient group	Recommendation	Guideline (Ref)
Coexisting hypertensive encephalopathy, heart failure or ischemia, aortic dissection, or continued intracerebral bleeding	Reduce blood pressure	102–105
Other stroke patients	Do not lower BP	86,103
Other stroke patients	Reduce BP if SBP>200 or SBP>220, MBP>130, or DBP>120–130	69,70,104,106
Other stroke patients	Do not reduce SBP below 160 mmHg	107
Other stroke patients	Do not reduce MBP by more than 20%	70
Other stroke patients	Do not reduce DBP below 110 mmHg	105
Previously normotensive stroke patients	Reduce MBP to <120 mmHg	102
Previously hypertensive stroke patients	Reduce MBP to 130–140 mmHg	102

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure=DBP+((SBP–DBP)/3).

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FURTHER READING

The following reviews extend discussion on this topic: Refs 26, 55, 77, 86–88.

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9.
Reopening occluded cerebral arteries

James F Meschia and Thomas G Brott

INTRODUCTION

Intravenous tissue plasminogen activator (t-PA) was approved in the United States for treating acute ischemic stroke within 3 hours of onset of symptoms in June 1996. Since then, there have been substantial improvements in neuroimaging. Additional randomized clinical trials of recanalization pharmacotherapies administered intravenously, intra-arterially, or by sequential intravenous-intraarterial routes have also been completed. Despite this growth in our understanding of thrombolytic therapy, there has yet to be approval of a second agent for treating acute ischemic stroke or broadening of the indications for use of t-PA in patients with stroke.

RATIONALE FOR THROMBOLYSIS

EXPERIMENTAL STUDIES AND EFFICACY OF THROMBOLYSIS

Intravenous tissue plasminogen activator was first isolated in pharmacological quantities in 1984.[1] Zivin et al. reported the first studies of t-PA in animal models of ischemic stroke.[2] Using a fragmented clot model in rabbits, they demonstrated improved neurologic outcome in animals treated with t-PA compared with those treated with placebo. Clot lysis was possible within 15 min of t-PA administration. Initiation of therapy could be delayed up to 45 min after embolization and still show efficacy. No benefit was seen when treatment was further delayed to 60 min.

In rodent models of embolic stroke, t-PA decreased infarct volume and mortality.[3,4] In a canine model of ischemic stroke, streptokinase given at 5 min, but not at 30 min, after embolization resulted in normalization of hemispheric blood flow, oxygen consumption, and oxygen extraction.[5] Treatment with intracarotid urokinase in a baboon model improved neurologic outcome,[6] but treatment with intravenous t-PA did not.[7] These studies and others demonstrated the efficacy of a variety of thrombolytic agents in a variety of species under variable experimental conditions.

CLINICAL ANATOMY OF THROMBI

Thrombolytic agents should only be effective for stroke if there is a thrombus occluding a cerebral vessel appropriate for the presenting symptoms when treatment is initiated. The frequency of such occlusive thrombi in acute ischemic stroke was addressed directly by several angiographic studies (Table 9.1).[8–11] These studies suggested that about 75% of patients with acute ischemic stroke have an angiographically detectable

thrombus. Most thrombi were large, and over 10% were tandem—e.g. the internal carotid artery (ICA) and ipsilateral middle cerebral artery (MCA) trunk. The rate of detectable thrombus in acute angiographic studies may not be representative of the rate of detectable thrombus in all patients. Early clinical presentation and early angiography are more frequently performed in cases of patients with severe neurologic deficits who develop symptoms in the presence of a spouse or bystander. Nonetheless, the findings of acute angiography studies may apply to a patient population amenable to early clinical evaluation and treatment.

Absence of an angiographic filling defect does not definitively exclude the presence of thrombus. One can only visualize the major cerebral arteries and their larger branches on conventional angiography. Some clots may be large enough to cause infarction but too small to be detected on angiography. Angiographically based studies of thrombolysis for ischemic stroke have not treated patients who lack visible clot on angiography.

Table 9.1 Presence and location of thrombi in acute ischemic stroke

Study (Ref)	No. of patients	Time of angiography (h)	Percentage with occlusion (%)[a]	Percentage of occlusions, ICA (%)[b]	Percentage of occlusions MCA stem (%)[b]
Fieschi et al.[10]	80	<6	76	23	33
Wolpert et al.[11]	139	<8	81	28	48
Del Zoppo et al.[8]	80	<6	74	N/A	50 (M1 or M2)
Lewandowski et al.[9]	34	3.0–3.3 median	65	N/A	N/A

N/A, not available.

[a] Inclusion and exclusion criteria differed among studies.

[b] No exclusive category, as some patients had tandem occlusions of the internal carotid artery (ICA) and middle cerebral artery (MCA).

Therefore, evidence is not available as to whether the rate of improvement in angiogram-negative patients might be high enough to suggest the presence of a thrombus in such patients. In addition, thrombolytic agents could have a beneficial effect if microvascular flow were altered, even in the absence of a macro-thrombus.

The National Institute of Neurological Disorders and Stroke (NINDS) t-PA study suggests that in-situ thrombosis or the lodging of acute emboli in small cerebral arteries or arterioles causes small-vessel infarction.[12] Stroke patients classified as having small-vessel infarction who were randomized to t-PA had significantly better outcomes at 3 months compared with those randomized to placebo. Patients with cardioembolic and atherothrombotic—atheroembolic strokes, types closely associated with arteriographically detectable clots, also had better outcomes following t-PA treatment, but efficacy was not superior for these stroke subtypes than for small-vessel venous infarcts.

COMPOSITION OF CEREBROVASCULAR THROMBI

Thrombolytic agents have been demonstrated experimentally to be superior for dissolution of fresh thrombi as compared to old thrombi.[13] Similar experiments suggest better dissolution of platelet-poor than platelet-rich thrombi.[14] Masuda et al. found emboli in a postmortem series to be composed of cholesterol crystals, platelets, red blood cells, and fibrin.[15] In a postmortem study of patients with emboli who died following

thrombolytic treatment, 3 of 12 patients had emboli described as 'fibrin-poor'.[16] Fibrin-poor emboli have also been reported in the setting of embolization to the retina.[17] Retinal studies are instructive as they demonstrate the heterogeneity of emboli. Platelet, fibrin, calcium, and cholesterol emboli are the common types identifiable by fundoscopic appearance. Organisms, fat, air, and foreign bodies may also embolize to brain and retina.

DYNAMICS OF CEREBROVASCULAR THROMBI

Spontaneous recanalization of acute thrombi is the common in the setting of acute stroke,[10] but recanalization usually occurs many hours or days after onset of symptoms. Several protocols have included serial angiography. In the study of intraduteplase by Mori et al.,[18] which included patients with carotid territory artery occlusion shown by arteriography within 6 hours of onset of symptoms, none of the 12 placebo-treated patients demonstrated complete recanalization at the time of the second arteriogram taken 60 min later, and two patients had partial recanalization. In a study by Yamaguchi et al, a baseline arteriogram was performed within 6 hours of onset of symptoms, and a second arteriogram was performed 60 min later.[19] The complete or partial recanalization rate for the 47 placebo-treated patients was 4.3%. In PROACT, the second angiogram in placebotreated patients showed a spontaneous recanalization rate of 14%.[8] Fieschi et al. reported a series of 80 ischemic stroke patients studied within 6 hours of symptoms onset with arteriography.[10] Fifteen patients with isolated occlusions of the MCA stem were studied again with either transcranial Doppler ultrasound (TCD) (n=8) or another arteriogram. Spontaneous recanalization was demonstrated for 10 of the 15 patients studied by TCD and five of the 8 patients studies with two arteriograms.

The mechanism of spontaneous recanalization is not known. Presumably, endogenous t-PA activates fibrin-bound plasminogen on the surface of the thrombus. A relationship of endogenous t-PA concentrations to spontaneous lysis has not been studied.

THROMBOLYTIC AGENTS IN USE OR UNDER CLINICAL INVESTIGATION

RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

Recombinant tissue plasminogen activator (alteplase, t-PA) is naturally synthesized and secreted by human endothelial cells. It occurs as either a single- or a double-chain polypeptide. The single chain contains 527 amino acid residues and has a molecular weight of 70,000 daltons (70 kDa). The two-chain form results from restrictive proteolytic cleavage of the singlechain form: tissue plasminogen activator is produced for clinical use by recombinant DNA techniques. The most widely used commercial preparation is the single-chain form, alteplase. Tissue plasminogen activator is a serine protease with a high affinity for fibrin, which 'targets' the enzymatic activity of t-PA to the clot.[20] When t-PA is bound to fibrin, the lytic activity of t-PA increases 400-fold.[21] In the absence of fibrin binding, t-PA has very limited capability for plasminogen activation, so consumption of circulating fibrinogen is minimized.

The primary regulator of t-PA activity is plasminogen activator inhibitor. Plasminogen activator inhibitor type 1 (PAI-1) rapidly inhibits t-PA in circulation, but PAI-1 slowly inhibits fibrin-bound t-PA.[22] Plasmin activator inhibitor type 1 inhibits t-PA by forming a stable one-to-one stoichiometric complex: it is a 45 kDa protein found in platelets. Whereas about 90% of the concentration of PAI-1 in circulating platelets is latent, in platelet-rich clots PAI-1 can be abundant enough to significantly inhibit t-PA activity. The presence of platelet PAI-1 may be one explanation for the resistance of platelet-rich thrombi to lysis.[23,24]

Rapid clearance of t-PA occurs largely through the liver.[25] The serum half-life of t-PA is about 4–6 min.[25] The half-life of t-PA in circulation can be extended greatly if it is bound to fibrin on clots because the primary inactivating sites are sequestered.

UROKINASE

Like t-PA, urokinase is a serine protease that directly activates plasminogen to plasmin. Urokinase is primarily a double-chain molecule with a total molecular weight of 54 kDa.[26] It does not have fibrin specificity in that it activates circulating and fibrin-bound plasminogen at equal rates. Accordingly, high concentrations of urokinase may deplete plasminogen, fibrinogen, alpha II antiplasmin, and coagulation factors V and VIII.

PRO-UROKINASE

Pro-urokinase (pro-UK) is the inactive single-chain precursor of urokinase which has been isolated from urine, plasma, and cultured cells.[27] Prourokinase has intrinsic plasminogen activating potential, but its efficiency is about 100-fold less than that of urokinase: it undergoes proteolytic activation by plasmin or kallikrein and has significant fibrin specificity, which may result from preferential conversion of pro-UK to urokinase at the fibrin surface.[28]

STREPTOKINASE

Clinical thrombolysis began in 1933 when Tillet and Garner reported that streptococci released a substance that dissolved blood clots.[29] Like proUK, streptokinase exhibits little or no intrinsic enzymatic activity. Streptokinase is a singlechain protein with a molecular weight of 47 kDa which forms a one-to-one stoichiometric complex with plasminogen. It is this streptokinaseplasminogen complex that activates plasminogen to plasmin. Like urokinase, streptokinase is not fibrin-specific. High circulating concentrations of streptokinase can deplete plasminogen, fibrinogen, alpha II antiplasmin, and coagulation factors V and VIII. Such depletion characterizes the lytic state, which may cause hemostatic failure. Depletion of platelet-bound fibrinogen may also occur, thereby interfering with platelet aggregation.

TENECTEPLASE

Tenecteplase is a fibrin-specific variant of tissue plasminogen activator with a long half-life.[30] Tenecteplase has fibrin specificity compared to alteplase for lysis, but has eight-fold less activity in the absence of fibrin than t-PA.[31] This results in at least an order of magnitude less potential for fibrinogen depletion in human plasma compared with t-PA. Tenecteplase may also be more potent with regard to lysis. In a rapid arteriovenous shunt model of clot lysis, tenecteplase was 7.5–13.5 times more potent than t-PA. Tenecteplase is about 90-fold more resistant to PAI-1, the primary inhibitor of t-PA. A pilot safety study of tenecteplase as treatment for ischemic stroke is in progress.

INTRAVENOUS THROMBOLYSIS

LARGE RANDOMIZED TRIALS OF T-PA

PART 1 OF NINDS T-PA STROKE STUDY

The NINDS t-PA study was conducted in two parts (see Table 9.2).[12] Part 1 was designed to test early clinical efficiacy. The primary endpoint was the proportion of patients with early improvement defined as complete resolution of neurologic symptoms at 24 hours, or improvement in the National Institutes of Health stroke scale (NIHSS) of γ4 points. Patients were randomized to receive either t-PA (0.9 mg/kg intravenously over 60 min, with 10% of the dose as a bolus; maximum dose, 90 mg) or placebo. Patients with all types of ischemic stroke were eligible provided that they could be randomized and treated within 180 min of symptoms onset. The principal exclusion criteria are listed in Table 9.3. At any given center, the number of patients in the 91–180 min group could never exceed the number of patients in the 0–90 min group by more than two. A total of 291 patients were randomized. Sixty-seven (47%) of the 144 patients randomized to t-PA had early improvement compared with 57 (39%) of the 147 patients randomized to placebo (relative risk 1.2, p=0.21). A post-hoc comparison of the median NIHSS scores at 24 hours showed a median score of 8 for the t-PA group and 12 for the placebo group (p<0.02). Symptomatic intracerebral hemorrhage occurred in 8 (6%) of the t-PA-treated patients and none of the placebotreated patients.

PART 2 OF NINDS T-PA STROKE STUDY

At the time of the final interim analysis of the results, Part 1, the Data and Safety Monitoring Committee determined that the 3-month outcome measures favored the t-PA treatment group. Accordingly, they recommended that a second trial be performed, Part 2, which would proceed with identical randomization procedures, eligibility criteria, and drug dosing but which would address the different primary hypothesis that there would be a consistent difference between the t-PA and placebo groups in the proportion of patients who recovered with minimal or no deficit 3 months after treatment. Recovery with minimal or no deficit was defined as an NIHSS score of 0 or 1, a Barthel index (BI) of 95 or 100, a modified Rankin scale (mRS) of 0 or 1, and a Glasgow outcome scale of 1 (see Table 9.2), computed as a global endpoint.[12]

Table 9.2 Randomized trials of intravenous tissue plasminogen activator for acute ischemic stroke

Study	No. of patients	Time window (h)	Treatment groups	Results
NINDS Part 1[12]	291	0–3	IV t-PA at 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus followed by remaining dose over 60 min versus placebo	No difference in rates of improvement in NIHSS at 24 hours
NINDS Part 2[12]	333	0–3	IV t-PA at 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus followed by remaining dose over 60 min versus placebo	The odds ratio for a favorable outcome at 3 months after stroke was 1.7 (95% CI 1.2–2. 6; p=0.008). Favorable outcome was defined using a global endpoint derived from NIHSS, mRS, BI and GOS

Study	No. of patients	Time window (h)	Treatment groups	Results
ECASS[35]	620	0–6	1.1 mg IV t-PA versus placebo	No difference in BI or mRS at 90 days (primary endpoint; ITT analysis)
ECASS II[36]	800	0–6	IV t-PA at 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus followed by remaining dose over 60 min versus placebo. Subcutaneous heparin permitted in first 24 hours	No significant difference in favorable mRS at 90 days with mRS dichotomized at 1–2 (primary endpoint). t-PA group had a significantly higher rate of favorable outcome with mRS dichotomized at 2–3
ATLANTIS[41]	613	3–6	IV t-PA at 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus followed by remaining dose over 60 min versus placebo	No significant difference in the proportion of patients achieving NIHSS of 0 or 1 at 90 days (primary outcome measure). The rates at 10 days of symptomatic and fatal ICH were greater in the t-PA group
TTAIST[42]	142	0–6	IV t-PA at 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus followed by remaining dose over 60 min versus placebo	4-point NIHSS improvement at 24 hours was significantly greater in the t-PA group, but rate of 4-point NIHSS improvement was significantly less in the t-PA group at 30 days

BI, Barthel index; GOS,Glasgow outcome scale; ICH, intracerebral hemorrhage; ITT, intent-to-treat; IV, intravenous; mRS, modified Rankin scale; NIHSS, NationalInstitutes of Health stroke scale; t-PA, tissue plasminogen activator.

Three hundred and thirty-three patients were randomized to receive t-PA or placebo, and 163 (49%) were randomized within 90 min of symptom onset. Outcome at 3 months favored the t-PA-treated patients for each of the four outcome measures. The t-PA treated patients were 32–55% more likely to recover with minimal or no deficit by the four measures compared with the placebo-treated patients. Absolute differences in the rates of good outcomes in the t-PA and placebo groups were 11–13%, implying that about 8–9 patients would need to be treated to have one additional patient recover with minimal or no deficit.Symptomatic hemorrhage occurred in 12 (7%) of the t-PA-treated patients compared with 2 (1%) of the placebo-treated patients.

Table 9.3 National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) stroke study exclusion criteria

Clinical exclusion criteria

Stroke or head trauma within the preceding 3 months

Major surgery within 14 days

Any history of intracranial hemorrhage

Systolic blood pressure above 185 mmHg

Diastolic blood pressure above 110 mmHg

Rapidly improving or minor symptoms
Symptoms suggestive of subarachnoid hemorrhage
Gastrointestinal hemorrhage or urinary tract hemorrhage within 21 days
Arterial puncture at a noncompressible site within 7 days
Seizure at the stroke onset
Radiological exclusion criterion
No evidence of intracranial hemorrhage on computed tomography (CT) of the brain
Laboratory exclusion criteria
Patients taking anticoagulants with a prothrombin time greater than 15 s
Patients receiving heparin within 48 h and an elevated partial thromboplastin time
Platelet count below 100 000
Blood glucose level below 50 mg/dl (2.7 mmol/1)
Blood glucose level above 400 mg/dl (22.2 mmol/1)

COMBINED RESULTS OF PART 1 AND PART 2 OF NINDS T-PA STROKE STUDY

The US Food and Drug Administration (FDA) acute treatment for stroke. In the combined considered the NINDS t-PA Stroke Study as two separate trials when it approved t-PA as an analysis, the benefits of t-PA at 3 months were demonstrated for each of the four outcome measures. No pretreatment characteristics significantly altered response to treatment.[32] The overall symptomatic hemorrhage rate was 6.4% for the t-PA-related patients compared with 0.6% in the placebo-treated patients ($p<0.001$). However, mortality at 3 months was 54 (17%) of 312 t-PA-treated patients and 64 (21%) of the 312 placebo-treated patients ($p=0.30$), indicating that mortality was not higher in the t-PA group despite the excess of symptomatic hemorrhage. Using the two lowest categories on the four outcome scales as a measure of severe disability and death, there was not an excess of patients with severe disability or death in the t-PA group. The beneficial effects of t-PA were shown to be durable up to 12 months after stroke.[33] An exploratory analysis suggested that earlier treatment was associated with better outcomes.[34]

EUROPEAN CO-OPERATIVE ACUTE STROKE STUDY

The European Cooperative Acute Stroke Study (ECASS) was a randomized, prospective, multicenter, double-blind, placebo-controlled trial of t-PA (alteplase) as treatment for acute ischemic stroke (see Table 9.2).[35] Patients with acute hemispheric ischemic stroke who could be treated within 6 hours from the onset of symptoms were randomized to receive intravenous 1.1 mg/kg of alteplase (1.1 mg/kg over 60 min with 10% as bolus) or placebo. Administration of heparin, oral anticoagulants, hemorheological agents, and brain protective substances were prohibited during the first 24 hours. Patients were excluded if they had very severe or mild neurologic deficit or were already improving. The protocol called for exclusion of patients with more than 33% of MCA territory showing major early infarct signs on the baseline computed tomography (CT) scan. Early infarct signs included diffuse sulcal effacement, parenchymal hypodensity, and loss of gray —white differentiation. The first hypothesis was that there would be a difference between the t-PA-treated and the placebo-treated groups in the activities of daily living, defined as a difference of 15 points on the BI at 90 days after treatment. The second hypothesis was that there would be a difference between the t-PA and the placebo groups in the global clinical impression, defined as a difference of one grade on the mRS at 90 days after treatment.

Investigators enrolled 620 patients between 1992 and 1994. In the intent-to-treat analysis, there was no statistically significant difference in either of the two primary endpoints (see Table 9.2). To derive the target population, 109 patients were excluded from the intent-totreat group: 66 for abnormalities on CT scan, 52 for major early infarction, 2 for primary hemorrhage, and 12 for an unavailable or unreadable CT. For the 511 remaining patients in the target population, there was no statistically significant difference in the BI between the t-PA and placebo groups at 90 days after treatment. For the mRS, the difference significantly favored the t-PA group. The median score at 90 days was 2 for the t-PA group and 3 for the placebo group (p=0.035). Mortality at 30 days was not significantly different (17.9% for the t-PA-group and 12.7% for the placebo group). Mortality at 90 days was 18.9% in the t-PA-treated patients compared with 15.8% in the placebo-treated patients (p=0.04). Parenchymal hematoma was more common in the t-PA group, occurring in 19.8% compared with 6.5% for the placebotreated patients (p<0.001). ECASS investigators noted that protocol violation in the group treated with alteplase led to poor 7-day survival. They attributed this in large part to treatment of patients with signs by CT scan of major cerebral infarction.

SECOND EUROPEAN-AUSTRALASIAN ACUTE STROKE STUDY

In the second European-Australasian Acute Stroke Study (ECASS II), 800 patients were randomized to alteplase or placebo at 108 centers in 14 European countries and Australia and New Zealand to determine whether alteplase given intravenously within 6 hours of symptoms onset improved clinical outcome (see Table 9.2).[36] The dose of alteplase was the same as for NINDS (0.9 mg/kg body weight; maximum dose, 90 mg) but lower than in ECASS. Another similarity to the NINDS Study was the use of a standardized protocol for control of blood pressure. Computed tomography exclusion criteria were intracerebral hemorrhage and parenchymal hypoattenuation or brain swelling exceeding one-third of the MCA territory. The primary endpoint was the proportion of patients with favorable outcome (mRSγ1) at 90±14 days after treatment. The absolute difference in favor of alteplase for achieving the primary endpoint was 3.7% (40.3% vs 36.6%; p=0.277). When the proportion of patients achieving independence (defined as mRSγ2) at 90±14 days was used as an endpoint in a post-hoc analysis, there was an 8.3% absolute difference (54.3% vs 46. 0%; p=0.024) in favor of alteplase treatment. In a second post-hoc analysis of ECASS II data using bootstrap statistics, t-PA appeared to significantly improve the mRS.[37] There was no difference in the mortality rate for the two treatment groups. ECASS II did not show efficacy for alteplase when given within 3 hours of symptom onset, but the ability to detect a real difference was limited because only 158 patients were in this subgroup.

By itself, ECASS II could not be construed as compelling evidence that alteplase is efficacious when given as late as 6 hours after symptoms onset. However, meta-analysis suggests that alteplase does reduce odds of death or disability when given within 3 hours after symptoms onset.[38] After ECASS II, there were calls by some for still larger confirmatory studies.[39] It would seem more productive to better define a highresponder target population. Standard CT scanning might not be that useful in defining an optimal target population. Kalafut et al. found that agreement for emergency physicians, neurologists, and general radiologists for detecting the presence of infarction in scans rated as >1/3 MCA was 78%.[40] In ECASS II, 42.6% of patients had no signs of infarction on baseline CT. Advances in brain imaging such as CT angiography and multimodal magnetic resonance imaging (MRI) now permit rapid identification of clots in large intracranial arteries, and MRI may also identify patients with a salvageable brain.

ALTEPLASE THROMBOLYSIS AS ACUTE NONINTERVENTIONAL THERAPY FOR ISCHEMIC STROKE

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) was a double-blind placebo-controlled randomized trial of alteplase given within 3–5 hours of symptoms onset.[41] Investigators randomized 613 patients, 31 within 3 hours before introduction of a protocol amendment (see Table 9.2). Enrollment criteria and t-PA dose mimicked those used in the NINDS study. The primary endpoint was excellent neurologic recovery at day 90 (defined as an NIHSS γ1). No benefit was observed for alteplase for patients treated within 3–5 hours of symptoms onset. Risk of symptomatic intracranial hemorrhage significantly increased with alteplase (7.0% vs 1.1%; $p<0.001$). This symptomatic hemorrhage rate is comparable to the rate observed in the NINDS study. ATLANTIS, ECASS II, and NINDS t-PA study[34] suggest that ischemic delay does not dramatically influence the likelihood of symptomatic intracerebral hemorrhage (ICH).

THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE TRIAL

The Thrombolytic Therapy in Acute Ischemic Stroke Trial (TTAIST) was a randomized doubleblind placebo-controlled trial of intravenous t-PA given within 6 hours of symptoms onset (Table 9.2).[42] Eligibility criteria were virtually identical to the NINDS t-PA Study, and t-PA dose was the same. The study was halted early due to safety concerns in the 5- to 6-hour groups with only 142 patients entered. Giving t-PA did not improve any prespecified efficacy endpoint at either 30 or 90 days. Symptomatic intracranial hemorrhage at day 10 was significantly increased by t-PA (18.2% vs 0%; $p=0.03$). The t-PA group also had a higher death rate at 90 days (36.1% vs 4.2%; $p=0.01$).

LARGE RANDOMIZED TRIALS OF STREPTOKINASE

MULTICENTER ACUTE STROKE TRIAL—EUROPE

The Multicenter Acute Stroke Trial—Europe (MAST-E) was a multicenter, placebo-controlled, randomized trial carried out at 48 centers in France and the UK (Table 9.4).[43] Patients with moderate to severe ischemia in the territory of the MCA were randomized within 6 hours after onset of the symptoms to receive either intravenous streptokinase (1.5 million units over 1 hour) or placebo. The primary efficacy endpoint was combined mortality and severe disability (mRSγ3) at 6 months. Investigators planned to recruit 600 patients, but the Data Monitoring Committee halted the study after recruiting only 310 patients because of increased mortality in the streptokinase-treated patients secondary to intracerebral hemorrhage. At 6 months, 124 (79%) of the streptokinase-treated patients had died or were disabled compared with 126 (82%) of the placebo-treated patients; mortality was 47% for the streptokinase-treated patients compared with 38% for the placebo-treated patients ($p=0.06$). Investigators demonstrated that the difference in mortality could be attributed largely to the higher rate of hemorrhagic transformation of cerebral infarction in the streptokinase-treated patients. Symptomatic intracerebral hemorrhage occurred in 21% of the streptokinase-treated patients compared with 2.6% of the placebotreated patients ($p<0.001$).

Unlike many of the t-PA studies, MAST-E permitted the use of heparin, oral anticoagulants, and aspirin during the first 24 hours. Thirty-one percent of the streptokinase group and 12% of the placebo group received heparin within 12 hours of randomization ($p=0.04$), which could have adversely affected safety.

Table 9.4 Randomized trials of intravenous streptokinase for acute ischemic stroke

Study	No. of patients	Time window (h)	Treatment groups	Results
MAST-I[44]	622	0–6	1.5 MU streptokinase; 300 mg aspirin; both; or neither	Streptokinase alone or with aspirin was associated with an excess 10-day case fatality
MAST-E[43]	310	0–6	1.5 MU streptokinase or placebo	No difference in rates at 6 months of death or Rankin greater or equal to 3 (primary endpoint). Ten-day mortality rate was significantly higher in the streptokinase group
ASK[47]	340	0–4	1.5 MU streptokinaseor placebo	No significant difference in combination of death and disability at 3 months (primary endpoint)

MULTICENTER ACUTE STROKE TRIAL—ITALY

A second large randomized trial of streptokinase was the Multicenter Acute Stroke Trial—Italy (MAST-I) (Table 9.4).[44] Interpretation of the findings resulted in reporting separate interpretations of the same study.[45] The clinical investigators reported the design, results, and their interpretation of the study,[44] and the principal biostatisticians reported their differing interpretations.[45] The trial was designed to determine whether intravenous streptokinase, aspirin, or the combination of streptokinase and aspirin were superior to the absence of those therapies. Patients were eligible if they had symptoms compatible with acute ischemic stroke, could be treated within 6 hours of onset of symptoms, had a CT scan of the head showing no evidence of hemorrhage, were not comatose, and did not have rapid resolution of neurologic symptoms. The study was not placebo-controlled. A total of 157 patients were randomized to receive streptokinase, 153 were randomized to receive aspirin (300 mg daily until poststroke day 10), 156 were randomized to receive streptokinase plus aspirin, and 156 were randomized to receive neither drug. Intravenous heparin, oral anticoagulants, and non-protocol antiplatelet regimens were to be avoided, but subcutaneous heparin up to 15 000 U/day was allowed. A sample size of about 1500 was anticipated,[46] but each was stopped because of excess early hazard in thrombolytic therapy. For streptokinase, 196 of the 313 actively treated patients were dead or disabled at 6 months compared with 200 of the control patients, a negligible difference. For aspirin, 193 of the aspirin-treated patients were dead or disabled at 6 months compared with 203 of the 313 control patients, again a negligible difference. Therefore, the study was negative. However, patients treated with streptokinase and aspirin had a higher case fatality rate than patients treated with streptokinase alone, aspirin alone, or with neither drug ($p<0.001$)

AUSTRALIAN STREPTOKINASE TRIAL

In the Australian Streptokinase Trial (ASK),[47] patients were randomized within 4 hours from symptom onset, earlier than in MAST-E or MAST-I (Table 9.4). In addition, the authors prospectively planned a comparison of those patients randomized within 3 hours of symptoms onset to those patients randomized 3–4 hours from symptom onset. The sample size was designed to be 600, but the Safety Monitoring Committee advised that the trial be suspended after recruiting only 340 patients because of significantly poorer outcomes among streptokinase-treated patients receiving treatment more than 3 hours after stroke.[48] The rate of recruitment

of patients for randomization within 3 hours following symptoms onset was considered too low to justify continuing the trial for that group alone. The treatment groups were well balanced for baseline characteristics. The primary outcome measure was the combination of death and disability at 3 months, with disability defined as a BI<60 at 3 months after the stroke. This unfavorable outcome occurred in 48.3% of streptokinase-treated patients compared with 44.6% for the placebo-treated patients (the relative risk for an unfavorable outcome following streptokinase treatment was 1.08 [95% confidence interval (CI), 0.74–1. 86]). It is of interest that there was a significant difference in rates of unfavorable outcome between those treated early and late (p=0.04). The relative risk for an unfavorable outcome following streptokinase treatment in patients treated within 3 hours was 0.66 (95% CI, 0.28–1.58). However, for patients treated beyond 3 hours from stroke onset, the relative risk for an unfavorable outcome in the streptokinase-treated patients was 1.22 (95% CI, 0.80–1.86).

This difference with regard to onset-to-treatment time was not noted in the incidence of intracerebral hematoma. Overall, hematoma occurred in 13.2% of the streptokinase-treated group (12.6% symptomatic) and in 3% in the placebo-treated group (2.4% symptomatic) (p<0.01). The hematoma rate in patients treated within 3 hours was 9.8% for the streptokinasetreated patients and 0% in the placebo-treated patients. The differential effect with regard to treatment within 3 hours compared with treatment beyond 3 hours demonstrated in ASK is a finding consistent with the time effect reported from the NINDS t-PA Study.[34] In addition, when time was used as a continuous variable, there was a trend toward increased death and disability with later streptokinase treatment (p=0.10).

In addition to intracranial hematoma formation, patients treated with streptokinase also experienced hypotension. A decrease in systolic blood pressure of >20 mmHg within a few minutes of initiation of streptokinase or placebo treatment occurred in 33% of the streptokinasetreated patients compared with 6% of the placebo-treated patients. Four patients (2.2%) had anaphylactic shock.

The negative results from these streptokinase studies are unsettling (Table 9.4). The differences in results from those reported in the NINDS t-PA Stroke Study[12] could relate to time of treatment, dose of streptokinase, and differences in thrombolytic drugs. In contrast to the NINDS study, a small minority of patients in the streptokinase trials was treated within 3 hours of symptoms onset. In MAST-I, 26% of the patients were randomized within 3 hours. In ASK, 21% of the patients were randomized within 3 hours. In the NINDS study, all 624 patients were randomized within 3 hours, and 302 (48%) were randomized within 90 min. Such very early treatment occurred in only 3 (1%) of the 340 ASK patients. Later treatment may be particularly important if patients with signs of major cerebral infarction by CT scan are not excluded from treatment. These patients had a particularly high rate of adverse outcomes in ECASS.[35] The dose of intravenous streptokinase used in the three trials was identical to the dose used for myocardial infarction (1. 5 MU). In contrast, the doses of t-PA used in the NINDS study and the ECASS studies were significantly lower than those used for myocardial infarction. The lower dose of t-PA used in the NINDS trial was determined by prior dose escalation safety trials. One pilot trial with 52 patients was performed prior to initiation of the streptokinase trials.[48]

POTENTIAL LESSONS FROM SELECTED CASE SERIES

VERTEBROBASILAR SYSTEM INFARCTION

For acute vertebrobasilar system infarction, sufficient numbers of patients were not enrolled in the randomized studies of t-PA or streptokinase to drawn inferences regarding efficacy in this clinical setting. Of the 51 consecutive cases recently reported by the Heidelberg Group with vertebrobasilar system

infarction,[49] only 6 patients were treated intravenously (70–100 mg of t-PA), and the results of the intravenous treatment of those patients are not reported separately from those of the total group. Case series of thrombolytic therapy for vertebrobasilar disease are almost exclusively reports of regional or local intra-arterial therapy. Mortality rates remain high even in experienced hands (Table 9.5). Spontaneous symptomatic cerebral hemorrhage rates may be prohibitively high for certain regimens.[50]

INTERNAL CAROTID ARTERY OCCLUSION

For acute internal carotid artery (ICA) occlusion, Jansen and colleagues[51] reported the results of intravenous t-PA for 16 patients with intracranial ICA occlusion for whom treatment was administered within 8 hours after symptoms onset. Recanalization was achieved in only two (12.5%) patients. Intracranial hemorrhage occurred in 1 of 16 patients, and outcomes were generally poor. In the dose-escalation safety study of t-PA (duteplase) carried out by the Burroughs— Wellcome Study Group,[52] ICA occlusion was identified in 28 (20%) of 139 patients with acute stroke who had cerebral arteriography within 6 hours of symptoms onset. The recanalization rate for intracranial ICA occlusion was 8%.[52]

HIGH-DOSE THROMBOLYSIS

In the case series of Trouillas and colleagues[53] discussed below, the dose of t-PA was 0.8 mg/kg. In the NINDS t-PA Stroke Study,[12] the dose of t-PA was 0.9 mg/kg. The dose was 1.1 mg/kg in ECASS.[35] The highest dose thus far tested is 100 mg of t-PA (alteplase), an experience reported by von Kummer and Hacke.[54] They wished to test whether high-dose t-PA given in combination with intravenous heparin would be safe in patients with acute ischemic stroke. Thirty-two patients with severe ischemic stroke (NIHSS score >18) were studied with cerebral angiography. Following identification of an MCA or intracranial ICA occlusion, t-PA was infused over 90 min. Simultaneously with t-PA, the patients were given a bolus of 5000 U heparin and an ongoing infusion of heparin of 1000–1500 U/h, adjusted to double the activated partial thromboplastin time. Angiography was repeated immediately after the t-PA infusion.

Reperfusion was reassessed at 12–24 hours by TCD (n=30) or a third angiogram (n=5). The

Table 9.5 Local intra-arterial thrombolysis for vertebrobasilar occlusion: non-randomized studies with n >20 published in 1983 or later

Study	No. of patients	Agent	Time from onset to treatment (h)	Time from treatment to recanalization (h)	Partial (P) or complete (C) recanalization	Intracranial hemorrhage	Mortality
Brandt et al.[49]	44[a]	UK	<48	N/A	23 (52%) C or P	3 (7%)[b]	35 (80%)
Zeumer et al.[77]	28	UK or t-PA	8 (mean)	2	21 (75%) C 7 (25%) P	0	18 (64%)
Fox et al.[78]	30	UK	13 (mean)	N/A	7 (23%) C 14 (47%) P	N/A	19 (63%)

UK, urokinase; t-PA, tissue plasminogen activator; N/A, not available.
[a] All patients had occlusion of the basilar artery.
[b] Denominator includes 6 patients treated with intravenous t-PA and one patient treated with intra-arterial t-PA.

authors reported 3 parenchymal hematomas (9%), all fatal, and 9 hemorrhagic infarctions (28%), of which 4 were associated with poor outcome. The rate of complete or partial reperfusion was 34% at 8 hours. An additional 3 patients had complete or partial reperfusion at 24 hours; 2 more patients with combined ICA and M1 occlusions had partial recanalization of the M1 occlusion; 14 of 32 (44%) of patients had good outcome; and reperfusion and effective collateral blood flow were associated with small infarct volume and good clinical outcome.

LOW-DOSE THROMBOLYSIS

No firm evidence is available to indicate that doses of t-PA (or streptokinase) lower than those evaluated in the larger randomized trials are ineffective. In the NINDS dose-escalation pilot studies,[55,56] no dose-response was seen for very early improvement, even though a dose— response was identified for intracerebral hemorrhage.[55] Likewise, in the Burroughs— Wellcome dose-escalation study,[14,52] good outcomes were not restricted to the patients receiving higher doses of duteplase, and a dose —response for efficacy was not noted. In an open-label study, Trouillas and colleagues[53] evaluated patients between the ages of 20 and 81 years with all types of ischemic stroke in the carotid territory who could be treated within 7 hours of stroke onset. Patients were given the 0.8 mg/kg dose of t-PA (alteplase) over 90 min. Heparin was given according to two consecutive protocols: the first protocol used immediate intravenous heparin and the second protocol used intravenous heparin at the same doses but beginning at 24 hours after stroke. Fortythree consecutive patients were treated with a mean onset-to-treatment time of 232±79 min. At 3 months, 25 patients (58%) had complete resolution of symptoms and only two patients had died (4.6%); three patients had post-thrombolysis hematomas (6.9%), and one of these patients died. These efficacy results and the hematoma rates are very similar to those reported in the NINDS study, even though the patients treated in this trial had their treatments initiated much later than those in the NINDS study and heparin was initiated early for 10 of the patients.

These three studies suggest the hypothesis that a dose of t-PA lower than the 0.9 mg/kg used in the NINDS study could be efficacious. A second, related, hypothesis would be that patients with less severe neurologic deficits presumably also have smaller occlusive thrombi and might benefit from lower doses of t-PA. This latter hypothesis could be tested in a trial of patients with lacunar syndromes or restricted MCA-distribution syndromes, randomized to receive either standard dose t-PA (0.9 mg/kg) or lower doses.

PREDICTORS OF GOOD OUTCOME

A subgroup analysis of the NINDS study looked at 29 baseline variables that might influence the outcome after ischemic stroke, regardless of treatment.[32] In the univariate analysis, baseline systolic blood pressure showed a significant interaction with t-PA treatment. Because univariate analyses do not control for confounding, a multivariate model was constructed. In the final model, none of the examined variables significantly interacted with treatment. In other words, patients of a particular age, race, or gender had neither more nor less likelihood of benefiting from t-PA. This implies generalized efficacy of t-PA for acute ischemic stroke when given according to the NINDS protocol.

Predictors of good outcome have also been examined by the ECASS investigators.[57] In their initial report, they suggested that age γ70 years, treatment with recombinant tissue plasminogen activator (rt-PA), normal baseline CT scan, a favorable Scandinavian Stroke Scale score, and the absence of diabetes, cardiac conditions, and hypertension may predict a good outcome. In addition, they categorized their MCA territory infarctions into subcortical and combined cortical/subcortical.[58] Because they saw no difference in the

number of subcortical infarctions in the t-PA group (23%) compared with the placebo group (21%), they hypothesized that thrombolysis does not prevent subcortical infarction.

In the large randomized trials of streptokinase, subgroup analyses have also been performed in an attempt to generate hypotheses regarding ideal patients for treatment. The MAST-E investigators[59] reported that good outcome, after exclusion of patients with symptomatic hemorrhage, was predicted only by the united neurologic score. They did not identify a subgroup that either fared better or worse with streptokinase therapy as compared with placebo. The ASK investigators identified time-to-treatment[47,60] as significantly influencing response to thrombolytic therapy. In their study as a whole, treatment of acute ischemic stroke with streptokinase was not beneficial. However, poor outcomes were confined to those patients receiving therapy beyond 3 hours after onset; those receiving therapy at γβ hours from symptom onset had improved outcome.

The degree of collateral circulation and clot size are probably important determinants of good outcome. Once again, the large randomized trials of t-PA and streptokinase could not address this point because they were not angiographically controlled. Case series document the importance of good collateral circulation as a determinant of good outcome.[61–63] von Kummer and colleagues[64] prospectively studied 77 patients clinically, by CT, and before and after thrombolysis with cerebral arteriography. When they categorized collaterals as good or scarce, recanalization at less than 8 h from symptom onset had no predictive value for good outcome independent of the collaterals. Predictors of poor outcome were parenchymal hypodensity by CT scan at the time of treatment involving γ50% of the MCA territory (p=0.002), scarce collaterals (p=0.009), and site of occlusion (p=0.017).

INTRACRANIAL HEMORRHAGE FOLLOWING INTRAVENOUS THROMBOLYSIS

The principal adverse effect of thrombolysis in the setting of treatment for acute cerebral infarction has been intracranial hemorrhage (ICH).

The presenting signs and symptoms of symptomatic intracerebral hemorrhage in the setting of intravenous thrombolytic therapy[52,55] are similar to those of spontaneous intracerebral hemorrhage.[65] Decline in level of consciousness, headache, nausea, vomiting, abrupt rise in systemic blood pressure, increase in the presenting neurologic deficit, or appearance of a new neurologic deficit should prompt an emergency CT scan. The case-fatality rate following symptomatic thrombolysis-associated intracerebral hematoma is also similar to that for spontaneous intracerebralhemorrhage.[52,55,66]

Information regarding risk factors of intracranial hemorrhage following intravenous thrombolysis is limited because of the small absolute number of patients with thrombolysis-related intracranial hemorrhage. Later time-to-treatment, higher dose of thrombolytic, elevated blood pressure, and severity of neurologic deficit have been suggested as potential risk factors. In the Burroughs-Wellcome dose-escalation safety study, patients with hemorrhage transformation were treated with t-PA later (6.1±1.5 hours) than patients without hemorrhagic transformations (5.3±1.7 hours, p<0.05). In addition, the rate of intracranial hemorrhage in the randomized trials of intravenous thrombolysis was lowest in the NINDS study (6.4%) in which all patients were treated within 3 hours, nearly half within 90 min. Nonetheless, onset-to-treatment time has not been firmly established as a risk for hemorrhage. A multivariate analysis of intracerebral hemorrhage occurring in patients treated in the NIH t-PA pilot studies did not show an association between onset-to-treatment time and intracranial hemorrhage,[24] but the rate of symptomatic hemorrhage in the NINDS study[12] was not significantly different among patients treated at 0–90 min compared with those treated at 90–180 min.

Extant data suggest that higher doses of thrombolytic increase the rates of intracranial hemorrhage. In those studies using doses of either t-PA[35] or streptokinase[43,44,47] approaching or equivalent to the doses used for myocardial infarction, the rates of intracranial hemorrhage have been higher than in the NINDS study,[12] where the dose was about 75% of that used for myocardial infarction. Other differences in these trials make inference difficult. Nonetheless, in the NIH t-PA pilot studies,[55] intracranial hemorrhage did not occur in patients treated with γ0.6 mg/kg of t-PA, and the multivariate analysis of that patient population did show that dose of t-PA was significantly related to intracerebral hematoma.[24] Trouillas and colleagues[53] reported the lowest hematoma rate of any study treating patients with a thrombolytic agent beyond 4 hours after stroke onset. With 0.8 mg/kg of t-PA over 90 min, the hematoma rate for the 43 treated patients was only 6. 9%, essentially identical to that of the NINDS study where the dose was 0.9 mg/kg, but patients were treated earlier and without early heparin.

Severe hypertension is a suspected risk factor for thrombolysis-related intracranial hemorrhage. In the NIH pilot studies, diastolic hypertension was significantly associated with intracranial hemorrhage.[24] However, in the much larger NINDS study, neither systolic nor diastolic blood pressure were significantly associated with the occurrence of symptomatic hemorrhage among the t-PA-treated patients in the final multivariate model.[67] This model was the primary model for the hemorrhage analysis and included only the 20 symptomatic hemorrhages that occurred in the t-PA-treated patients. The small number of hemorrhages limited the predictive power of the model. When investigators combined symptomatic with asymptomatic hemorrhage in both the t-PA-treated patients and the placebo-treated patients, the final multivariate model included pulse pressure (odds ratio 1.02, 95% CI 1.004–1.035) and minor external bleeding.[67] Because pulse pressure was so highly correlated with other indices of blood pressure, such as systolic blood pressure and diastolic blood pressure, those variables too could have been associated with the occurrence of symptomatic or asymptomatic intracranial hemorrhage. Severe hypertension has not been reported as a risk factor for intracranial hemorrhage in ECASS,[68] MAST-E,[69] or MAST-I.[70]

Severity of initial neurologic deficit was associated with the occurrence of symptomatic intracranial hemorrhage in the NINDS study.[67] Patients with a baseline NIHSS score of >20 (very severe deficit) were 11 times more likely to develop a symptomatic intracranial hemorrhage than patients with an initial NIHSS score of γ5 (mild deficit). ECASS investigators found clinical severity of stroke (odds ratio 2.5) to be a risk factor for hemorrhagic infarction.[71] The risk factor for parenchymal hematoma was advanced age (odds ratio 1.3 by 10 years of age). Finally, MAST-I investigators[70] have also reported that neurologic severity at baseline was a significant predictor of subsequent hemorrhagic transformation.

Baseline CT scan has been particularly important for predicting intracranial hemorrhage following thrombolytic therapy. ECASS investigators were first to suggest this possibility[35] in their initial report in which protocol violators who received t-PA had a significantly worse outcome than the other patients. They subsequently followed up with an analysis of CT scans and other factors that might predict subsequent thrombolysis-related intracranial hemorrhage.[71] von Kummer and colleagues read all baseline CT scans unblinded to clinical deficits and subsequent scans. They scrutinized not only obvious hypodensity but also subtle signs of early ischemia, including subtle hypodensity, sulcal effacement, loss of insular ribbon or gray-white differentiation, and asymmetry of the basal ganglia. They found that the presence of early ischemic changes on the baseline CT scan resulted in an odds ratio of 3.5 (p=0.001) for the occurrence of subsequent hemorrhagic infarction. In the NINDS study, CT scans were read differently. The baseline, 24-hour, 7-day, 10-day, and 3-month CT scans were read separately by one neuroradiologist, who had no information regarding the clinical deficit. The incidence of early mass effect and edema (hypodensity) was low. For symptomatic intracerebral hemorrhages occurring in the t-PA-treated patients, the final multivariate model included the presence of mass effect or brain edema on baseline CT. The odds ratio was

7.8 (95% CI 2.2–27.1). However, because of the low incidence of these findings, the limitations of this predictive model are considerable. In MAST-E, the degree of abnormality on the baseline CT scan was also found to be a predictor of hemorrhagic transformation.[69]

A detailed analysis of risk factors for severe hemorrhagic transformation was performed in ECASS II.[72] Hemorrhagic transformations were classified using clinical and radiographic criteria as hemorrhagic infarction, parenchymal hemorrhage, and symptomatic intracranial hemorrhage. Parenchymal hemorrhage and symptomatic intracranial hemorrhage were associated with t-PA, but hemorrhagic transformation was not. Increasing age was a risk factor for both parenchymal hemorrhage and symptomatic intracranial hemorrhage in the t-PA group. Extent of parenchymal hypoattenuation on baseline CT was a risk factor for symptomatic ICH in the t-PA group. One study suggested that basal ganglia hypointensity on baseline CT scanning can predict hemorrhage after intravenous t-PA.[73]

Arterial recanalization has been suspected for some time of being a risk factor for hemorrhagic conversion and intracranial hemorrhage. However, the angiographic studies have not identified arterial recanalization as a risk for hemorrhage.[18,19,52]

PREVENTION AND TREATMENT OF THROMBOLYSIS-RELATED INTRACEREBRAL HEMORRHAGE

Thrombolytic therapy should be initiated as soon as possible. Use of intravenous t-PA should be limited to patients who can be treated within 3 hours. Patients with severe hypertension should not be treated; specifically, treatment should be limited to patients with an initial systolic blood pressure of γ 185 mmHg or diastolic blood pressure of γ110 mmHg. Patients should be monitored carefully for deterioration in consciousness, worsening neurologic deficit, and the occurrence of headache, nausea, vomiting, or acute hypertension. One or more of these symptoms or signs could herald the beginning of intracranial hemorrhage and should prompt immediate interruption of thrombolytic therapy and re-imaging by CT. In the NINDS study, an algorithm for detection and treatment of intracerebral hemorrhage was employed (see below), but the superiority of this approach over other potential approaches has not been established.

SYSTEMIC HEMORRHAGE

Systemic hemorrhage has not been a major problem in the trials of intravenous thrombolytic therapy for stroke. In the NIH t-PA pilot stroke studies,[56] one case of fatal pericardial tamponade was reported, and a second case was recently reported by the Emergency Management of Stroke (EMS) investigators.[9] In the NINDS study,[12] serious systemic bleeding occurred in 5 of the t-PA -treated patients and in none of the placebo-treated patients; none of these events was fatal. In ECASS,[35] 4 t-PA-treated patients and two placebo-treated patients had systemic bleeding complications, but none required transfusion. For the streptokinase trials, neither the MAST-E investigators[43] nor the ASK investigators[47] reported any serious systemic hemorrhagic complications. In MAST-I,[44] systemic bleeding was observed in two patients receiving streptokinase and in seven patients receiving aspirin. Severe systemic hemorrhage occurred in two patients, one receiving streptokinase and one aspirin; these episodes required transfusion of at least one unit of blood.

POTENTIAL NONHEMORRHAGIC COMPLICATIONS OF THROMBOLYTIC THERAPY

REPERFUSION INJURY AND EDEMA

Theoretically, delayed lysis of a thrombus in the stem of the MCA or one of the larger branches following the beginning of substantial irreversible neuronal injury could result in edema, secondary to breakdown of the blood-brain barrier or the effects of free radical-related amplification of neuronal injury. Two cases suggestive of severe reperfusion edema have been reported.[74]

ARTERIAL REOCCLUSION

Arterial reocclusion after successful thrombolysis is a potential complication. The symptombased intravenous thrombolysis trials were not designed to directly assess arterial reocclusion. In an angiographically based series of high-dose t-PA,[54] reocclusion at 24 hours occurred in 1 of 11 patients with complete or partial recanalization at 8 hours. Theoretically, the likelihood of reocclusion in the setting of cerebral infarction should be less than in myocardial infarction. With ischemic stroke, patients treated with thrombolysis in large part have either a cardioembolic or an atheroembolic mechanism for their stroke. The embolus lodges in a distal vessel where the vessel wall is usually normal. With lysis of the clot, no underlying complex atherosclerotic plaque is left behind to trigger the molecular and cellular cascade once again, leading to acute thrombus formation—the situation in the setting of thrombolysis for acute myocardial infarction.

SECONDARY EMBOLIZATION

The majority of patients with ischemic stroke treated in the randomized and nonrandomized thrombolytic trials were thought to have a cardioembolic or atheroembolic etiology. Accordingly, systemic thrombolysis has the potential to dislodge further embolic material from the source of the original thrombus.[75] In addition, unintended embolism from thrombolysis could result from fragmentation of the original occluding thrombus. For example, when an M1 thrombus is broken up by an intravenous lytic agent, the resulting smaller fragments may be large enough to lodge downstream in M2 or M3 branches.

LOCAL INTRA-ARTERIAL THROMBOLYSIS

The delivery of thrombolytic agents at or within the occluding thrombus has the advantage of providing a higher local concentration of the agent where it is needed while minimizing the systemic concentration. Hence, local intraarterial thrombolysis has the potential for greater efficacy with less bleeding. The technique involves performing a cerebral arteriogram, locating the occluding clot, and navigating a microcatheter to the clot. The clot is usually penetrated, and small amounts of lytic agent are given distal to the clot. The microcatheter is then withdrawn into or just at the proximal end of the clot where further thrombolytic agent is administered, usually over 30–120 min.

RANDOMIZED TRIALS

PROLYSE IN ACUTE CEREBRAL THROMBOEMBOLISM TRIAL

In the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT),[8] patients who could be treated within 6 hours and who had an acute stroke localized to the MCA were eligible for angiography if the baseline NIHSS score was >4 and <30 (Table 9.6). Patients were then taken to angiography. If an M1 or M2 occlusion was identified, the patient was randomized on a 2:1 basis to receive either 6 mg of pro-UK or placebo. The angiogram was repeated after 60 min. Patients were followed clinically, NIHSS scores were assessed, and bleeding was monitored with post-treatment CT scans. Forty-six patients were randomized and 40 were treated, 26 being treated with pro-UK and 14 with placebo. Baseline NIHSS scores were 17 for both treatment groups. Mean onset-to-treatment time was 5.2 hours for the pro-UK-treated patients and 5.6 hours for the placebo-treated patients. Early CT changes were seen in about 60% of patients in both groups. Partial or complete recanalization was seen in 15 of 26 pro-UK-treated patients (58%) compared with 2 of 14 placebo-treated patients (14%) (p=0.017). Intracranial hemorrhage with deteri

Table 9.6 Randomized trials of IA and IV/IA thrombolysis for acute ischemic stroke

Study	No. of patients	Time window (h)	Treatment groups	Results
EMS[9]	35	3	IV t-PA at 0.6 mg/kg, 60 mg max, 10% bolus with remainder over 30 min followed by IA t-PA at 10 mg/h up to 20 mg or placebo followed by IA t-PA at 10 mg/h up to 20 mg	No difference in 7–10 day or 3 month outcomes. Recanalization was better in the IV/IA group than in the placebo/IA group. The only two life-threatening bleeds occurred in the IV/IA group
PROACT[8]	46	6	6 mg IA r-pro-UK and IV heparin or sham IA and IV heparin	Recanalization was associated with r-pro-UK (p=0.017)
PROACT II[76]	180	6	9 mg IA r-pro-UK and IV heparin or IV heparin only	40% of r-pro-UK group and 25% of control group had slight or no neurologic disability at 90 days (p<0.04)

BI, Barthel index; IA, intra-arterial; ITT, intent-to-treat; IV, intravenous; pro-UK, prourokinase; r, recombinant; t-PA, tissue plasminogen activator.

oration occurred in 4 of 26 pro-UK-treated patients (15%) and in 2 of 14 placebo-treated patients (14%). Outcomes were not significantly different; 5 of the pro-UK-treated patients had an NIHSS score of γ1 compared to 1 of the placebohigher dose of heparin was used early in the treated patients. Both groups received heparin. A study than later in the study. Higher recanalization but higher bleeding rates were noted with high-dose heparin.

SECOND PROLYSE IN ACUTE CEREBRAL THROMBOEMBOLISM STUDY

The best proof to date that intra-arterial thrombolysis can improve patient outcomes comes from the Second Prolyse in Acute Cerebral Thromboembolism (PROACT II) study.[76] study was a randomized controlled open-label study with blinded follow-up conducted at 54 North American centers. A total of 180 patients

with stroke of less than 6 hours' duration caused randomized to receive 9 mg of intra-arterial recombinant prourokinase (r-pro-UK) plus heparin (n=121) or heparin only (n=59).

Patients needed a minimum NIHSS score of 4, except for isolated aphasia or isolated hemianopia. Computed tomography exclusion criteria were intracranial hemorrhage, significant midline shift, and hypodense parenchymal lesion or effacement of cerebral sulci in more than one-third of MCA territory. Angiographic inclusion criteria were total or subtotal occlusion of the M1 segment or M2 division of the MCA. Mechanical disruption of clot was not permitted. The full dose of pro-UK was given even if angiographically complete lysis occurred before ending the infusion. All patients received a 2000 U bolus and 500 U/h infusion of heparin for 4 hours, beginning at the time of angiography. Patients had severe strokes at baseline (median NIHSS score=17). The recanalization rate was greatly enhanced by intra-arterial proUK (66% vs 18%; p<0.001). The pro-UK group also had a higher proportion of patients achieving the primary endpoint of independence (mRS ϒ2) at 90 days (40% vs 25%; p=0.04). There was no significant difference in any of the secondary endpoints. Prourokinase significantly increased the 24-hour intracranial hemorrhage rate (35% vs 13%; p=0.003). Seven patients needed to be treated with intra-arterial pro-UK to make 1 patient independent. The study suggests that PROACT II-eligible patients represent only a small proportion of all cases of acute ischemic stroke. Only 180 (2%) of 12 323 screened patients were randomized. The small number of patients enrolled led to chance differences in baseline characteristics, including CT hypodensity and diabetes, both of which have been correlated in other studies to alter stroke outcomes.

THROMBOLYSIS FOR VERTEBROBASILAR OCCLUSION

Cerebral infarction in the vertebrobasilar distribution has been of particular interest to centers experienced with local intra-arterial thrombolysis. Three large case series[49,77,78] have been published since 1991 (see Table 9.5). The great majority of the 102 patients treated were administered local intra-arterial urokinase. No patient was reported in these series as being treated within 3 hours of symptoms onset. The median time from beginning of treatment to the time of recanalization was reported by Zeumer et al.[79] to be 120 min. Complete recanalization was reported for 28 of 58 patients (48%), and partial recanalization was reported for 21 of the same 58 patients (36%). For the total group of 102 patients (see Table 9.5), complete or partial recanalization was accomplished for 72 (71%). Mortality remained very high, with only about one-third of patients surviving. Good outcome was related to arterial recanalization, collateral circulation, and earlier onset of treatment.

Because good outcomes were achieved in some of the patients reported above and in earlier series of patient with basilar artery occlusion, some investigators have not favored randomized trials of local intra-arterial therapy for vertebrobasilar occlusion. They favor open therapy because of the bleak prognosis in untreated patients, particularly those with basilar artery occlusion. However, in a consecutive series of 22 patients with angiographically proven occlusions of the caudal vertebral artery or the basilar artery,[80] 20 did not receive thrombolytic therapy and all 20 survived for more than 1 year. Magnetic resonance imaging was performed on 17 cases, and 14 had a brainstem infarct identified.

TIME DELAYS IN DELIVERY AND IN ACCOMPLISHING LYSIS

Arterial recanalization rates suggest an advantage of intra-arterial delivery of therapy over intravenous deliveries. However, the clinically relevant issue is patient outcome. Intravenous thrombolysis has the advantages of wider availability and the earlier initiation of therapy. There can be major delays in the

initiation of local intra-arterial therapy, a limitation for all case series accomplished to date. Even after the patient has been evaluated neurologically to the degree where intravenous treatment could be initiated safely and appropriately, intra-arterial treatment involves considerable delays. In the Emergency Management of Stroke (EMS) trial, patients were first randomized to receive intravenous t-PA or placebo before proceeding to cerebral angiography and local intra-arterial thrombolysis.[9] The mean interval from intravenous treatment to intra-arterial treatment time was 1 hour and 40 min. Once intra-arterial therapy is initiated, significant delays in lysis have been reported in nearly all series. In the EMS trial after 29 patients had been enrolled, the time from initiation of intra-arterial therapy to best degree of clot lysis was 1.9 hours. Zeumer et al.[77] reported treatment initiation to recanalization times of 1.5–2.0 hours, Ezura and Kagawa[81] reported 2. 8 hours, and Barnwell et al.[82] reported 2 hours.

COMBINATION THROMBOLYTIC THERAPY

MULTIDRUG THROMBOLYSIS

With intravenous thrombolysis, most studies have involved single drugs. The high-dose regimen investigated by von Kummer and Hacke[54] was an exception in that full-dose heparin was also used. With local intra-arterial thrombolytic therapy, heparin in varying doses was used almost without exception.

Because of delays in recanalization with urokinase and with t-PA, Freitag and colleagues[83] tested the use of lys-plasminogen in combination with t-PA. The proximal stump of a thrombus presents a small surface area to any agent. Most of the substance administered in bolus form refluxes back into the ICA or to the contralateral hemisphere; plasminogen may even be leached off the surface of an acute clot because of the high concentrations of lytic agent in the adjacent plasma substrate. These investigators used an experimental model to determine the concentration of lys-plasminogen and the concentration of t-PA that would result in effective concentrations in plasma. They then tested this combination intra-arterially in 20 patients with acute carotid distribution cerebral infarction. The final combination was 2500 IU of lys-plasminogen and 10 mg of t-PA. Recanalization was complete for 12 of 14 cases with usually lysable emboli and the average lysis time was 60 min. With urokinase or t-PA, lysis was complete for 14 of 22 cases and the average time to lysis was 60 min. Sixty percent of the patients treated with lys-plasminogen plus t-PA had a final Barthel index score between 90 and 100 compared with 16 of 40 patients treated with urokinase or t-PA. The rate of hemorrhagic transformation without clinical deterioration was 25% in the combination group compared with 12% in the urokinase or t-PA group; however, one patient in the urokinase and t-PA group had clinical deterioration associated with hematoma.

COMBINED INTRAVENOUS AND INTRA-ARTERIAL THROMBOLYSIS

Combining the speed of intravenous thrombolysis with the superior recanalization rates of intraarterial thrombolysis was the goal of the EMS investigators.[9] They studied acute stroke patients with an NIHSS score of ɣ6 who could be randomized within 3 hours of symptoms onset. Thirtyfive patients were randomized to receive either intravenous t-PA (0.6 mg/kg over 30 min) or placebo followed immediately by cerebral arteriography. If an acute thrombus related to the symptoms was identified, patients from both groups received local intra-arterial t-PA at 10 mg/h via microcatheter for up to 20 mg over 2 hours. A clot was identified in 22 (63%). Full or partial recanalization was accomplished for 8 (67%) of the patients treated with combination intravenous and intra-arterial t-PA and in 6 (60%) of the intravenous placebo and intraarterial t-PA patients. Three patients had lifethreatening hemorrhagic events, all in the group that

received preangiographic intravenous t-PA. The proportion of patients with early neurologic recovery was similar in the two groups. The authors concluded that combination intravenous and intra-arterial thrombolytic therapy was feasible and that safety was probably related to the dose of t-PA received. Partial recanalization rates following combination thrombolysis did not appear to be significantly different from those reported for local intra-arterial therapy. A larger phase III trial of combination thrombolysis is underway to determine safety and potential efficacy. Combination thrombolysis will be compared to standard intravenous t-PA or to intraarterial-only thrombolysis.

CARE OF PATIENTS UNDERGOING THROMBOLYSIS

HYPERTENSION

In the NIH pilot studies of t-PA for stroke and in the NINDS trials, aggressive management of hypertension was not allowed in patients screened but not yet enrolled in the studies. The assumption was that aggressive treatment of hypertension in the setting of acute ischemic stroke could be detrimental. For patients who fulfilled blood pressure eligibility criteria and are treated with a thrombolytic drug, it is desirable that severe hypertension be avoided. Table 9.7 lists the method used in the NINDS t-PA study,[84] derived and modified from a blood pressure management algorithm designed for stroke patients not receiving thrombolytic therapy.[85,86] Cautious treatment of severely elevated blood pressure may decrease the incidence of thrombolysis-related hemorrhagic complications, particularly during the first 24 hours. The methods described in Table 9.7 were designed to provide rapid onset of blood pressure lowering with a modest effect.

ANCILLARY CARE DURING THE FIRST 24 HOURS

Patients receiving thrombolysis need frequently repeated assessments of blood pressure and neurologic status. This can only happen if the nurse/patient ratio is high. It is recommended that all patients treated with thrombolytic therapy, either intravenous or intra-arterial, should be admitted to an intensive care unit or an acute stroke unit.[12,87,88] Arterial lines, central venous lines, nasogastric tubes, and bladder catheters should not be placed unless absolutely necessary.

An emergency head CT scan should be obtained if the occurrence of intracerebral hemorrhage is suggested by severe headache, nausea, vomiting, abrupt rise in systemic blood pressure, deterioration in consciousness, increase in neurologic deficit, or appearance of new neurologic deficit. When intracranial bleeding was suspected in the NINDS study, blood was drawn to measure the patient's activated partial thromboplastin time (PTT), prothrombin time, internal normalized ratio (INR), platelet count, and fibrinogen concentration. Blood was typed and crossmatched with preparation for transfusion of 6–8 U of cryoprecipitate or fresh frozen plasma and 10 U of single donor platelets. If the emergency CT scan confirmed intracerebral hemorrhage, the blood products were transfused to reverse the fibrinolytic state. Neurosurgical consultation should be obtained to evaluate the patient for possible hematoma evacuation.

During the first 24 h after administration of thrombolytic therapy, the use of antiplatelet or

Table 9.7 Emergency management of arterial hypertension for persons receiving thrombolytic drugs for acute ischemic stroke: the NINDS Study Group method

Monitor arterial blood pressure during the first 24 h after starting treatment as follows:

•	Every 15 min for 2 h after starting the infusion, then
•	Every 30 min for 6 h, then
•	Every 60 min until 24 h after starting treatment
If systolic blood pressure is 180–230 mmHg or if diastolic blood pressure is 105–120 mmHg for two or more readings 5–10 min apart:	
•	Give intravenous labetalol 10 mg over 1–2 min; the dose may be repeated or doubled every 10 min up to a total dose of 150 mg
•	Monitor blood pressure every 15 min during labetalol treatment and observe for development of hypotension
If systolic blood pressure is >230 mmHg or if diastolic blood pressure is in the range of 121–140 mmHg for two or more readings 5–10 min apart:	
•	Give intravenous labetalol 10 mg over 1–2 min; the dose may be repeated or doubled every 10 min up to a total dose of 150 mg
•	Monitor blood pressure every 15 min during labetalol treatment and observe for development of hypotension
•	If no satisfactory response, infuse sodium nitroprusside (0.5–10 mg/kg/min)[a]
•	Continue monitoring blood pressure
If diastolic blood pressure is >140 mmHg for two or more readings 5–10 min apart:	
•	Infuse sodium nitroprusside (0.5–10 mg/kg/min)[a]
•	Monitor blood pressure every 15 min during infusion of sodium nitroprusside and observe for development of hypotension

[a] Continuous arterial monitoring is advised if sodium nitroprusside is used. The risk of bleeding secondary to an arterial puncture should be weighed against the possibility of missing dramatic changes in pressure during infusion.

antithrombotic drugs is not recommended.[87] Since heparin, aspirin, and warfarin were all prohibited during the first 24 hours in the NINDS trial, insufficient data exist regarding the safety and efficacy of these agents in the setting of thrombolysis within 3 hours.

EXPANDING THE POPULATION ELIGIBLE FOR ARTERIAL RECANALIZATION

Any therapy for ischemic stroke will not have a major impact upon public health unless large numbers of patients with acute stroke can be treated within a few hours of onset. At present, only a very small proportion of patients with acute ischemic stroke are being evaluated within that time frame. For example, in the NINDS study, over 15 000 patients who sustained stroke were screened to enroll 624 patients. Progress must be made in public education, out-of-hospital care, and treatment within emergency departments.

PUBLIC EDUCATION

In a Gallup poll conducted in 1996 for the National Stroke Association (Englewood, CO), 90% of those surveyed were aware of stroke, but more than onethird did not associate weakness or numbness of the face or limbs with stroke. Two-thirds did not associate difficulty speaking or slurred speech with stroke, and more than one-third were not aware that stroke occurs in the brain. Interestingly, 90% of the survey

respondents indicated that notifying the US emergency telephone number 911 is appropriate for acute stroke. A population-based telephone interview survey of the Cincinnati area in 1995 found that only 57% of respondents correctly listed at least one of five established warning signs of stroke.[89]

OUT-OF-HOSPITAL CARE

Systems of dispatchers, emergency medical technicians, and paramedics vary in the United States. The variability among European countries is even greater. Strategies for earlier evaluation and transport of stroke patients out of hospital must be designed at the local level to meet the challenges of the differing out-of-hospital care systems. The goal in developed countries should be evaluation and transport to a hospital within 30–60 min.

Out-of-hospital caregivers can expand the population eligible for thrombolysis. In the NIH t-PA pilot studies,[90] half of the screened patients used the 911 system as their first medical contact. During the course of the studies, this percentage increased to 65%. Out-of-hospital caregivers are often with the patient for up to 1 hour before the patient is seen by a physician. Clearly, if those caregivers are schooled in stroke therapy, they may begin appropriate general measures and notify destination hospitals that a potential candidate for thrombolytic therapy is en route. Such communication can reduce onset-to-treatment time by allowing early mobilization of appropriate in-hospital personnel.

EMERGENCY DEPARTMENT TRIAGE AND CARE: THE GOLDEN HOUR

Minimizing the time necessary to evaluate and treat stroke patients from the moment they arrive at the local hospital to the time the therapy is delivered requires a detailed analysis of the local hospital system. The approach taken by the eight centers involved the NINDS study has been reported:[91] these techniques may not be well suited to hospitals within different European countries. In December 1996, a symposium convened by the NINDS addressed the general topic of expanding the population of stroke patients eligible for thrombolytic therapy. The consensus was that in-hospital evaluation and treatment should be completed within 60 min of the patient's arrival at the emergency department.

DIAGNOSTIC AIDS

A general diagnostic challenge for stroke investigators is to develop the capability for rapidly detecting a clot, reversible cerebral ischemia, and irreversible cerebral infarction. The earlier the clinician has such information available, the earlier decisions can be made regarding potential benefits and risks of thrombolytic therapy.

COMPUTED TOMOGRAPHY

Computed tomography is an insensitive detector of a clot. In ECASS, in which all patients received CT scans within 6 hours of symptom onset, the hyperdense cerebral artery sign was detected in about 20% of patients. In MAST-E, the hyperdense cerebral artery sign was detected in a higher number, but still only 37% of the entire group.[69]

With regard to ischemia, early CT scans are more sensitive than was previous appreciated: von Kummer and colleagues have made significant contributions with regard to the importance of subtle signs of ischemia. In ECASS,[92] when these subtle signs or other signs were either absent or involved ɣ33% of the MCA

territory, the odds ratio for not being disabled in t-PA treated patients compared with placebotreated patients was 1.7, and the 95% CI 1.2–2.2. In contrast, if these subtle signs or other signs involved more than one-third of the MCA territory, the odds ratio for not being disabled in tPA-treated patients compared with placebotreated patients was 0.4, and the 95% CI 0.1–2.

von Kummer hypothesizes that regions of brain displaying signs of hypodensity by CT nearly always evolve to infarction. For example, in ECASS[93] placebo patients with normal initial CT scans, the subsequent infarct volume by CT was 35±51 cm^3. For those with hypodensity present but involving <33% of the MCA territory, the subsequent infarct volume was 87±67 cm^3. In those placebo patients in whom the hypodensity involved more than 33% of the MCA territory, subsequent infarct volume was 181± 71 cm^3. Spiral CT now offers the capability of CT angiography. In a recent study of 62 patients,[94] the findings by spiral CT angiography correlated very highly with the results of concurrent angiography (n=10), ultrasound (n=31), and magnetic resonance angiography (n=22). In that series, there was only one instance of a spiral CT angiogram that did not show a lesion detected by another modality.

MULTIMODAL MAGNETIC RESONANCE IMAGING

Multimodal magnetic resonance imaging (MRI) techniques have become particularly promising because of their potential to provide data on cerebral perfusion, tissue injury, and vessel occlusion.[95] Perfusion-weighted MRI may be superior with regard to very early (<3 hours from symptom onset) sensitivity when compared with diffusion-weighted MRI.[96] Diffusion-weighted abnormalities may be slower to evolve[97] but, by 6 hours after symptoms onset, the sensitivity of diffusion-weighted imaging probably exceeds 90%.[98,99] Schellinger and colleagues studied 51 patients with multimodal MRI that included MR angiography (MRA) and diffusion-, perfusionand T2-weighted imaging.[100] Patients were initially scanned at the mean time of 3. 33±1.29 hours after stroke onset and 41 patients underwent follow-up imaging. Fifteen of 45 patients showed recanalization on day 2. Vessel occlusion was associated with a perfusion—diffusion lesion volume mismatch. Outcome scores and lesion volumes differed significantly between patients experiencing recanalization and patients who did not. At this point, however, practical and historical issues have kept MRI as the second-line modality in evaluating patients with acute stroke. The pivotal randomized trials used CT, not MRI, to assess patient eligibility. In most clinical settings, the 24-hour emergency availability of personnel and equipment remains greater for CT than for MR imaging.

CONCLUSION

Intravenous administration of t-PA is the first acute therapy for stroke with proven efficiency. The rate of neurologic recovery is improved, and 1 additional patient with total or near-total recovery results from about every 8 patients treated. The risk for symptomatic intracranial hemorrhage is relatively low, and mortality is not increased. Angiography-based studies of intravenous thrombolytic therapy as well as case series of local intra-arterial therapy document (1) modest rates of arterial recanalization following thrombolytic therapy, and (2) extended time-tolysis following thrombolytic therapy, suggesting resistance of cerebral clots to thrombolysis with single-agent treatment.

A prospective multicenter phase IV study suggests that favorable clinical outcomes and low rates of symptomatic hemorrhage can be achieved outside of a clinical trial using intravenous t-PA for its approved indication.[101] Katzan and colleagues studied the experience of 29 hospitals in the Cleveland, Ohio metropolitan area. Just under 2% of patients admitted with ischemic stroke received intravenous t-PA and, of these patients, 15.7% (95% CI, 8.1%–26.4%) had symptomatic ICH. Half of the t-PA-treated patients had

deviations from US national treatment guidelines.[102] Lopez-Yunez and colleagues reviewed the Indianapolis community experience and found NINDS protocol violations to be common and associated with symptomatic cerebral and systemic hemorrhages.[103] At present, it is important to adhere closely to the NINDS protocol regarding the use of intravenous t-PA.

Mechanical disruption of the clot, combination therapies, and the use of second- and thirdgeneration thrombolytic drugs offer promise for the future. Improvements in early diagnostic evaluation of patients, particularly by MRI techniques, hold promise for better patient selection.

Finally, it may be possible in the future to supplement the benefits of arterial recanalization by neuronal protection, particularly if both strategies are used simultaneously, and if they can be used very early following symptom onset.

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10.
Anticoagulant therapy

Jacob S Elkins and Raymond A Swanson

INTRODUCTION

Although heparin and other anticoagulants have been used for over 50 years, clinicians remain divided as to their efficacy in acute stroke. Surveys have consistently shown widely differing practice patterns, with anticoagulant use ranging from rare to routine.[1–4] These differences likely reflect historically opposing factors: the intuitive appeal of treating a thromboembolic disease with anticoagulants on the one hand, and the paucity of useful clinical data on the other. This situation is changed somewhat with the recent publication of several large clinical trials and stroke registry records. In this chapter we will review the mechanisms of action and pharmacokinetics of anticoagulants and the clinical data pertaining to their use in acute stroke.

Anticoagulants are broadly defined as agents that reduce either the activity or concentration of endogenous clotting factors.[5] Standard, unfractionated heparin and low-molecularweight heparin are the most widely used anticoagulants in acute stroke. There is little experience to date with newer anticoagulants such as direct thrombin inhibitors and defibrogenating agents, and these will be discussed only briefly. Oral anticoagulants, such as warfarin, are generally not used in acute stroke treatment because of their delayed onset of action. Antiplatelet agents and thrombolytics are discussed in other chapters.

MECHANISMS OF HEPARIN ANTICOAGULATION

Heparin consists of a heterogeneous mixture of glycosaminoglycans, ranging from 3000 to 30 000 Da in molecular weight. Although heparin was first identified in 1916,[6] its anticoagulant mechanism was largely unknown until 1973.[7] It is now established that heparin dramatically enhances the ability of antithrombin to form inhibitory complexes with thrombin (factor IIa) and factors IXa, Xa, XIa, and XIIa. Of these, thrombin and factor Xa are the most susceptible to clinically significant inhibition.[8] Only a small fraction of heparin binds to antithrombin, but this fraction is primarily responsible for heparin's anticoagulant effects.[9] The interaction of heparin and antithrombin is dependent on a unique pentasaccharide sequence that occurs randomly along the heparin chains. This pentasaccharide sequence causes a conformational change in antithrombin that increases its affinity for factor Xa, for example, by about 1000-fold.[10] By inhibiting thrombin, heparin not only prevents fibrin deposition but also prevents the thrombin-mediated activation of factor V and factor VIII.[11,12] In addition to its effects on clotting factors, heparin also induces secretion of tissue factor pathway inhibitor,[13] inhibits von Willebrand factor-dependent platelet adhesion,[14] and increases vessel wall permeability.[15] These additional effects may contribute to hemorrhagic complications of heparin use, independent of its direct anticoagulant effects.[16]

Naturally occurring heparin is also termed ‘unfractionated heparin’ to distinguish it from semi-synthetic, low-molecular-weight heparin. Low-molecular-weight heparin is processed to contain polymers with an average molecular weight of about 5000 Da. Unfractionated and low-molecular-weight heparin differ significantly in their interactions with thrombin and factor Xa. The interaction between heparin, antithrombin, and thrombin requires the formation of a ternary complex that requires heparin chains of at least 18 saccharide units.[17] While the majority of unfractionated heparin chains are of this length, fewer than half of the chains in low molecular weight-heparin are of this length.[18] Consequently, unfractionated heparin has significant activity against both thrombin and factor Xa, whereas low-molecular-weight-heparin acts primarily through factor Xa inhibition. The relevance of this selective factor Xa inhibition is highlighted by the recent chemical synthesis of the operative pentasaccharide in heparin. This compound acts exclusively as an antithrombin-dependent inhibitor of factor Xa[19] and has been shown to be more effective than low-molecular-weight heparin in preventing deep vein thrombosis after hip replacement.[20]

HEPARIN PHARMACOKINETICS

Unfractionated heparin can be administered as a continuous intravenous infusion or as twice-perday subcutaneous injections. Peak anticoagulant effects occur nearly immediately after intravenous injection and 3–4 hours after subcutaneous injection.[21] Clearance of unfractionated heparin has a rapid, saturable phase, caused by adhesion to endothelial cells and macrophages, followed by a slower phase of renal excretion.[22,23] These clearance rates vary widely between individuals and, consequently, intravenous heparin infusions require careful monitoring to achieve a therapeutic anticoagulant effect without overshoot. Clinicians typically aim for an activated partial thromboplastin time (aPTT) of 1.5–2.5 times normal; however, anti-factor Xa levels may provide a more accurate monitor of heparin anticoagulation, especially when doses exceed 35 000 U/day.[24] In general, weight-based nomograms provide the most effective dosing strategies.[25] Intravenous heparin administration is often initiated with a bolus injection in other clinical settings, but many clinicians omit the initial bolus in acute stroke treatment to reduce the risk of hemorrhagic complications.[26] Heparin anticoagulation can be rapidly reversed with protamine sulfate at a ratio of approximately 1 mg per 100 U of heparin. Only the heparin given during the previous few hours should be used in the calculation of the protamine dose, as the half-life of unfractionated heparin is approximately 60 min (e.g. 30 mg of protamine to reverse heparin anticoagulation in a patient receiving an heparin infusion of 1250 u/h).[8]

Low-molecular-weight heparins have a more predictable pharmacokinetic profile than unfractionated heparin, an advantage due in part to reduced binding of shorter heparin chains to plasma proteins and endothelium.[10] However, a disadvantage to low-molecular-weight heparins is that the standard aPTT cannot be used to monitor anticoagulant effects; instead, antifactor Xa activity must be used if it is necessary to titrate the dose. The optimal therapeutic range of low-molecular-weight heparin in stroke is not known, but in other clinical settings the established target range is 0.6–1.0 anti-factor Xa U/ml, measured 4 hours after subcutaneous injection.[27] A second potential disadvantage of low-molecular-weight heparin is that protamine sulfate does not bind as effectively and does not fully reverse its anti-factor Xa activity. Whereas protamine has reversed bleeding caused by lowmolecular-weight heparin in laboratory animals,[28] its efficacy in the clinical setting is not established.

ANTICOAGULANT USE IN ACUTE STROKE

The primary objective for anticoagulant use in the acute stroke setting is to prevent recurrent stroke. Although anticoagulation could theoretically limit ischemia due to ongoing thrombosis and clot propagation, this pathophysiology has only rarely been documented as a cause of stroke progression.[29–31] Rather, it appears that clinical deterioration is far more commonly due to edema and metabolic changes than to extension of thrombus.[29,32,33] Anticoagulants are also used to prevent deep venous thrombosis and pulmonary embolism in patients immobilized after stroke. However, this can be effectively achieved with much lower heparin dosing (typically 5000 U subcutaneously, twice per day) than is required to prevent arterial thromboembolism. Some authors have also suggested that heparins may be neuroprotective in stroke by mechanisms unrelated to their anticoagulant effects.[34–37] Although neuroprotective effects have been observed in animal models of ischemia, their relevance to human stroke treatment is unknown.

RISKS OF ANTICOAGULANT THERAPY IN ACUTE STROKE

The potential benefits of anticoagulants in acute stroke must be carefully weighed against the potential complications. The presence of infarcted tissue in brain greatly increases the risk of intraparenchymal brain hemorrhage with anticoagulation after stroke. In addition, extracranial bleeding carries the added risk of extending infarct volume in the acute stroke period by inducing hypotension. Accordingly, patients presenting with conditions such as atrial fibrillation, for whom anticoagulation might otherwise be indicated, may not necessarily be suitable anticoagulation candidates in the first few days after a stroke.

The incidence of anticoagulant-induced complications in the acute stroke setting can only be approximated, because this has been prospectively evaluated only in small and mostly nonrandomized studies. These studies report the incidence of symptomatic intracranial hemorrhage to vary between 0 and 7. 8% in stroke patients over 7 days of anticoagulation with dose-adjusted intravenous unfractionated heparin.[38–41] The incidence of other major bleeding complications varied from 2.9 to 12.3%. Although the studies did not specify whether these complications were of sufficient severity to cause hypotension, in all cases they resulted in termination of heparin infusions. Not all of these bleeding complications can be ascribed to heparin, of course, as a small number of placebo-allocated patients also develop these complications.

While hemorrhagic complications of anticoagulant use are largely unpredictable, several characteristics may help to limit anticoagulant use in stroke patients at high risk for bleeding. Risk factors for hemorrhage include acute hypertension with mean arterial pressure greater than 130 mmHg,[26,42] early focal hypodensity or large infarct on computed tomography (CT) scan,[43,44] and clinical findings correlating to greater than 15 points on the National Institutes of Health stroke scale (NIHSS).[45] Importantly, the risks of both intracranial and extracranial hemorrhage increase with increasing intensity of anticoagulation.[45,46]

Heparin-induced thrombocytopenia is an additional, but less frequent, complication of anticoagulant use. The syndrome is identified by a drop in the platelet count of 50% or more, usually in the presence of immunoglobulin G (IgG) antibodies to heparin and platelet factor [48,47] The drop in circulating platelet count stems from platelet aggregation, and these patients are at risk for multiple arterial and venous thrombi. This syndrome most commonly develops about 5 days after start of heparin therapy, but can develop acutely in susceptible patients who have received heparin at any time within the previous 100 days.[48] The frequency of heparin-induced thrombocytopenia varies in different clinical situations, occurring more often in surgical patients where the rate can approach 3%.[49,50] Of note, heparin-induced thrombocytopenia occurs less frequently with low-molecular weight heparin than with unfractionated heparin.[50] Anticoagulant use is also

associated with rare cases of heparin-induced skin necrosis and other anaphylactic reactions,[51] and use of heparin for periods greater than 3–4 months may lead to osteoporosis.[52]

RISK OF ACUTE RECURRENT STROKE

The risks of anticoagulant administration in the acute stroke setting must be balanced with the potential benefit of preventing recurrent stroke. The overall risk of acute recurrent stroke, assessed without consideration of stroke etiology, appears to be in the range of 1.2–4.5% over the initial 2 weeks. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) reported recurrent stroke in 1.7% in 628 placebo-treated patients at 10 days.[45] Similarly, the International Stroke Trial (IST) reported recurrent stroke in 214 of 4859 stroke patients after 14 days in the control group receiving neither aspirin nor heparin (2.2%/week).[46] The placebo arm of the large Chinese Acute Stroke Trial (CAST), with over 10 000 stroke patients, showed an even lower rate of 2.1% stroke recurrence at 30 days.[53]

A second indication of stroke recurrence risk is provided by stroke registry data. The NINDS Stroke Data Bank, which includes patients admitted to several US hospitals, reported recurrent ischemic stroke in 10 of 1273 patients (1.2%) within 7 days of initial stroke,[54] and the Northern Manhattan Stroke Study, which draws from a mixed ethnic urban community, reported a recurrence in 18 of 323 (6%) within 30 days.[55] The recurrence rates in these populations are in close agreement with the low recurrence rates reported in the control arms of the clinical trials despite the fact that the registries include patients who were treated, as well as patients who for various reasons would have been excluded from the clinical trials.

Although the overall risk of acute stroke recurrence appears to be low, this assessment may mask subgroups of patients with very high risks of stroke recurrence. The optimal risk-benefit ratio for anticoagulant use is in situations with a low risk of hemorrhage and a high risk of recurrent stroke.[56] Clinical trials and stroke registries also provide a means of assessing the risk of recurrent stroke in specific patient subgroups, and these studies show that stroke etiology is a major factor in determining the risk of recurrent stroke.

RECURRENCE IN PATIENTS WITH CARDIOEMBOLIC STROKE

Stroke in patients with atrial fibrillation is often assumed to be of cardioembolic origin, although other etiologies are obviously possible. The risk of initial stroke in patients with atrial fibrillation is several fold higher than age-matched controls,[57] and oral anticoagulation is effective in reducing this stroke risk.[58–60] Acute anticoagulation as a treatment for cardioembolic stroke is less well studied. Initial reports from case series and uncontrolled trials suggested a recurrent risk from cardioembolic stroke of roughly 12% (range 2–22%) over 2 weeks,[26,61–64] but more recent studies suggest this risk may be less.[45,46,54,65–67] The TOAST study included 266 patients with strokes classified as cardioembolic.[66] Recurrent strokes within 7 days occurred in only 2 of 123 patients (1.6%) receiving placebo.[45] The IST trial[46] enrolled 3169 patients with stroke and atrial fibrillation. In untreated patients, atrial fibrillation was associated with only a modestly higher recurrent stroke risk: 4.9% at 14 days compared with 3.6% in patients without atrial fibrillation. In stroke registry reports, atrial fibrillation was associated with roughly a doubling of the stroke recurrence risk, but the absolute rate of stroke recurrence in this group was still less than 5% at 30 days.[54,67]

In summary, many studies indicate an increased risk for early recurrent stroke in patients with atrial fibrillation, but the absolute recurrence risk is likely to be in the range of 3–8% at 2 weeks rather than the higher rates previously thought. Other cardiac conditions may carry a much greater risk of recurrent cardioembolic stroke than atrial fibrillation. Rheumatic heart disease, prosthetic valves, acute myocardial

infarction, and intracardiac thrombus have each been associated with significantly higher rates of early recurrent stroke than atrial fibrillation without organic heart disease.[68]

RECURRENCE AFTER LARGE-ARTERY ATHEROTHROMBOTIC STROKE

Large-artery atherosclerosis is generally considered to be the cause of stroke when there is evidence of proximal atherosclerotic narrowing.[66] This stroke subtype is associated with an increased risk of early stroke recurrence in registry data and natural history studies.[54,55,67] In both the NINDS Stroke Data Bank[54] and the Northern Manhattan Stroke Study,[55] the atherosclerotic stroke subgroup had an approximately 8% rate of stroke recurrence within 30 days. This rate was significantly greater than in the atrial fibrillation group, although the two groups may have received differing treatment.

RECURRENCE AFTER LACUNAR STROKE

Lacunar strokes[69] appear to have a lower risk of early recurrence than other stroke subtypes. Stroke recurrence in registry series is about 2.2% at 30 days in patients presenting with lacunar stroke.[54] In the TOAST study, stroke recurrence in the first week was 1.3% in 148 patients with small-artery occlusion. Although initial worsening of deficits is common, spontaneous improvement rates are high in lacunar strokes, with the majority improving by 4 days regardless of treatment.[70] In a recent analysis of the TOAST data, patients with lacunar strokes were more than three times as likely to have favorable outcomes at 90 days after multivariate adjustment.[71]

RECURRENCE AFTER OTHER STROKE TYPES

Approximately 5% of ischemic strokes are secondary to the relatively uncommon but identifiable causes such as endocarditis, vasculitis, non-atherosclerotic vasculopathies, hypercoagulable states, and arterial dissection. Some of these conditions may have very high risks of stroke recurrence. In particular, numerous case series have documented a high rate of cerebral ischemia following both traumatic and spontaneous dissection of the carotid and vertebral arteries.[72–76] In one series of 80 patients with dissection confirmed, angiographically cerebral or retinal ischemia occurred in 46% of patients after presentation, usually within the first 7 days.[72] Strokes secondary to infectious and inflammatory disorders are generally not treated with anticoagulants because more specific therapy is usually available and unacceptable rates of hemorrhage are reported.[77]

EFFICACY OF ANTICOAGULANT THERAPY IN ACUTE STROKE

A recent meta-analysis suggests that anticoagulation with heparin reduces the rate of stroke recurrence by about nine fewer strokes per 1000 patients treated.[78] This analysis included all randomized trials of both unfractionated and low-molecular-weight heparins at varying doses and differing routes of administration. The efficacy of intravenous, dose-adjusted unfractionated heparin has been studied in only one small randomized trial[38] and remains largely unknown. In the IST trial, heparin-treated patients had a recurrent stroke rate of 2.9% at 14 days vs 3.8% for other patients.[46] In the TOAST study,[79] after 90-days of follow-up, recurrent strokes occurred in 4.0% of heparin-allocated patients vs 5.9% of patients in the placebo group. Although these studies showed convincingly that anticoagulation can reduce stroke recurrence, they also showed an increase in intracerebral hemorrhage in the heparin-treated groups, and this increase in

hemorrhagic complications outweighed the reduction in recurrent stroke.[78] In the IST trial, this pattern also held true in the subgroup of patients who presented with atrial fibrillation and stroke.[46]

Although anticoagulants have failed to show any benefit in randomized clinical trials,[78] many authors feel that these trials have been inadequate.[34,80,81] With the exception of one small, uncontrolled trial,[82] no randomized anticoagulant study has had an average time-to-treatment less than 15 hours, and this delay in anticoagulant administration may have reduced the ability of existing trials to detect benefits of anticoagulant use. In addition, heparin use in specific highrisk subgroups has never been prospectively examined. A post-hoc subgroup analysis of the TOAST trial suggested a net benefit of heparin on 90-day outcome in patients with large-artery atherosclerotic stroke,[79] but this finding has not been replicated. Of note, the use of anticoagulants as a treatment for cerebral venous sinus thrombosis has been established in two randomized trials and case reports.[83–85] Even in the presence of intracerebral hemorrhage, anticoagulants were associated with lower mortality,[83] and consensus guidelines now recommend anticoagulation as first-line treatment for this condition.[86]

ANTICOAGULANTS FOR THE PREVENTION OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Deep vein thrombosis and pulmonary embolism are important causes of morbidity and mortality after stroke. Numerous studies have documented the benefits of anticoagulants in the prevention of these complications in a variety of surgical and medical conditions.[87–91] A recent meta-analysis of anticoagulation for the treatment of acute stroke found that the use of anticoagulants was associated with a highly significant reduction in deep vein thrombosis, similar to that seen with prophylactic heparin use after surgery.[78] Similarly, in the IST trial, pulmonary embolism was significantly less common in heparin-treated patients compared with placebo-treated patients, although it was uncommon in both groups (0.5% vs 0.8% over 14 days). Although anticoagulants have not been rigorously compared with alternative treatments such as pneumatic compression devices or compression stockings after stroke, low-dose subcutaneous heparin appears to be both safe and effective for the prevention of deep vein thrombosis and pulmonary embolism.

THROMBIN INHIBITORS AND DEFIBROGENATING AGENTS

Several new anticoagulant drugs have been employed in clinical practice in recent years but have had only limited evaluation in the acute stroke setting. Direct thrombin inhibitors have a theoretical advantage over heparin in that they are able to directly inactivate thrombin bound to fibrin and fibrin degradation products,[92,93] and thereby produce a more focused anticoagulant effect. Hirudin, a direct thrombin inhibitor, has been shown in randomized trials to be more effective than heparin in reducing cardiac morbidity during acute myocardial ischemia.[94,95] Its use, however, has been limited by an excess incidence of hemorrhage in treated patients, a problem that makes it unlikely to be useful for treatment of stroke. Defibrogenating agents reduce effective plasma concentrations of the procoagulant fibrinogen. The principal agent in this class is ancrod, a component of snake venom. Ancrod cleaves fibrinopeptide A into a fibrin monomer, resulting in lower concentrations of fibrinogen and reduced blood viscosity.[96,97] Small trials suggest that ancrod can be used safely in the setting of acute ischemic stroke.[98,99] One large recent randomized, placebocontrolled trial found that ancrod was associated with a significantly better outcome at 90 days when administered within 3 hours of symptom onset;[100] however, this result was not replicated in a follow-up study using a time window of 6 hours.[101]

SUMMARY

Alternative agents are on the horizon, but standard unfractionated heparin and low-molecularweight heparin remain the primary agents now available for anticoagulation in the acute stroke setting. Of these, low-molecular-weight heparin may have some advantages because of its more predictable pharmacokinetics and lower propensity to induce thrombocytopenia, but clinical experience with these agents is less extensive than with unfractionated heparin. Risk of recurrent stroke varies significantly with stroke etiology, ranging from less than 2% over 2 weeks in large series of unselected patients to over 40% in small series of carotid dissections. The risk of bleeding complications, on the other hand, increases with increasing anticoagulant intensity, stroke size, and blood pressure. The decision to administer anticoagulants to a patient in the acute stroke setting requires an assessment and balancing of the risk of recurrent stroke versus the risk of anticoagulant-induced bleeding and other complications.

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11.
Antiplatelet therapy in acute brain ischemia

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INTRODUCTION

Platelets are formed by the fragmentation of megakaryocytes in the bone marrow. They are the smallest cellular elements of blood, 2–4 μm in diameter, 0.75 μm thick, and with a mean volume of approximately 7–10 fl. Each platelet is made of an assembly of multiple microskeletal layers. Platelets are anucleate and hence, cannot divide and have a limited capacity for de-novo protein synthesis. Under normal physiological conditions, platelets circulate in the bloodstream as tiny disks without interactions with the vessel wall or with each other. Several factors regulate normal blood flow, including the biophysical properties of flowing blood, the net electrical charge of its cellular elements, and the release of anti-aggregating factors by the endothelium such as adenosine diphosphate (ADP)—degrading enzymes, ADPase, nitric oxide, and prostacyclin.[1–6] Endothelial ADPase converts ADP released from erythrocytes and activated platelets to inactive adenosine monophosphate (AMP), adenosine, and inosine. Nitric oxide (also known as endothelium-derived relaxing factor) and prostacyclin induce the relaxation of vascular smooth muscle and inhibit platelet aggregation.[7]

The main role of platelets is to provide the first line of defense against hemorrhage—a process termed primary hemostasis. They are involved in a number of other processes, however, including phagocytosis, inflammation and other immune reactions, angiogenesis, interaction with tumor cells, and in the pathophysiology of atherosclerosis and thrombosis.[2] Platelet recruitment at sites of injury proceeds in two distinct steps: adhesion followed by aggregation.[8,9] When platelets are exposed to a non-endothelial surface they adhere, flatten, and spread on the surface, forming a pavement-like monolayer. Most platelets recruited at sites of injury do not adhere to subendothelial structures but aggregate together in a growing hemostatic plug. The initial monolayer provides the matrix upon which passing-by platelets attach and accumulate in successive layers. Platelet activation, the moving force beneath adhesion, aggregation, and the release reaction, occurs upon exposure of adhesion receptors to soluble and matrix-bound ligands and upon binding of soluble agonists to specific membrane receptors. Platelet activation is an energy-dependent process in large part mediated through polymerization of microskeletal proteins (e.g. actin, spectrin, vinculin). In normal individuals, platelets have a life span of 7–10 days. Approximately one-third of the platelet pool remains sequestered in the splanchnic circulation. Increased splanchnic pooling explains in part the thrombocytopenia commonly associated with splenomegaly. Platelet homeostasis is regulated by thrombopoietin, a polypeptide hormone produced in the kidney and liver.

The role of platelet in atherothrombosis was shown in the early 1970s but definitive evidence was provided by the trials of secondary prevention, which demonstrated the effectiveness of antiplatelet regimens in a variety of disorders, including myocardial infarction, unstable angina, and ischemic stroke.[10]

The role of antiplatelet therapy in the acute phase of arterial thromboembolism is a more recent concept. It was underscored by the landmark second International Study of Infarct Survival (ISIS-2) trial, which compared in a 2×2 factorial design, systemic streptokinase, aspirin, both agents, and neither. This study showed that aspirin (160 mg daily) started within 24 hours of acute myocardial infarction onset, was as efficacious as systemic streptokinase in reducing the 1-month mortality rate, and that the effect of both agents was cumulative (i.e. 2.5% absolute reduction per agent and 5% combined).[11] The advent of platelet glycoprotein (GP) Ilb-IIIa antagonists and combined antiplatelet regimens, such as aspirin and the thienopyridine ADP receptor antagonist clopidogrel, have underscored the role of more intense platelet blockade. Globally, parenteral GP Ilb-IIIa antagonists reduce the 1-month rate of ischemic complications after percutaneous coronary intervention (PCI) from 12% to 9%.[12–22] More recently, a combined regimen of aspirin (75–325 mg daily) and clopidogrel (300 mg loading followed by 75 mg daily), started within 24 hours of acute coronary syndrome, was more efficacious than aspirin alone in reducing rates of cardiovascular death, nonfatal myocardial infarction, or stroke at 1 year. Interestingly, the benefit of the combined regimen became apparent within 24 hours of the start of treatment.[23]

Despite the overwhelming impact of acute antiplatelet therapy in coronary artery disease, it has received little attention in acute ischemic stroke until recently. Two large trials, the International Stroke Trial (IST)[24] and the Chinese Acute Stroke Trial (CAST),[25] demonstrated a small, nevertheless clinically meaningful, benefit of aspirin started within 48 hours of stroke for reducing early stroke recurrence and the 6– month mortality and functional dependency rates.

This chapter focuses on the role of platelets in atherothrombosis and the current status of antiplatelet therapy in the acute treatment of ischemic stroke, including the possible role of newer agents. We also include a section on contemporary platelet physiology and relationships to atherothrombosis.

ATHEROTHROMBOSIS

Atherosclerotic plaque disruption exposes the flowing blood to the thrombogenic stimulus of subendothelial matrix (e.g., collagen, fibronectin, laminin, and von Willebrand factor) and plaque contents (e.g., tissue factor, lipid core).[26–29] Thrombosis arises from the parallel activation of platelets and coagulation, culminating to thrombin generation and formation of a platelet-fibrin lattice. Over the ensuing hours, the platelet-fibrin lattice becomes more resistant to plasmin degradation, in part owing to the phenomena of fibrin cross-linking and clot retraction.

Fibrin cross-linking involves the formation of covalent bonds between adjacent strands, mediated via activated factor XIII.[30,31] Activator factor XIII is generated by the catalytic cleavage of thrombin on zymogen factor XIII. Another effect of thrombin results in diminished susceptibility to fibrinolysis: namely the activation of TAFI (thrombin-activatable fibrinolysis inhibitor), a fibrinolysis inhibitor expressed on the thrombus surface.[32] Clot retraction occurs as a result of ‘outside in’ signaling of the activated GP Ilb-IIIa receptor (γ2bγβ integrin) transduced onto the platelet microskeleton and triggering the polymerization of actin and other microskeletal proteins.[33,34] These events lead to platelet contraction and retraction of the platelet-fibrin lattice. Defective fibrin polymerization due to congenital factor XIII deficiency causes a bleeding diathesis. Abnormal clot retraction contributes to the increased bleeding mechanism in Glanzmann’s thrombasthenia (i.e., congenital deficiency of GP IIb–IIIa).[33,34]

Additional factors influence the extent and severity of thrombus formation after atherosclerotic plaque rupture. These include the degree of plaque disruption, severity of stenosis, systemic catecholamines, the renin-angiotensin system, local vasoconstriction, and the patient’s individual fibrinolysis and coagulation responses.[35–40] Vasoconstriction is thought to arise from an imbalance between the release of relaxing (e.g.,

prostacyclin and nitric oxide) and contracting factors from the endothelium (e.g., endothelin-1) and platelets (e.g., serotonin and thromboxane A_2). Platelet activation enhances the production of endothelin-1, an extremely potent vasoconstrictor peptide made by endothelial cells.[35,36] Under physiologic condi tions, serotonin releases endothelium-derived relaxing factor from healthy endothelium and promotes vasodilatation. In atherosclerotic vessels, however, serotonin induces vasoconstriction and may cause vasospasm. The release of serotonin and other vasoconstrictors by aggregating platelets may contribute to the pathophysiology of acute coronary syndromes and transient ischemic attacks. In experimental models of coronary artery occlusion, intermittent vasoconstriction occurs, as evidenced by cyclic flow variations in the occluded vessel.[41,42] Cyclic flow variations within occluded coronary vessels may underscore the episodic nature of chest pain and electrocardiographic ischemic changes seen in unstable angina.[43] Blockade of the platelet release reaction by parenteral GP Ilb-IIIa antagonists may contribute to improved flow during PCI and may facilitate the phenomenon of 'dethrombosis' documented with the use of these agents.[20]

Evidence exists that plaque rupture may occur in asymptomatic individuals and without formation of mural thrombus.[26] A possible explanation for this phenomenon may lie in individual patient responses for platelet and coagulation activation, fibrin formation and its susceptibility to lysis, fibrinolytic activity, inflammatory response, and other variables. Ongoing studies of single nucleotide polymorphisms among these mechanisms and the detection of gene activation by microarrays may shed light in the future on these individual patient responses.[44]

CORONARY ARTERY DISEASE

A great deal of knowledge on the pathophysiology of atherothrombosis came from the studies of symptomatic coronary artery disease during the last two decades or so, coupled with advances in the field of vascular biology. In recent years, the focus has clearly shifted from the severity of vessel stenosis to plaque morphology, composition, and its thrombogenic propensity. The rupture or fissure of a vulnerable plaque leading to mural thrombosis underlies most cases of acute coronary syndromes.[26] Most commonly, these friable plaques occlude no more than 50% of vessels.

Atherosclerosis and its complications are beyond the scope of this review. Briefly, atherosclerosis is currently viewed as an inflammatory reaction in response to injury. The multifocal nature of atherosclerosis across several vascular beds was underscored by the trials of antiplatelet agents in secondary prevention. These studies showed that the onset of symptomatic illness, irrespective of the involved territory, increases the risk of vascular death, myocardial infarction, or stroke. Early atherosclerotic lesions occur during the second decade of life and subsequent plaque formation evolves over several decades.[27] Atherosclerosis involves complex interactions among endothelial cells, monocytes and macrophages, T lymphocytes, smooth muscle cells, and thrombogenic and hemodynamic factors. Several cellular mechanisms are involved, including inflammation, expression of adhesion receptors, smooth muscle cell proliferation, lipid oxidation, angiogenesis, and extracellular matrix synthesis. The expression of adhesion receptors on endothelium, monocytes, and T lymphocytes and the release of growth factors (e.g., platelet-derived growth factor, vascular endothelial growth factor) are important driving forces. Crosstalk between integrin and growth factors signaling is an important area of vascular biology research at the moment.[27]

Vulnerable plaques harbor a number of characteristics, including a substantial lipid core containing mostly liquid cholesteryl esters; a relative paucity of smooth muscle cells and collagen; a thinned-out collagen cap; marked inflammation with increased activated macrophages ('foam cells') and T lymphocytes, and increased neovascularization.[26] The gruel of vulnerable plaques has a soft, 'toothpaste-like' consistency. Of note, data on vulnerable plaque characteristics have been obtained mostly from analysis of

samples from patients with acute coronary syndromes, and their overall role in atherosclerosis pathophysiology is uncertain.

Interestingly, coronary atherosclerosis involves only the epicardial vessels. The absence of lesions within endocardial vessels has been ascribed to effect of ventricular contractions, effectively dispersing the various blood constituents and minimizing contact time with the endothelium. Subendocardial ischemic syndromes, including unstable angina and non-Q wave myocardial infarction, and increase in cardiac enzymes (e.g., creatinine phosphokinase, troponins) after PCI, are due to distal embolization of platelet-fibrin and plaque debris into the distal microcirculation. Improvements of left ventricular contractility and ejection fraction documented with the adjuvant use of parenteral platelet GP Ilb-IIIa antagonists during PCI or with thrombolytics for ST-elevation myocardial infarction underscore the important role of the coronary microcirculation in disease pathophysiology.[20,43]

CEREBROVASCULAR DISEASE

The pathophysiology of ischemic cerebrovascular syndromes is frequently extrapolated from that of symptomatic coronary artery disease. However, there are a few important differentiating features that deserve mention (Table 11.1). First, coronary artery disease occurs *in situ,* whereas ischemic cerebrovascular disease involves mostly atheroembolism in extracranial vessels (e.g., carotid bifurcation, aortic arch, left cardiac chambers). Non-embolic basilar artery occlusion is one notable exception, being more akin to coronary artery disease, and involving insitu atherothrombosis. Secondly, coronary thrombosis occurs during diastole (i.e., blood flows through the coronaries during diastole only) and, hence, under lower shear stress than systolic flow elsewhere throughout the body. In cerebrovascular ischemia, hemodynamic factors, including the shear stress during systole and turbulence around stenotic lesions, may play a more important role in plaque disruption. The relationship between degree of carotid stenosis and risk of ipsilateral stroke has been clearly shown in the randomized trials of surgical endarterectomy. Thirdly, data on plaque morphology and clinical correlates have been obtained in real time, during the acute phase of coronary ischemia, whereas they originate mostly from endarterectomy specimens or retrospective studies in carotid occlusion in the case of cerebrovascular disease.[45,46] Overall, the available data suggest that plaque ulceration and thrombosis are involved in cerebral ischemia, at least concerning carotid lesions. Additional data are required, however, on the precise mechanisms of plaque disruption, including cellular mechanisms and the relative contribution of lesions involving intracerebral vessels. Lastly, the importance of the microcirculatory flow has been alluded to in coronary artery disease. Microvascular thrombosis involving delayed platelet activation and fibrin formation has been shown in experimental models of cerebral ischemia.[47–49] The relative contribution of ongoing microvascular thrombosis post initial event in ischemic stroke, and the relationship with infarct progression in human is unknown. Attenuation of ongoing thrombosis within the microcirculation of the ischemic territory underscores in part the rationale for the study of parenteral GP Ilb-IIIa antagonists such as abciximab in acute ischemic stroke.[50]

ROLE OF PLATELETS

Platelet recruitment at sites of lesion occurs mostly through classic mechanisms of transmembrane stimulus-response coupling.[51] Signaling through adhesion receptors or ligand-specific membrane receptors results in a transient increase or decrease in the concentration of intracellular molecules termed secondary messengers. Prominent among these are 3′5′-cyclic adenosine monophosphate (cAMP), 3′5′-cyclic

guanosine monophosphate (cGMP), 1,2-diacylglycerol (DAG), inositol 1,4,5-triphosphate (IP3), and Ca2 +.[2,51]

ADHESION

Recruitment of platelets in atherothrombosis depends on their capacity to adhere to the vessel wall and participate in mural thrombus forma

Table 11.1 Features of coronary artery disease vs ischemic cerebrovascular disease

Feature	Coronary artery disease	Ischemic cerebrovascular disease
Main clinical syndromes	Unstable angina, non-Q wave myocardial infarction, ST-elevation myocardial infarction	Ischemic stroke, transient ischemic attacks
Pathophysiology	Mostly atherothrombosis from in-situ coronary lesions. Artery-to-artery embolism plays a role in subendocardial ischemia	Mostly atheroembolic from extracerebral lesions. In-situ atherothrombosis involved in lacunar infarcts and basilar thrombosis
Reperfusion therapy	Systemic thrombolytics and direct PCI reduce mortality in ST-elevation myocardial infarction Six-hour time interval from symptom onset for treatment Number of patients studied: several thousands Risk of intracranial hemorrhage with thrombolytics: 0.5–1%	Systemic recombinant tissue plasminogen activator significantly improves functional outcome but not mortality Six-hour time interval from symptom onset for treatment Number of patients studied: few hundreds Risk of intracranial hemorrhage: 6%
Revascularization Surgical	Surgical revascularization of left main coronary artery occlusion superior to medical treatment alone	Surgical endarterectomy superior to medical treatment alone for symptomatic carotid stenosis > 70%
Percutaneous intervention	PCI established in the treatment of ST-elevation myocardial infarction or acute coronary syndrome with persistent ischemia	Role unknown. Comparative trials to surgical endarterectomy underway
Antiplatelet therapy Oral	Acute aspirin reduces 1-month mortality by approximately 3% in ST-elevation acute myocardial infarction Combined: ASA/thienopyridine ADP receptor antagonist reduces rate of stent thrombosis ASA monotherapy and combined: ASA/thienopyridine ADP receptor antagonist effective in secondary prophylaxis	Acute aspirin reduces functional dependence by approximately 1% at 6 months ASA monotherapy and combined ASA/dipyridamole effective in secondary prophylaxis
Parenteral GP Ilb-IIIa antagonists	Reduce ischemic complications post-PCI	Role in primary treatment of ischemic stroke unknown

ADP, adenosine diphosphate; ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention.

tion at high-shear rates. Under high-shear conditions, thrombosis is mostly initiated by platelet adhesion to subendothelial von Willebrand factor (vWf) via the adhesion receptor GP Ib-IX–V.[34] Experimental studies under flow conditions have shown that platelets adhere in a biphasic process, first initiated by binding of the

followed by the binding of vWf to the activated GP Ilb-IIIa receptor (i.e., γ2bγβ integrin).[51] GP Ib-IX–V binding to vWf mediates initial contact, whereas binding to γ2bγβ establishes platelet immobilization and firm adhesion to the vessel wall. Under low-shear conditions, adhesion and thrombus formation appear independent of GP Ib-IX–V and involve other adhesion molecules GP Ib-IX–V complex to immobilized vWf and such as the large family of collagen receptors (e.g., GP VI, γ2bγ1, and others).

Platelets can also roll on the activated endothelium, a process also involving the GP-Ib-IX-V complex. Like neutrophils, circulating platelets roll and stick to vascular endothelium *in vitro* after treatment with tumor necrosis factor-γ (TNF-γ).[1,2,51] In arterioles, platelet rolling is dependent upon expression of endothelial cell P-selectin. P-selectin resides within the Weibel-Palade bodies of endothelial cells and platelet γ-granules and is expressed upon cell activation. P-selectin expression can occur from cell activation by inflammatory cytokines. GP Ib-IX-V and PSGL-1 have been proposed as platelet counter-receptors for endothelial P-selectin. Platelets can also roll on chronically activated endothelium via E-selectin. These studies provide a framework to explain thrombosis in the absence of endothelial cell denudation. They also support a dual role for the GP Ib-IX–V complex by mediating platelet adhesion to subendothelial matrix via vWf and to the activated endothelium via P-selectin or E-selectin. The GP Ib-IX–V complex also promotes interactions between platelets and neutrophils via its recognition of the leukocyte adhesion receptor Mac-1 (γMγ2). [51] In addition, the GP Ibγ subunit binds thrombin with high affinity and is involved in mediating platelet activation by this agonist.

In brief, the above discussion underscores the complex interactions between hemostasis and inflammatory mechanisms. These interactions are involved in a wide variety of disease processes, including rupture of atherosclerotic plaques, ischemic infarction, and reperfusion injury.

ACTIVATION

Platelet activation, the next step in the process, ensues as cells engage their adhesive ligands and encounter soluble agonists (e.g., ADP, thrombin, epinephrine, serotonin, platelet activating factor, thromboxane A_2). The majority of platelet agonists bind to surface membrane receptors coupled to heterotrimeric G-proteins.[52] The G-proteins are molecular switches linking platelet surface receptors to membrane or intracellular effectors. To date, nine G proteins have been identified in platelets. Their effector targets include phospholipases C and A_2 and adenyl cyclase.[52]

Platelet activation is an energy-dependent process that is associated with a number of events. The most important of these events are as follows:

1. A shape change, from a disk to a sphere with extending filopodiae.
2. Release of vasoactive amines, platelet agonists, and other products—e.g., type 1 plasminogen activator inhibitor (PAI-1), fibrinogen, thrombospondin, vitronectin—from platelet-dense granules and γ-granules.
3. A change in conformation of the GP Ilb-IIIa receptor, causing increased affinity for its soluble ligands.
4. Membrane receptor expression for coagulation factors Va and Xa.
5. Generation of platelet-derived microparticles. Platelet-derived microparticles are small membrane vesicles with procoagulant properties and their release during platelet activation appears to involve the GP Ilb-IIIa receptor. Microparticles have been documented in clinical conditions associated with platelet activation, including transient ischemic attacks.[53,54]

AGGREGATION

Platelet activation and aggregation are triggered by the release of excitatory agonists from nearby platelets and other activated cells (e.g., monocytes, endothelium, lymphocytes) that bind to specific membrane receptors.[1] These structurally diverse agonists, include γ-thrombin, ADP, collagen, epinephrine, thromboxane A_2, platelet activating factor (PAF), serotonin, vasopressin, and epinephrine. The local recruitment of nearby platelets by other activated platelets constitutes a powerful amplification mechanism. ADP and γ-thrombin may be the initial physiologic stimuli for aggregation and their specific receptors appear to play a predominant role in thrombosis and hemostasis.

Aggregation proceeds in two distinct phases. During the primary phase, platelets are loosely interlaced together in a reversible process. The secondary wave occurs after the time lag required for platelets to release their granule contents and sustain stable aggregation. A number of inhibitory agonists including certain prostaglandins (PGI_2, PDG_2) and nitric oxide, counteract the pro-adhesive stimuli of excitatory agonists by inhibiting or reversing the process of γ2bγ3 affinity modulation. [1,51] Inhibitory agonists interact with specific platelet prostanoid receptors. In addition to soluble agonists, shear stress plays an important role in platelet function by directing which adhesive interactions take place.

Platelet aggregation is mediated by γ2bγ3, a membrane integrin found only on platelets and megakaryocytes.[55–57] Each platelet has approximately 80 000 copies of this receptor on its membrane surface and additional molecules translocate to the membrane from their γ-granules upon activation.[55] Regardless of the agonist, the final step in the formation of a platelet thrombus is platelet aggregation mediated by γ2bγ3. Platelet activation induces a conformation change in γ2bγ3 that increases its affinity for fibrinogen and other soluble ligands (e.g., vWf, vitronectin, thrombospondin). Fibrinogen and vWf are multivalent molecules and, hence, can attach simultaneously to activated GP Ilb-IIIa receptors on two different platelets. Thus, binding of fibrinogen or von Willebrand factor to activated GP Ilb-IIIa receptors results in platelet cross-linking and aggregation. When this process is repeated several times, a platelet thrombus is formed.

ACETYLSALICYLIC ACID

Acetylsalicylic acid (ASA) is the prime example of a naturally occurring compound with pharmacological properties and multiple mechanisms of action whose history has evolved over centuries. Hippocrates used willow bark for its analgesic properties around 400 BC. In the mid 1700s, the Reverend Edward Stone in England found relief of fever and rheumatic flare after having accidentally chewed on a twig of the white willow tree *(Salix alba),* and subsequently devised a method for drying and pulverizing the bark. Karl Friedrich Gerhardt, a chemistry professor at Montpellier University discovered the molecular structure of salicylic acid around the mid 1800s. Felix Hoffman, a chemist at Bayer, synthesized acetylsalicylic acid in 1895, in an attempt to improve upon the properties of salicylic acid, the only remedy of its class at the time. Anecdotally, his effort was fueled by the lack of response of his father's severe arthritis to salicylic acid. The name aspirin was coined in 1899 for this new drug:—*a* for acetyl, *spir* for the Spirea plant family from which salicylic acid had been extracted, and *in* to round it off. Aspirin has been since the mainstay of anti-inflammatory, antipyretic, and analgesic drug treatment. The mechanism of action of aspirin would wait until 1971, when Smith, Willis and Vane demonstrated that it blocked the formation of prostaglandins.[58]

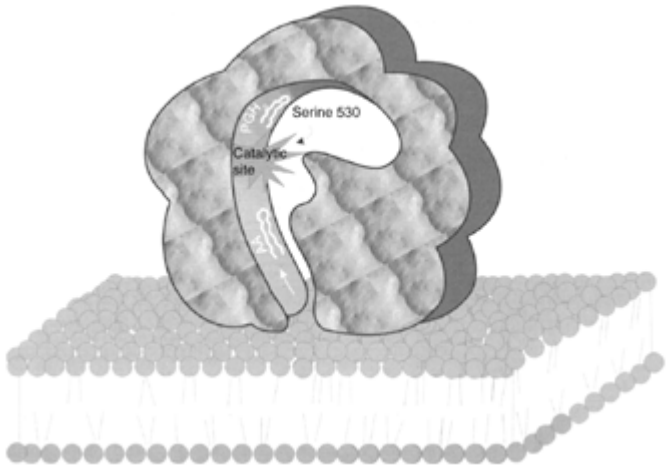

Figure 11.1 Mechanism of action of acetylsalicylic acid (ASA): **binding to cyclooxygenase.**

The acetyl group of ASA binds to serine 530 at the NH_2 terminus of cyclooxygenase and blocks the access of arachidonic acid to the active site of the enzyme.

MECHANISM OF ACTION

Aspirin selectively and irreversibly inhibits prostaglandin G/H synthase, better known as cyclooxygenase, the enzyme that catalyzes the transformation of arachidonic acid to prostaglandins and other eicosanoids.[59–61] The acetyl group of ASA binds to serine-530 at the NH_2 terminus of cyclooxygenase, located within a narrow hydrophobic channel in the core region of the enzyme (Fig. 11.1). Blockade of this channel by ASA prevents the access and binding of arachidonic acid to the active site of the enzyme.

Prostaglandins are a family of lipid-soluble hormones that bind to cell-surface receptors. There are at least 16 different prostaglandins in nine different chemical classes, designated PGA–PGI. Prostaglandins are part of an even larger family of 20 carbon-containing hormones called eicosanoids. In addition to prostaglandins, they include prostacyclins, thromboxanes, and leukotrienes. Eicosanoids are synthesized from a common precursor, arachidonic acid. Arachidonic acid is the principal long-chained unsaturated fatty acid in mammalian tissues. It is freed from membrane phospholipids by the action of phospholipases, namely phospholipase A_2 and phospholipase C: A_2 phospholipases are a family of enzymes that hydrolyze phospholipids to generate lysophospholipids and fatty acids. Exposure of platelets to stimuli such as thrombin and collagen increases the activity of phospholipase A_2.

There are two known isoforms of cyclooxygenase—cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Acetylsalicylic acid blocks both forms of the enzyme. Cyclooxygenase-1 appears to be the constitutive form, expressed in most cells, and whose main function is to regulate the physiological functions of prostaglandins, including local tissue perfusion, hemostasis, and integrity of gastrointestinal mucosa. Cyclooxygenase-2, the inducible form, is expressed in response to mediators of inflammation (e.g., cytokines, lipopolysaccharide), growth factors, and tumor promoters. The expression of COX-1 and COX-2 is increased in the synovia of inflamed joints and in atherosclerotic plaques.

In platelets, thromboxane A_2 is the major metabolite of prostaglandin synthesis and is generated via the action of COX-1. Thromboxane A_2 induces platelet aggregation and the platelet release reaction, and it is a potent vasoconstrictor. Prostacyclin (PGI_2) is the principal prostaglandin by-product of endothelial and

smooth muscle cells: it inhibits platelet activation and aggregation, induces smooth muscle cell relaxation, and exerts cytoprotective activity of the gastric mucosa. Both thromboxane A_2 and PGI_2 are unstable compounds with half-lives of approximately 3–5 min and 30 s, respectively.

Acetylsalicylic acid inhibits both thromboxane A_2 synthesis in platelets and PGI_2 synthesis in endothelial cells, although to varying degrees.[59,60] The effect of ASA on platelets is irreversible and persists for the life span of the platelet. The effect is irreversible because platelets are unable to synthesize new enzyme molecules. Hence, the rationale for once daily administration is to irreversibly acetylate new platelets entering circu lation. This is important since platelet function is largely restored when as few as 10% of circulating platelets are non-acetylated. In contrast, endothelial cells are nucleate elements and have the ability to replenish their cyclooxygenase pool. Cells of the vessel wall can recover their ability to synthesize PGI_2 within hours after ASA exposure. These observations underlie the rationale for the lower dose ASA regimens (i.e. 75–325 mg), aimed at reducing thromboxane A_2 production while minimizing inhibition of PGI_2 production and gastrointestinal risk.

After oral administration, there is rapid absorption of ASA by the upper gastrointestinal tract. *In vivo,* ASA is rapidly converted to sodium salicylate and has a half-life of only 15–20 min.[60] As much as 50% of orally administered ASA is hydrolyzed by tissue esterases before it enters the systemic circulation. Acetylation of platelet cyclooxygenase occurs within minutes, even at micromolar concentrations of ASA. This inhibitory effect is rapid, occurring even before the appearance of the drug in the systemic circulation, probably as a result of the acetylation of platelet cyclooxygenase in the portal circulation.

OTHER INHIBITORS OF CYCLOOXYGENASE

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) bind to the active site of cyclooxygenase and reduce platelet thromboxane A_2 synthesis: they block both isoforms of cyclooxygenase, COX-1 and COX-2. In contrast to aspirin, however, the inhibition of cyclooxygenase by NSAIDs is reversible and lasts for only a portion of the dosing interval. The effectiveness of NSAIDs in the secondary prevention of atherothrombosis is unknown in view of the limited amount of data in this area. On the other hand, since many cardiovascular patients take both NSAIDs and aspirin, the potential for pharmacodynamic interactions between these two classes of agents exists. A recent study in healthy volunteers showed that intake of ibuprofen (400 mg) before ASA (81 mg) prevented the inhibition of platelet function normally achieved by ASA. On the other hand, intake of ASA before ibuprofen produced maximal inhibition of COX-1 activity and impairment of platelet aggregation. In the same study, delayed-release diclofenac (75 mg twice daily) had no inhibiting effect on the pharmacodynamics of ASA. This study underscores the need for additional data in this area.

SELECTIVE INHIBITORS OF CYCLOOXYGENASE-2

A novel class of anti-inflammatory drugs that selectively block COX-2 (also called coxibs) was developed and the Food and Drug Administration (FDA) has recently approved some of these agents. Cyclooxygenase-2 inhibitors bind to a side pocket present in the hydrophobic channel of COX-2 but not in that of COX-1.[62] Coxibs were developed under the premise that they would exert more selective anti-inflammatory effects while minimizing the risk of gastrointestinal complications.

Coxibs have no inhibitory effect on platelet COX-1 but reduce endothelial production of prostacyclin.[63] Theoretical concerns have been raised on potential cardiovascular implications of reducing vascular prostacyclin production without concomitant platelet inhibition.[64] These concerns were underscored by a recent metaanalysis of coxibs trials showing a small absolute increase in cardiovascular complications.[62] Although this meta-analysis was criticized on methodological grounds, it nevertheless raises the question as to whether cardiovascular patients treated with coxibs should receive concomitant low-dose aspirin and, if so, could it diminish the therapeutic advantage of lower gastrointestinal toxicity afforded by these agents? Clearly, further data are needed in this area.

TREATMENT OF ACUTE ISCHEMIC STROKE

Aspirin is the only antiplatelet agent that has been evaluated in the acute treatment of ischemic stroke. Early treatment with aspirin was evaluated in three randomized trials totaling more than 40 000 patients. The Multicentre Acute Stroke Trial-Italy (MAST-I) compared, in a 2×2 factorial design, streptokinase, aspirin (325 mg daily), both, or neither.[65] The International Stroke Trial (IST) compared, in a 2×2 factorial design, subcutaneous heparin, aspirin (300 mg daily), both, or neither.[24] The Chinese Acute Stroke Trial (CAST) compared aspirin (160 mg daily) with placebo.[25] In the IST and CAST trials, eligible patients were treated within 48 hours of stroke onset, whereas in MAST-I they were treated within 6 hours. A pooled analysis of these studies shows a 1% absolute reduction of death and dependency at 6 months in favor of aspirin (Table 11.2). Of note, the aspirin versus placebo comparison in IST showed essentially the same results as the aspirin versus the 'avoid aspirin' group. Pooled analysis of the IST and CAST studies also reveals a significant reduction in the rate of recurrent ischemic stroke at 2 weeks among the patients treated with aspirin (2.5%) vs 3.2% among those not treated with aspirin. A subgroup analysis stratified by time-from-stroke onset suggests a dose relationship for the effect of aspirin (Table 11.3). In the IST and CAST trials, there were slight excess (0.2%) of hemorrhagic stroke or hemorrhagic transformation of infarct.

Globally, the lower rate of early stroke recurrence with aspirin coupled with improved outcomes at 6 months mitigate for a net clinical benefit in favor of aspirin. Although the absolute benefit afforded by acute aspirin treatment is low, at around 1%, its very low cost and wide availability could have a significant impact on stroke outcome at a population level, including those of developing nations where ischemic stroke incidence is on the rise in view of increased smoking.[66] Following the path of acute coronary syndromes, a combined regimen of ASA and thienopyridine ADP receptor antagonist could be envisioned in future. However, the potential risk of intracranial hemorrhage due to the blockade of two platelet activation pathways and the need for loading dose with the available ADP receptor antagonists (in view of their delayed onset of action) would need to be weighed in.

Whether the apparent benefit of aspirin treatment arises from a direct effect on the acute disease process, early start of secondary prevention, or both factors is unknown. A number of mechanisms could account for an acute effect of aspirin, including its antiplatelet, antiinflammatory and antipyretic properties.[67–69] Alternatively, the slight improvement in functional outcomes at 6 months could be due mainly to the early prevention of stroke recurrence.

Table 1 1.2 Aspirin in the acute treatment of ischemic stroke—pooled analysis of randomized trials[a]

Study	Death or dependency		Absolute reduction	Odds ratio	95% CI
	Control	Aspirin			
MAST-I (*n*=309)	106/156 (68%)	94/153 (61%)	7%	0.71	0.45–1.14

Study	Death or dependency		Absolute reduction	Odds ratio	95% CI
	Control	Aspirin			
IST (*n*=19435)	6125/9715 (63%)[b]	6000/9720 (62%)	1%	0.95	0.89–1.00
CAST (*n*=20 655)	3266/10 320 (32%)	3153/10 335 (31%)	1%	0.95	0.90–1.01
All	9497/20 191 (47%)	9247/20 208 (46%)	1%	0.95	0.91–0.99[c]

[a] Method of Antiplatelet Trialists' Collaboration.[10]
[b] 'Avoid aspirin': subcutaneous heparin (4855 patients) and placebo control (4860 patients).
[c] 2*p*=0.01.

Table 11. 3 Aspirin in the acute treatment of ischemic stroke—pooled analysis of randomized trials stratified by time from stroke onset[a]

Study	Death or dependency		Absolute risk reduction	Odds ratio	95% CI
	Control	Aspirin			
More than 24 hours from onset:					
IST	4133/6379 (65%)	4032/6374 (63%)	2%	0.93	0.87–1.00
CAST	363/5422 (7%)	325/5481 (6%)	1%	0.89	0.76–1.04
All	4496/11 801 (38%)	4357/11 855 (37%)	1%	0.93	0.87–0.99
Less than 12 hours from onset:					
IST	2412/3649 (66%)	2331/3576 (65%)	1%	0.91	0.82–1.00
CAST	203/2650 (8%)	181/2673 (7%)	1%	0.88	0.72–1.09
All	2615/6299 (42%)	2512/6249 (40%)	2%	0.90	0.83–0.98
Less than 6 hours from onset:					
MAST-I	106/156 (68%)	94/153 (61%)	7%	0.71	0.45–1.14
IST	1096/1570 (70%)	1057/1571 (67%)	3%	0.89	0.77–1.04
CAST	114/1200 (10%)	91/1250 (7%)	3%	0.78	0.58–1.04
All	1316/2926 (45%)	1242/2974 (42%)	3%	0.87	0.77–0.98
More than 3 hours from onset:					
IST	298/422 (71.6%)	292/414 (71%)	0.1%	0.93	0.69–1.26
CAST	55/419 (13%)	39/446 (9%)	4%	0.67	0.44–1.04
All	353/841 (42%)	331/860 (38%)	4%	0.84	0.66–1.08

[a] Method of Antiplatelet Trialists' Collaboration.[10]

GP IIB-IIIA ANTAGONISTS

PARENTERAL AGENTS

Three parenteral platelet GP Ilb-IIIa antagonists are currently approved in the United States and other countries for the management of symptomatic coronary artery disease: abciximab (ReoPro®), eptifibatide (Integrilin®), and tirofiban (Aggrastat®).[70] Abciximab is the Fab fragment of a chimeric human-mouse monoclonal antibody directed against the human GP Ilb-IIIa receptor (γ2bγβ integrin). Eptifibatide is a cyclic heptapeptide based on the KGD (Lys-Gly-Asp) sequence of the snake venom barbourin, a natural

disintegrin. Tirofiban is a tyrosine derivative, non-peptide mimetic of the RGD (Arg-Gly-Asp) recognition sequence. Abciximab is the only one among these agents, that is under currently under evaluation for the treatment of acute ischemic stroke. The antagonist in this setting can be summarized as follows. First, the proof of the concept of more intense platelet blockade than aspirin has been demonstrated with parenteral GP Ilb-IIIa ship between efficacy and time-from-stroke the need to improve upon the safety of recombinant tissue plasminogen activator and broaden the time interval during which it can be given beyond 3 hours from stroke onset.[71,72]

The rationale for the use of a GP Ilb-IIIa antagonists in the setting of PCI and with the combination of ASA and thienopyridine ADP receptor antagonists in prevention of coronary stent thrombosis and ischemic complications post acute coronary syndrome.[23] Studies in experimental stroke models have documented reductions in platelet accumulation, fibrin accretion, and infarct volume with GP Ilb-IIIa blockade.[47–49] Secondly, the apparent relationonset in the pooled analysis of IST, CAST, and MAST-I suggests that earlier blockade of impetus for novel reperfusion agents stems from platelet function may improve overall efficacy results. Thirdly, there are a few additional mechanisms that are unique to abciximab or have been better substantiated with this agent: these additional effects include 'dethrombosis' and cross-reactivity with the γVγ3 and γMγ2 integrins.

Reversal of ADP-induced platelet aggregation by abciximab has been documented *in vitro* and 'dethrombosis' has been observed in studies of PCI for the treatment of ST-T segment elevation myocardial infarction. In the ADMIRAL trial,[20] a randomized comparison of Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up, 17% of patients in the abciximab treatment group had restored complete coronary flow before PCI, compared with 5% among placebo patients. Dethrombosis may be due to the competitive displacement of fibrinogen by abciximab, which has much greater affinity for γ2bγ3 (than fibrinogen). There may also be an enhancement of endogenous fibrinolysis by reducing the release of PAI-1 from platelet γ-granules. Abciximab cross-reactivities with γVγ3 and γMγ2 integrins may reduce endothelial reactivity and leukocyte-platelet interactions, respectively.[73–77]

Preliminary experience in a placebo-controlled, randomized, dose-escalation study of 74 ischemic patients has been encouraging since there were no cases of symptomatic parenchymal hemorrhage and there were trends of improved outcome at 3 months in favor of abciximab.[20]

ORAL AGENTS

In contrast with the marked success of parenteral agents, oral GP Ilb-IIIa antagonists have been disappointing.[78–83] Not less than 10 oral agents have been developed and evaluated at various stages of clinical development. These agents are selective GP Ilb-IIIa antagonists and have been mostly prodrugs, which are absorbed and then converted to active compounds *in vivo*. These agents were designed to achieve similar inhibition of platelet aggregation as parenteral agents, with twice daily or three times daily dosing regimens. Phase 3 trials have consisted mostly in the prevention of ischemic complications following acute coronary syndrome or PCI. Unfortunately, all trials of oral GP Ilb-IIIa antagonists have been discontinued due to adverse events that included higher mortality and increased incidence of nuisance bleeding or other serious hemorrhage, or failed efficacy. The principle of more intense receptor blockade for chronic use, derived from the results obtained with parenteral agents, was eminently logical at the time. However, the results of clinical trials once again bring invaluable lessons and have brought forward new hypotheses pertaining to platelet physiology.

A number of mechanisms have been proposed for the failure of oral agents, including γ2bγ3 receptor activation from outside-in signaling, fluctuation in plasma levels yielding inadequate plasma levels between doses, and the rapid off-rate of some agents from the receptor.[79] Outside-in signaling may activate platelets further. As plasma levels of antagonist fall between doses, there would be a lower number of blocked GP Ilb-IIIa receptors, allowing fibrinogen and other soluble ligands binding. The profile of parenteral antagonists, characterized by a more stable platelet receptors blockade and superior efficacy, provides indirect support for the above-stated mechanisms. Also, aspirin and thienopyridine ADP receptor antagonists provide constant levels of platelet inhibition and have yielded consistent efficacy results in the secondary prevention of atherothrombosis.

SUMMARY

Platelets are crucial cellular elements of blood and are involved in several processes, including primary hemostasis, inflammation, atherosclerosis, and pathophysiology of atherothrombosis. Careful observations of patients with congenital bleeding disorders over the years, along with translation of clinical trials results and advances in vascular biology, have brought platelet research to a new era. Contemporary platelet research focuses among other things on the elucidation of signaling mechanisms in response to a variety of stimuli, including exposure to extracellular matrix constituents, soluble agonists, and growth factors. The evidence linking platelets to atherothrombosis is overwhelming, as evidenced by the results of clinical trials of antiplatelet agents in a variety of disease states. The effect of aspirin in the treatment of acute coronary syndromes and ischemic stroke is intriguing, particularly since it has yielded improved outcomes despite the start of therapy several hours after symptom onset. Parenteral platelet GP Ilb-IIIa antagonists are currently under investigation in the treatment of ischemic stroke, and initial results have been encouraging.

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Intensive care of ischemic stroke

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INTRODUCTION

Successful treatment of stroke patients starts with the knowledge that stroke is a medical emergency just like acute myocardial infarction. Some stroke physicians believe that stroke patients who require critical care are best admitted to specialized neurocritical care units. Stroke intensive care units (ICUs) and stroke units implement acute treatment strategies, such as the reopening of occluded cerebral arteries (see Chapter 9), and employ specialized multimodal monitoring and specific interventions to control complications during the further course of the disease, for example, conservative and invasive treatment of elevated intracranial pressure (ICP). Successful stroke therapy depends on early recognition and rapid referral of patients to an institution that provides diagnostic and therapeutic expertise. Prevention of secondary complications may influence survival and outcome of critically ill stroke patients. This chapter discusses current strategies in intensive care stroke management, with a focus on multimodal monitoring and the conservative and invasive therapy of elevated ICP.

EMERGENCY MANAGEMENT

Acute management of severe stroke requires that certain procedures take place simultaneously. In the emergency room, neurologic and vital functions must be assessed while acute, life-threatening conditions are being treated. The initial examination includes observation of breathing function, assessment of blood pressure and heart rate, and the determination of O_2 saturation using infrared pulse oximetry. The initial neurologic examination should focus on the level of consciousness, behavioral deficits, pupillary and oculomotor signs, the severity of hemiparesis, head turning, and eye deviation.

Additional emergency work-up should include electrocardiography (ECG) and laboratory values—blood chemistry, hematologic, coagulation, and urine analysis. To optimize patient management, diagnostic procedures, including computed tomography (CT), Doppler sonography, and magnetic resonance imaging (MRI), should be initiated without any delay. Computed tomography scanning reliably distinguishes between hemorrhagic and ischemic stroke: CT signs of early ischemia can be detected as early as 2 hours after stroke onset,[1] but they may also develop later. Very extensive early infarct signs in the first hours after stroke onset indicate severe ischemia, which involves a higher risk of secondary hemorrhage or of large edema formation, both being strong predictors of fatal outcome.[2] In addition, modern CT techniques, such as spiral CT scanning and CT angiography, rapidly and reliably show not only vessel occlusion but also the state of the collaterals.

Diffusion-weighted magnetic resonance imaging (MRI) is even more sensitive and may identify ischemic tissue within 30 min after stroke onset and perhaps distinguish between reversible and irreversible ischemia.[3] Oppenheim et al. showed that the quantitative measurement of the volume of abnormalities by diffusion-weighted MRI is a reliable and non-invasive tool for predicting malignant middle cerebral artery (MCA) infarction in stroke patients and produces high-quality images even in restless patients.[4]

Ultrasonography is frequently performed in stroke centers and includes continuous-wave Doppler, transcranial Doppler (TCD), and duplex sonography of the extra- and intracranial vessels. These methods are used to identify vessel occlusion, the state of collaterals, and recanalization. Selective digital subtractions angiography should be performed in all patients with suspected acute cerebrovascular disease suitable for interventional neuroradiological procedures, including basilar occlusion and severe subarachnoid hemorrhage.[5–8]

TECHNICAL APPLIANCES FOR INTENSIVE CARE STROKE MANAGEMENT

MULTIMODAL MONITORING

Clear guidelines for instituting multimodal monitoring in severe stroke have not yet been established.

Intracranial pressure monitoring may provide data for sensible treatment of elevated ICP. However, ICP monitoring to evaluate cerebral perfusion pressure (CCP) may not reflect the needs of the individual patient if it is the only method used.[9–11] Using jugular venous oxygen saturation (SjO_2) as an additional instrument also presents a problem, at least in stroke patients, since the variability in measurements as a result of shunting is great.[12,13] Furthermore, this technique is prone to technical difficulties.

The continuous measurement of the partial oxygen pressure of brain tissue ($pbrO_2$) by microprobes within brain tissue of the frontal white matter may represent an important alternative in the monitoring of comatose patients on neurologic intensive care units.[14–16] Several experimental studies have shown that the continuous measurement of the $pbrO_2$ in animals significantly reflects changes in blood oxygenation, ventilation, and ICP and CPP.[17,18] Clinical experience with $pbrO_2$ monitoring has mainly been gained from patients with severe brain injury.[11,14,16,19–21]

In our ICU, we usually monitor ICP/CPP, temperature and, occasionally, $pbrO_2$ unilaterally (probes in the noninfarcted contralateral hemisphere) or bilaterally within the white matter of the frontal lobe. In our multimodal monitoring system, ICP is measured using either piezoelectronic or pneumatic signal transmitting probes. $pbrO_2$ is registered using a polarographic microprobe and temperature is measured continuously with microprobes. Data are processed in a computer to compensate for the temperature dependency of $pbrO_2$. Probes are inserted through one screw. Only pneumatic ICP probes require a separate drill hole. If a hemicraniectomy has been performed, we insert this probe through the trepanation.[21a]

Multimodal monitoring can help not only to control therapy but also to optimize the timing of therapies in two ways:

1. by avoiding a potentially dangerous therapy too early
2. by identifying those patients who will profit most from this therapy at an early stage in the course of the disease.

NEUROPHYSIOLOGICAL ASSESSMENT

The main goals of neurophysiological monitoring are to evaluate central nervous system functions in unresponsive patients and to predict neurologic deficit.[22,23] In principle, electroencephalograms (EEGs) reflect cortical electrical activity deriving from synergy of cortical and subcortical structures, whereas evoked potentials comprise the sum of electrical responses at various levels of the neuroaxis within a particular sensory pathway following repetitive stimuli.

EVOKED POTENTIAL MONITORING

Although there are a number of useful features of evoked potentials in the assessment of unresponsive patients receiving narcotics and analgesics, there are several limitations as well:

1. data acquisition, signal processing, and analysis are difficult and require sophisticated machinery, software, and well-trained staff
2. only short latency-evoked potentials are resistant to external variables such as anesthetics, barbiturates, and hypothermia
3. the specificity of signal pattern abnormalities is low.

Several studies of nontraumatic coma revealed that the early bilateral absence of cortical somatosensory-evoked potentials is associated with death, persistent coma, locked-in-syndrome, or the development of a vegetative state.[24] The anatomical level of brainstem destruction, brainstem infarction by basilar artery occlusion, and brainstem impairment after massive cerebellar or hemispheric infarction has been correlated with abnormal patterns of brainstem auditory evoked potential (BAEP).[25–31]

Motor-evoked potentials (MEP) can be safely recorded in patients on a neurointensive care unit and yield important results. In patients with brainstem lesions, MEPs correlate with radiological findings, predict final motor function more accurately than clinical findings, and are a reliable diagnostic tool for assessing motor function in unresponsive patients.[32] A major shortcoming, however, is the susceptibility of MEP to various drugs used on an ICU, such as sedatives and antiepileptic drugs.

EEG MONITORING

Well-known benefits of EEG include detection of seizure activity, close correlation with the cerebral metabolic rate, and sensitivity to hypoxia. Electroencephelographic monitoring may also help to manage medically induced coma.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler ultrasonography provides important information concerning the intracranial vasculature, the collateral flow, and signal characteristics of the various arteries.[33] In the neurocritical care unit, the basal cranial arteries can be examined by TCD at the bedside. There is a strong correlation between TCD blood flow velocity and angiographically confirmed stenosis and vasospasm. Therefore, TCD can reliably detect cerebral vasospasm in subarachnoidal hemorrhage and thus be used to guide specific therapy.[34] If the ICP is raised, a progressive reduction in end diastolic velocity is seen, as reflected by the elevated pulsatility index. Close-meshed, intermittent TCD monitoring in acute cerebrovascular occlusion may accompany thrombolytic therapy to demonstrate recanalization.

With transcranial color-coded duplex sonography (TCCS), intracranial hemodynamics and parenchymal structures can be imaged at the bedside. This technique provides reliable information regarding midline shift in space-occupying hemispheric stroke.[35,36] Furthermore, TCCS has been shown to identify intracerebral hemorrhage, a possible complication of malignant hemispheric infarction.[37]

INTENSIVE CARE THERAPY OF STROKE

The treatment of acute stroke is based on three principles:

1. The treatment of a patient's general physiological condition, which needs to be optimized in the setting of an acute stroke. This is usually referred to as 'general therapy'.
2. The specific therapy of aspects of stroke pathogenesis, either recanalization of a vessel or prevention of several mechanisms of neuronal injury, that may occur after brain ischemia (neuroprotection).
3. The treatment of complications, either neurologic (e.g., secondary hemorrhage, brain edema, and seizures) or medical (e.g., infections, decubital ulcers, and deep vein thrombosis).

As previously stated, this chapter focuses on the conservative and invasive therapy of elevated ICP. For further information about general care in the acute phase, including metabolic issues and management of blood pressure, see Chapters 7 and 8; for detailed information about reopening strategies, anticoagulant therapy, and antiplatelet therapy, see Chapters 9·10, and 11, respectively.

CONSERVATIVE AND INVASIVE TREATMENT OF SPACE-OCCUPYING HEMISPHERIC STROKE

INTRODUCTION

Patients with acute, nearly complete MCA or panhemispheric infarction may develop massive concomitant edema with significant midline shift or compression of the basal cisterns, resulting in clinical signs of uncal herniation, a condition termed 'malignant' MCA infarction.[38] This syndrome has been defined clinically and according to CT scanning criteria. The patients are somewhat younger (about 10 years on average) than other stroke patients. Standard antiedema treatment often fails to prevent herniation and brain death, which may occur in up to 80% of the cases.[38]

Shaw and coworkers studied the time course of edema formation after stroke.[39] Brain edema was manifest within the first day after onset of symptoms involving the gray and white matter surrounding the infarcted tissue. Swelling was maximum on days 3–5, with edema subsiding within 2 weeks. Severe brain swelling following cerebral infarctions is known to cause transtentorial and uncal herniation with clinical deterioration and progressive brainstem dysfunction.[40] The patients rarely survive and, if they do, they are often severely disabled or in a vegetative state.

Occlusion of the distal internal carotid artery (ICA, carotid T) or the proximal MCA trunk are the main causes of complete MCA territory infarction. However, this occlusion pattern only leads to a space-occupying infarct if the leptomeningeal collaterals are not functioning well. The stroke is often of embolic etiology with cardiogenic and emboli from arterial dissections. In patients with distal ICA (carotid T-occlusion), the anterior cerebral artery (ACA) territory and, rarely, the posterior cerebral artery (PCA) territory can be involved, leading to complete carotid territory (MCA+ACA) or panhemispheric territory (ICA+PCA) infarction.

Outcome is fatal in the majority of these patients, with a mortality of about 80% with standard treatment.[38,41]

Clinically, these patients present with a severe hemispheric syndrome with head turning and eye deviation. Somnolence may be present as early as 3 hours after stroke onset and the patients may present like those with large intracerebral hemorrhages. Consciousness usually declines rapidly in these patients and they develop signs of herniation 2–4 days after onset of symptoms. Most patients require intubation and artificial ventilation. During the further clinical course, medical treatment for elevated ICP fails. Once the ICP has moved into critical values (20 mmHg or beyond), signs of herniation can be seen both clinically and on CT. Brain death usually occurs between days 2 and 5 after onset of stroke.

The prognostic significance of early changes on CT scan within the first few hours after MCA occlusion has been elaborated. Von Kummer et al.[2] reported on the early initial CT findings in 77 patients with MCA occlusion. They showed that a hypodensity covering more than 50% of the MCA territory or local brain swelling (effacement of sulci, compression of the lateral ventricle) is a strong predictor of fatal outcome. The authors demonstrated that large (>50%) or total hypodensity in the MCA territory predicted fatal outcome in 85% (11/13), with a high specificity (94%) but moderate sensitivity (61%). In the ECASS trial, early major infarction signs were prognostic concerning the development of spaceoccupying edema and death due to herniation even in the placebo group.[42]

CONSERVATIVE TREATMENT OF ELEVATED ICP

Conservative treatment of increased ICP in acute ischemic stroke includes standard medical and nursing procedures (Table 12.1), hyperventilation with continuous, mandatory ventilation, and osmotherapy.

Osmotherapy

Hyperosmolar therapy for raised ICP extracts water and reduces the volume of the normal brain. The duration and degree of ICP reduction depend on the volume of remaining normal brain

Table 12.1 Therapy of elevated ICP

Step 1: Basic treatment		
Prevention of physical stress, pain, cough, fever, hyponatremia		
Elevated head position		
Step 2: ICP reducing medication, artificial ventilation		
Glycerol 10%1	i.v.	4×125 up to 250 ml
Glycerol 50%	p.o.	4×50 ml
Mannitol 20%1	i.v.	100 ml bolus up to 6/day
HS-HES (NaCl 7.5%, HES 6%)[1,2]	i.v.	150 ml bolus
Intubation and artificial ventilation		
Prevention of muscle movement		Muscle relaxation (vecuronium, atracurium)
THAM buffer[3–5]		1 mmol/kg body wt as a bolus, 0.25 mmol/kg body wt continuous infusion
Step 3: Invasive strategies		

Craniotomy		
Hypothermia		
ICP crises		
Barbiturates[4,6–8]		250–500 mg bolus (thiopental) 40–80–100 mg bolus (methohexital)
Hyperventilation, short term, of a temporary nature only[10]		Increasing ventilation frequency and ventilation volume
1.	Serum osmolarity	<320 mOsm/1
2.	Serum Na	<155 mEq/1
3.	pH	<7.5–7.55
4.		Central venous line necessary
5.		Disturbance of renal function
6.		Disturbance of liver function
7.	CCP	ɣ70 mmHg
8.		Reduction of blood pressure
9.		Tissue necrosis
10.	PaCO2	30–35 mmHg

CCP, cerebral perfusion THAM, pressure; ICP, intracranial pressure; i.v., intravenously; $PaCO_2$, arterial pressure of carbon dioxide; p.o., orally; tris-hydroxy-methyl-aminomethane.

that is subject to shrinkage, the proportion of disrupted blood-brain barrier, the initial ICP, and the dose of agent used. The goal of osmotherapy is to increase serum osmolarity to approximately 315–320 mOsm/1. For dosages and therapeutic aims refer to Table 12.1.

Glycerol. Glycerol can be administered enterally or intravenously, being more effective via the enteral route. The occurrence of a rebound phenomenon is the subject of debate.[43,44] Glycerol has a shorter duration of action than mannitol because of greater brain penetration and tubular reabsorption. Fluid overload, hemolysis, and electrolytic disturbances are difficulties to consider. However, dehydration contributing to hypotension is deleterious in acute stroke and may be less pronounced than with mannitol. Other occasional side effects include nausea, vomiting, diarrhea, hemoglobinuria, and bleeding diathesis.

Mannitol. Currently mannitol is used for more severe cases, such as impending transtentorial herniation, because of its slightly faster onset of action and because mannitol preferably affects edematous brain tissue.[45] We use mannitol (20% solution) up to every 4 hours if glycerol fails to control elevated ICP. Mannitol should be administered only briefly, because once a plateau of osmolarity is reached, transient intravascular fluid overloads may evoke rebound intracerebral hypertension.[43,46]

Hypertonic saline solutions. Hypertonic saline (HS) solutions have been primarily employed for 'small volume resuscitation' (SVR) in patients with hemorrhagic shock. Compared with standard shock therapy, SVR produces a more rapid volume expansion, increases cardiac output, systemic blood pressure, and microvascular perfusion, and may improve survival. In particular, the subgroup of patients with severe head injuries seems to show higher survival rates after SVR.[47] Various animal experiments of hemorrhagic shock and head trauma demonstrated that SVR lowers ICP and improves CPP.[48] Although SVR was primarily

employed in patients with hemorrhagic shock, hypertonic saline (HS) with or without dextrans/hydroxyethyl starch (HES) has been successfully used in some small clinical series of euvolemic head trauma patients even after the failure of conventional therapy. We found HS-HES more effective in lowering elevated ICP than mannitol: HS-HES could still be used successfully after mannitol had failed.[49]

THAM buffer

In some cases, THAM buffer (tris-hydroxymethyl-aminomethane) can be infused to control ICP. The mode of action of THAM is probably related to neutralization of an acidosis-related vasodilatation and thus a decrease in ICP.[50,51] It can be used to raise blood pH independently from respiratory function, and is given by continuous intravenous infusion via a central venous catheter (paravascular infusion leads to severe soft tissue necrosis). THAM buffer is cleared by the kidney. As a rule, ICP monitoring should be available if THAM buffer solution treatment is planned. The efficacy of THAM can be assessed by infusing 1 mmol/kg body weight in 100 ml of 5% glucose over 45 min; the ICP should fall within 15 min. If THAM is shown to be effective, it is continuously infused to reach a pH of between 7.5 and 7.55.

High-dose barbiturate therapy

Since the early 1970s high doses of barbiturates have been used to control ICP in head trauma, intraoperative brain swelling, or as a neuroprotective agent. A variety of clinical studies have produced inconclusive results, however; Ward et al.[52] found no value in prophylactic barbiturate coma for severe head trauma. On the other hand, Eisenberg et al.[53] found a fourfold greater chance of controlling ICP in patients treated with pentobarbital for refractory, elevated ICP in the absence of pretreatment of arterial hypotension. Routine use of barbiturates to control elevated ICP has often been questioned since it may cause severe side effects, such as hypotension, decreased cardiac performance, or severe infections. There are only limited data on the use of barbiturates in the therapy of ischemic brain edema following severe hemispheric infarction. So far, no improved outcome has been reported with barbiturate coma in the treatment of increased ICP following stroke.[54]

The complications of high-dose barbiturate administration (safety limit approximately 10 mg/kg/day) include hypotension, most pronounced at the time of bolus administration, and a possible predisposition to infection. Cardiovascular side effects may be aggravated by concomitant dehydration caused by osmotherapy and diminished cardiac filling pressures.

Hyperventilation

Hypocarbia causes cerebral vasoconstriction: whereas cerebral blood flow (CBF) is reduced almost immediately, ICP reduction may take up to 30 min to peak after PCO_2 is changed. Profound hyperventilation may jeopardize oxygen delivery to the brain tissue at risk.[55] The beneficial effect of sustained hyperventilation on ICP is unresolved. Hyperventilation should therefore only be used for patients with ICP crisis in case of a planned intervention (hemicraniotomy, hypothermia). A reduction from 35 to 29 mmHg, which is best achieved by raising the ventilation rate at constant tidal volume (12–14 ml/kg), lowers ICP by 25–30% in most patients. In selected patients with poor cerebral compliance, strict hyperventilation may paradoxically elevate ICP as a result of increasing thoracic venous and cerebrospinal fluid (CSF) pressure. ICP reduction should cease when the pH of CSF reaches equilibrium; however, in practice this

may not occur for many hours. As with osmotherapy, adverse rebound effects may occur if normoventilation is resumed too rapidly.[56]

Hypothermia

Rationale. Moderate hypothermia (33–36°C) has been shown to reduce secondary brain injury and infarction size and to improve neurologic outcome in animal models with both focal and global ischemia.[57–60] Most of these studies used a narrow time window between 60 and 90 min. However, several clinical trials in head-injured patients have shown a significant reduction in ICP and CBF, better neurologic outcome, and limited secondary brain injury, although the time window varied between 6 and 16 hours. The duration of hypothermia varied from 24 to 48 hours, while neither the optimal duration of hypothermia nor the optimal time after the trauma for therapy could be identified in these patients.[61–64]

Clinical application of hypothermia in stroke. Elevation of ICP during rewarming was also observed in a large study of 50 patients with malignant MCA infarction.[65] Hypothermia was induced with a mean of 14 hours after the ischemic injury and maintained over 72 hours to overcome the maximum brain swelling, which is known to occur between days 2 and 5 after ischemia. All patients in this study fulfilled the criteria for diagnosis of a 'malignant MCA infarction. The mortality was 44% and the survivors reached Barthel indices ranging from 60 to 85. Hypothermia significantly reduced the ICP. However, rewarming the patients constantly led to a secondary rise in ICP, which required additional ICP therapy with mannitol. In some cases it even exaggerated the initial ICP levels. This rebound after rewarming might be due to a proposed hypermetabolic response after induced hypothermia, as described after cardiopulmonary bypass.[64] Study of another series of patients indicates that a modified rewarming protocol seems to reduce ICP elevation, which occurs during and after rewarming:[66] however, patient numbers are still too small to draw firm conclusions.

Side effects. Ventricular ectopy and fibrillation limit the extent of hypothermia, but this is known to occur only at temperatures below 30°C. In the above-mentioned study, pneumonia and septic syndrome were severe side effects of moderate hypothermia. Other side effects of hypothermia, which have been shown in animal studies, are clotting abnormalities and coagulopathy.[67,68] In men, the enzymatic reactions of the coagulation cascade were shown to be strongly inhibited by hypothermia.[69,70] An elevation of serum amylase and lipase levels is frequently observed; in most cases, however, these values return to normal after rewarming.

DECOMPRESSIVE SURGERY

Although case reports have impressively shown a dramatic reduction in mortality in patients with both cerebellar and hemispheric space-occupying infarction if decompressive surgery is performed, there are no controlled data to support the superiority of this method over others.

Rationale

The rationale for decompressive surgery is to allow expansion of the edematous tissue away from the lateral ventricle, the diencephalon, and the mesencephalon so as to reduce ICP, increase perfusion pressure, and preserve CBF by preventing further compression of the collateral vessels. These factors may help to increase CBF in areas surrounding ischemic regions, thereby preventing further brain tissue necrosis. The hypothesis is supported by a recent experimental stroke study on the value of decompressive surgery.[71,72] The procedure has been tested in head trauma patients with varying results.[73,74] In human spaceoccupying

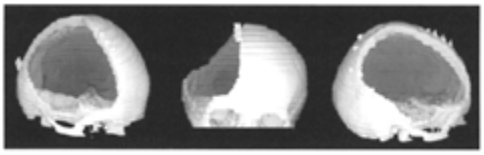

Figure 12.1 "Three-D-reconstruction of CT imaging of a large craniectomy in three different angles.

Note that the craniectomy caudally reaches down to the bottom of the middle cerebral fossa. The upper limit of the craniectomy is at the midline and exceeds the venous sinus." WH

hemispheric infarction, surgical treatment has been reported to lower mortality and improve the unfavorable outcome.[75]

Surgical methods

The volume of the ischemic hemisphere can increase by almost 50%. Given a volume of roughly 500 ml in a healthy hemisphere, this represents an increase by almost 250 ml, which can hardly be compensated for by fluid shifts. It has been shown in a spherical model that the diameter of the craniectomy has to be at least 12 cm.

In our intensive care unit, the anteroposterior diameter is 14–15 cm and the diameter from the temporal base to the region of the sagittal sinus is about 10–12 cm. The temporal bone should be resected to the skull base (Fig. 12.1). The dura is opened and an adjusted, biconvex-shaped dural patch (lyophilized dura or homologous temporal fascia) is placed into the incision. In surviving patients an artificial bone flap is re-implanted 6–12 weeks after surgery.

There is some controversy as to whether infarcted tissue should be resected. There are some reports of positive results in outcome and neurologic function.[76–79] However, since in acute stroke the margins of the infarction are poorly defined and the differentiation between definitely damaged tissue and the ischemic penumbra is not possible, we do not remove the ischemic tissue.[41,80]

Surgical Complications

Surgical complications include infections, subdural or epidural hematoma, space- occupying subdural CSF hygroma, and paradoxical herniation after the swelling period. Close clinical follow-up, including palpation of the trepanation site, ICP monitoring, and daily B-mode scanning of the affected hemisphere for detection of epidural or subdural blood and space-occupying effect on the lateral ventricle, may detect these events in time and prevent unfavorable outcome in these patients.

The Heidelberg trials on decompressive surgery in stroke

The two Heidelberg trials are the only prospectively designed trials and included data from a nonrandomized control group.[41,81]

In the first trial, space-occupying MCA infarction was defined as massive supratentorial infarction involving the territory of the MCA or both MCA and ACA. The definition also included the dynamic aspect of the syndrome by including reversible signs of herniation: increasing spaceoccupying edema with a midline shift of more than 10 mm at the septum pellucidum level documented on serial CT.[41] Thirty-two

patients underwent surgery. The historical control group consisted of 21 patients with left hemispheric malignant MCA infarcts or patients whose relatives did not give consent to perform the operation.

Without surgery, 76% of patients (16/21) with space-occupying hemispheric infarction died from herniation despite maximal conservative treatment: only 5 patients survived, all of them moderately disabled. Mortality of the surgically treated group was significantly lower (32%, 11/32). In all, 21 patients survived. Seven of the survivors were rated as severely disabled and dependent, while 14 of the surviving patients were independent and only mildly or moderately disabled. More than 80% reached a Barthel index of 60 or above.

During the evaluation of the pilot study we realized that in some patients the intervention seemed to come too late. Furthermore, it seemed feasible to identify patients who are prone to develop malignant MCA infarct within the next 24–36 hours according to the CT scan and the clinical course of the patients. We therefore changed the protocol: we no longer waited for signs of reversible herniation. Surgery was performed as soon as the CT scan showed a complete MCA infarction leading to significant mass effect with displacement of the lateral ventricle and midline shift and if the patient's consciousness level had deteriorated. Using these entry criteria, the medium time-of-stroke onset to intervention dropped from 39 hours to 21 hours in the second part of the study. We included 31 patients in that part of the trial. This approach led to a further decrease in mortality to 16% (5/31). The number of independent or moderately disabled patients was 17.[81]

Taking both trials together, we observed eight hemorrhages within the infarcted area, which did not require surgical intervention. Eight epidural bleedings occurred. They were all detected by daily B-mode ultrasound monitoring and easily evacuated. There were no deaths related to decompression surgery for MCA infarction.

Timing

Decompressive surgery should be performed early enough to prevent irreversible damage to adjacent brain structures. However, the procedure should not be performed too early so as to avoid including patients who probably would not need decompressive surgery for survival. Early CT signs of infarction, initial clinical presentation, and angiographic or other information— TCD or magnetic resonance angiography MRA—about arterial occlusion site and state of collateral blood flow (see above) can help to identify the optimal time point for surgery.

INVASIVE TREATMENT OF SPACE-OCCUPYING CEREBELLAR INFARCTION

The incidence of cerebellar infarction in a series of patients with stroke was approximately 1.5%.[82] A subgroup of patients with large cerebellar infarctions deteriorates after a variable interval. The main cause of this is probably infarct size, even though other factors such as underlying vascular lesion, hemorrhagic transformation, and poor collateral blood flow play a role as well. Neurologic deterioration occurs as a result of an increasing mass effect of the infarcted cerebellum in the posterior fossa, leading to compression of the brainstem and associated occlusive hydrocephalus, or due to progression of concurrent brainstem infarction. Therefore, close clinical monitoring and frequent CT scans to estimate the grade of obstructive hydrocephalus are mandatory. In our hospital, patients with a fast decline of consciousness will undergo decompressive surgery—with or without removal of infarcted cerebellar tissue—of the posterior fossa. Ventriculostomy alone may be a temporary measure, but great care has to be taken because it may promote

ascending herniation. In our ICU, we do not use this approach in patients with additional basilar thrombosis and large brainstem infarcts. As it is often difficult to clearly distinguish the mechanisms leading to further clinical deterioration, median nerve somatosensory- evoked potential (MSEP) and BAEP give further information for deciding about treatment in those patients. Patients with normal BAEP and somatosensory-evoked potential (SSEP) are treated with osmotherapeutics. Prolonged interpeak latencies in BAEP and altered amplitudes in SSEP indicate decompressive surgery, and just ventriculostomy is performed if CT only shows signs of hydrocephalus alone.

CONCLUSION

Elevated ICP from space-occupying edema after large cerebral ischemic infarction of the MCA territory ('malignant MCA infarction') is difficult to control only by administering conservative antiedematous treatment. Decompressive surgery and hypothermia may both reduce mortality in these patients. Early intervention seems to generate even better results in both reduction of mortality and quality of outcome. The time for intervention is reached when secondary deterioration of neurologic symptoms occurs which is not due to causes other than the ischemic lesion (for example, intracranial hemorrhages).

Multimodal monitoring can help to monitor therapy and also might help to increase our understanding of the pathophysiological mechanisms underlying postischemic edema formation. Therefore, we suggest a more widespread use of this type of monitoring.

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13.
What should become the treatment of cerebral hemorrhage?

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INTRODUCTION

The key to winning the fight against stroke is time to action. The first 24 hours in patients with intracerebral hemorrhage (ICH) are crucial because this is the time when a number of changes start to occur, including expansion of the hematoma, development of hydrocephalus, and accumulation of edema fluid around the hematoma. Clot removal at 3 hours has been proven to markedly reduce mass effect and perihematomal edema in animal studies, and very early surgery can improve clinical outcome in some patients.[1–3] While awaiting for the evaluation of early surgery in a randomized trial, medical therapy continues to be the main line of treatment in most patients with ICH.

Intracerebral hemorrhage is responsible for 10–15% of all strokes. It carries a 30-day mortality of at least 30%. The mechanisms of ICH are multiple. Frequent causes are vascular malformations and illicit drug use in the young, hypertension in the middle-aged, and cerebral amyloid angiopathy in the elderly. Other causes include head trauma, tumors, vasculitis, anticoagulants, thrombolytics, and other coagulopathies.[4–8] The location of the hematoma varies with the different causes, and the clinical presentation depends on both the location and the size of the hematoma.

MEDICAL MANAGEMENT OF INTRACEREBRAL HEMORRHAGE

GENERAL MEASURES

RESPIRATORY MANAGEMENT

Acute stroke patients are at risk for respiratory compromise, and systemic oxygen desaturation will exacerbate cerebral edema and increase intracranial pressure (ICP) by inducing cerebral vasodilation. The goal is to maintain the pO_2 between 100 and 150 mmHg.[9] Endotracheal intubation and mechanical ventilation should be guided by imminent respiratory insufficiency as indicated by hypoxia (pO_2 <60 mmHg or pCO_2 >50 mmHg) or obvious risk of aspiration, rather than an arbitrary cut-off point such as a specific Glasgow Coma Scale (GCS) score.[4] In order not to increase ICP by tracheal stimulation during endotracheal intubation it is useful to administer a short-acting barbiturate (e.g. thiopental 1.0–1.5 mg/kg intravenously) or lidocaine (1.0–2.0 mg/kg intravenously) during the procedure.[10]

Elevations in intrathoracic pressure can occur in situations of therapeutic use of positive end-expiratory pressure (PEEP), endotracheal suctioning, and chest therapy, and this can result in marked transient

increases in ICP.[9] This can be treated with short-acting sedatives like thiopental during these procedures or by using hyperventilation with 100% oxygen before and after suctioning.

FLUID MANAGEMENT

All stroke patients require an intravenous access line. Hypotonic intravenous fluids and intravenous glucose infusion are best avoided. Most patients should receive normal saline at full maintenance volume, with infusion rates of 75–125 ml/h to maintain intravascular volume and optimize brain perfusion.[11] Fluid balance is calculated by measuring daily urine production and adding for insensible water loss (urine output +500 ml for insensible loss +300 ml per degree of body temperature in febrile patients).[4]

GLUCOSE MANAGEMENT

Because there are no prospective randomized trials on glucose control, the recommendations are grade C, based on level V evidence, and based on principles to avoid extreme hyper- and hypoglycemia.[11] Many patients have a background history of diabetes. Even in nondiabetic patients, the physiologic stress of stroke frequently evokes a systemic sympathetic nervous system response that elevates blood sugar acutely. The effect of hyperglycemia on the outcome of stroke is believed to be detrimental. Employing a sliding scale to maintain a glucose level between 100 and 250 mg/dl is a reasonable strategy. Patients with serial blood glucose levels greater than 300 mg/dl should be placed in an intensive care setting for frequent blood glucose monitoring every 1–2 hours and should be started on an insulin drip. A sliding scale of regular insulin alone should not be used in such circumstances to avoid the potential 'peaks and valleys' of this type of regimen. Excessively rapid correction of blood glucose may induce cerebral edema and osmotic injury to the brain.[12] Dextrose-containing intravenous solutions in general should be avoided except in symptomatic hypoglycemia.

TEMPERATURE MANAGEMENT

Hyperthermia has deleterious effects on stroke patients. It increases the cerebral metabolic rate, CO_2 production and cerebral blood flow (CBF), resulting in increased ICP. Fever should be investigated for the source of infection and treated. In addition, fever should be reduced promptly with antipyretics and cooling blankets if necessary. Uncontrolled severe hyperthermia of central origin, which can be seen especially in large pontine hemorrhages, carries a dismal prognosis.

SEIZURES

Seizures are not infrequent in ICH. About 10–15% of all patients with ICH and 25–35% of those with lobar hemorrhages have seizures, usually at the time of stroke onset.[13] The rare occurrence of subsequent seizures is complicated by increased ICP, even in paralyzed patients.[14] The seizures should be treated with immediate use of intravenous diazepam, followed by loading doses of phenytoin, fosphenytoin, or phenobarbital. Seizure prophylaxis in ICH patients who have never seized is used in some centers, but data supporting this policy are lacking.[4]

OTHER MEDICAL TREATMENTS

Oral feeding should be avoided or minimized in the first 24 hours. The patient's ability to swallow must be assessed soon after admission and should precede initiation of feeding. Early evaluation and treatment intervention can decrease the possibility of aspiration pneumonia. Gastrointestinal prophylaxis (sucralfate, famotidine) should be started in the acute phase to prevent stress ulcers. Intermittent pneumatic compression devices can reduce the incidence of deep vein thrombosis (DVT). Elastic compression stockings help prevent superficial thrombophlebitis but do not seem to be effective in DVT prophylaxis.[15] Indwelling urinary catheters should be removed by day 4 to avoid urinary tract infection. External catheters, diapers, or intermittent catheterization could be used.

The head of the bed has to be elevated 30 degrees to enhance venous return and reduce ICP.[16] For every 10 degrees of head elevation, ICP decreases by 1 mmHg. Maintaining a neutral alignment of the head and neck and avoiding tight cervical collars are recommended to avoid disruption of normal cerebral venous outflow and to prevent increases in ICP due to increasing venous resistance. Frequent turning of the patient on a 2-hour schedule with attention to proper support and positioning of the plegic limbs is required. Heel protectors, gel mattresses, wheelchair seat cushions and air-flotation beds are useful to prevent pressure sores. Every effort should be made to achieve ambulation as soon as possible. Physical therapy can be started in the acute phase to assure adequate range of motion and proper positioning.

MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

The pressure inside the rigid skull is determined by the size of its contents, the brain parenchyma, cerebrospinal fluid (CSF), and blood. Brain injury due to ICH is primarily caused by the sudden development of an intracranial mass compressing and displacing brain tissue. Intracranial volume may further increase due to parenchymal edema and the development of hydrocephalus. Initially, ICP remains constant due to physiologic compensatory mechanisms that reduce the volume in the CSF and blood compartments of the skull. However, when the intracranial volume exceeds a critical level, ICP increases rapidly. Elevated ICP is defined as intracranial pressure >20 mmHg for >5 min.[4]

The management of elevated ICP consists of specific measures that treat the ICP itself and measures that control the factors that contribute to increased ICP. The aim of treating increased ICP is to maintain the cerebral perfusion pressure (CPP) in the normal range of 70–100 mmHg; this variable is dependent on ICP and mean arterial blood pressure (MAP), as CPP=MAP-ICP. The use of continuous ICP monitoring can be helpful in evaluating the treatment measures that are intended to decrease ICP. However, there is no conclusive evidence that the use of continuous ICP monitoring has an impact on the outcome of ICH.[17] The major therapies for acutely increased ICP are now considered.

HYPERVENTILATIONTION

Hyperventilation decreases arterial pCO_2, leading to a decrease in CSF pCO_2 and an increase in CSF pH. This effect results in cerebral vasoconstriction with subsequent reduction in ICP. The vasoconstriction only takes place in the brain areas that are unaffected by the ICH, since the vasculature in affected areas has lost its autoregulation. The therapeutic goal is to obtain a pCO_2 between 28 and 35 mmHg initially and, subsequently, in the 25–30 range if ICP continues to be elevated. Lowering the pCO_2 further may cause excessive vasoconstriction, leading to ischemia in healthy brain tissue. Hyperventilation rapidly decreases ICP, but this effect is short-lived. Since prolonged hyperventilation may be harmful to the brain, after 24–72 hours the patient should be slowly weaned off over 4–24 hours.[9,10] Hyperventilation is highly effective in

situations of acute decompensation with impending cerebral herniation or midline displacement in patients with ICH and who are in the process of receiving other more definitive therapies for the ICH, such as the insertion of a ventriculostomy catheter or surgical drainage of the hematoma.

OSMOTICDIURETICS

Osmotic diuretics help reduce ICP by increasing serum osmolality, leading to transport of water out of the brain. Mannitol (20–25%) is usually administered intravenously in a dose of 0.75–1 g/kg as a bolus, followed by 0.25–0.5 g/kg every 3–6 hours to maintain serum hyperosmolality (approximately 320 mosm/1) and euvolemia. Each bolus should be given over at least 10 min to avoid hemolysis. Loop diuretics such as furosemide can be used in combination with mannitol to keep the serum osmolality at the desired level. In addition to increasing serum osmolality, mannitol reduces CSF production and decreases blood viscosity.[9] Its main side effects include wide variations in blood volume and electrolytes, leading to hypo- or hypernatremia, hypokalemia, congestive heart failure, volume contraction, or renal failure. In patients with history of congestive heart failure, coronary heart disease, or renal insufficiency, a central line to measure central venous pressure is needed to keep the patient euvolemic.

A rebound of raised ICP after the abrupt discontinuation of osmotic agents has been described but it is rare. Because of this possibility, serum osmolality should be lowered slowly over 1–2 weeks. There appears to be no benefit in the use of intravenous glycerol in patients with ICH. A randomized, placebo-controlled trial of intravenous glycerol that included 107 patients in the treatment group and 109 controls showed no difference in mortality or functional outcome between the two groups.[18]

Osmotic agents should not be given routinely because they can diffuse into the hematoma, thus leading to a potential increase of its mass effect.

INTRAVENOUS BARBITURATES

Intravenous barbiturates play a limited role in the management of increased ICP. These agents reduce brain metabolism and decrease CBF and ICP. Side effects such as hypotension and interference with the neurologic examination, including assessment of brainstem reflexes, greatly limit their clinical usefulness. The most commonly used agent is pentobarbital at a dose of 3–10 mg/kg as a loading dose given as 1 mg/kg/min and followed by 1–2 mg/kg/h as a maintenance dose. The effect of the pentobarbital can be monitored by electroencephalography (EEG), aiming to burst suppression or isoelectric EEG. Intravenous barbiturates are not the first line of treatment to decrease ICP but are used only if there is no response to osmotic agents or hyperventilation.

CORTICOSTEROIDS

Corticosteroids (dexamethasone) in the setting of an acute ICH were not shown to be beneficial in a randomized clinical trial,[19] as treated patients fared worse than controls, mainly as a result of steroid-induced complications.

OTHER MEASURES

Factors that contribute to increased ICP include fever, hypoxia, seizures, hypertension, transient or persistent elevation of intrathoracic pressure, head positioning, pain, agitation, and certain medications (inhaled

anesthetics, hypnotics, ketamine, and succinylcholine). For the treatment of agitation, the underlying toxic-metabolic derangements and deficiency states should be treated. Delirium (agitated confusion) can cause autonomic instability, which may result in fluctuating arterial hypertension, which can increase the ICP. Pain should be treated with acetaminophen or stronger analgesics, but nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin should be avoided in patients with ICH.

MANAGEMENT OF HYPERTENSION

Hypertension is common in patients with ICH, as this stroke type is often caused by chronic or acute hypertension. However, in previously normotensive patients, hypertension can be the result of the ICH, in particular in the setting of elevated ICP (Cushing's phenomenon). Reduction of ICP may occasionally be sufficient to control blood pressure, which typically returns to premorbid levels after 7–10 days,[20] but more often pharmacological treatment is indicated. An increase in MAP results in an increase in CPP, which in turn produces increased CBF and ICP.[9,21] There are no specific guidelines for the treatment of hypertension in acute stroke, but there is agreement on treating a diastolic blood pressure >120 mmHg or MAP >125–135 mmHg.[10] A MAP >110 mmHg should be avoided in the immediate postoperative period after evacuation of the ICH. If systolic blood pressure falls below 90 mmHg, pressors should be given.

Aggressive lowering of high blood pressure in patients with ICH should be avoided, because of the risk of lowering the CBF to ischemic levels; this is particularly relevant in view of the growing evidence for a substantial area of ischemia at the peripheral portions of intracerebral hematomas. Pharmacological agents that cause cerebral vasodilatation, such as calcium channel blockers, nitroglycerin, and hydralazine, should be avoided because of their potential to increase cerebral blood volume and thereby increase ICP. In contrast, alpha- and beta-blockers, ganglion blockers and angiotensin-converting enzyme (ACE) inhibitors have little effect on cerebral blood volume.

Parenteral agents that allow rapid, controlled titration to target pressures are often useful in the hyperacute setting and include enalapril, labetalol, and nitroprusside. Although sodium nitroprusside is a vasodilator, its reliable control of blood pressure and easy titration offset that theoretical disadvantage. In a small prospective study of 10 patients with ICH, labetalol at doses between 5 and 25 mg as an adjunct therapy lowered the systolic blood pressure by 6–19% and the diastolic blood pressure by 3–26%,[22] without adverse effects on mental status or focal neurologic deficits. Subcutaneous clonidine can be given if there is contraindication to the above medications. Treatment of hypertension in ICH patients is summarized in Table 13.1.

MANAGEMENT OF COAGULOPATHY

In approximately half of anticoagulated patients with ICH, the bleeding evolves slowly over 12–24 hours and emergency reversal of anticoagulation is crucial.[23] Even patients who have atrial fibrillation or prosthetic heart valves should have anticoagulation corrected in the face of an ICH. In patients who have warfarin-related ICH, the correction of the coagulopathy can be started by the use of vitamin K1 (5–25 mg) intravenously or subcutaneously. Intravenous vitamin K, while effective, is associated with a small risk of serious anaphylactic reactions, and subcutaneous administration is safer. For patients who are excessively anticoagulated with warfarin, a small dose of subcutaneous vitamin K may not correct the coagulopathy, and higher doses must be considered for more rapid and complete reversal of anticoagulation by that route.[24] It takes 4–6 hours for vitamin K to work,[25] but the need for immediate normalization of coagulopathy often requires the use of fresh frozen plasma (15–20 ml/kg)— 1 U every 45 min.

Current guidelines on the reversal of warfarin anticoagulation in the event of ICH are not based on prospective randomized trials. Many patients receiving oral anticoagulation therapy have cardiac diseases such as congestive heart failure that do not permit rapid infusion of colloid volume. The fear of elevating the ICP also limits the administration of blood products. Infusion of individual factors concentrate, which contains high concentrations of activated vitamin K-dependent factors (II, VII, IX, and X), provides a potential solution to this dilemma. However, two problems limit the use of individual clotting factors:

Table 13.1 Blood pressure management in ICH (from Broderick et al.[4])

Elevated blood pressure (some suggested medications):	
Labetalol	5–100 mg/h by intermittent bolus doses of 10–40 mg or continuous drip (2–8 mg/min)
Esmolol	500 μg/kg as a load; maintenance dose, 50–200 μg/kg/min
Nitroprusside	0.5–10 μg/kg/min
Hydralazine	10–20 mg every 6 hours as needed
Enalapril	0.625–1.2 mg every 6 hours as needed
The following algorithm may be used in the first few hours of ICH (level of evidence V, grade C recommendation):	
1.	If systolic BP is >230 mmHg or diastolic BP >140 mmHg on two readings 5 min apart, institute nitroprusside
2.	If systolic BP is 180–230 mmHg, diastolic BP 105–140 mmHg, or mean arterial BP >130 mmHg on two readings 20 min apart, institute labetalol, esmolol, enalapril, or other smaller doses of easily titratable intravenous medications such as diltiazem, lisinopril, or verapamil. Choice of medication depends on other medical contraindications (e.g., avoid labetalol in patients with asthma)
3.	If systolic BP is <180 mmHg and diastolic BP <105 mmHg, defer antihypertensive therapy.
4.	If ICP monitoring is available, CPP should be kept at >70 mmHg
Low blood pressure	
Volume replenishment is the first line of approach. Isotonic saline or colloids can be used and monitored with central venous pressure or pulmonary artery wedge pressure. If hypotension persists after correction of volume deficit, continuous infusions of pressors should be considered, particularly for low systolic BP such as <90 mmHg. The recommended agents are:	
Phenylephrine	2–10 μg/kg/min
Dopamine	2–20 μg/kg/min
Norepinephrine	titrate from 0.05–2.0 μg/kg/min

BP, blood pressure; ICH, intracerebral hemorrhage; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

1. the fear of viral contamination
2. vascular thrombosis, which can be induced by the activated clotting factors.

Patients who bleed while receiving intravenous heparin therapy should have the coagulopathy normalized by the use of protamine sulfate. The dose of protamine sulfate needs to be adjusted depending on the time since the last heparin dose.

There are no useful data regarding the preferred treatment of ICH caused by thrombolytic therapy.[26] Fibrinogen (6–8 U), cryoprecipitate containing factor VIII, fresh frozen plasma (4–6 U), and 6–8 U of platelets are all recommended. The use of aminocaproic acid (5 g over 60 min loading dose, followed by 1 g/h until bleeding is controlled) is controversial, as definite benefit from it has not been shown, and it has the disadvantage of increasing the risk of DVT and pulmonary embolism.

SURGICAL MANAGEMENT OF INTRACEREBRAL HEMORRHAGE

There is a remarkable paucity of data addressing the issue of surgical versus medical treatment of spontaneous supratentorial ICH: most of the information on this subject is derived from clinical series with several types of biases. This issue will continue to be controversial until a welldesigned prospective randomized controlled trial comparing surgery with best medical management in patients with spontaneous supratentorial ICH is conducted.

CLINICAL SERIES COMPARING SURGICAL WITH NONSURGICAL THERAPY

One of the earlier randomized trials comparing surgical with nonsurgical treatment of supratentorial ICH was reported by McKissock et al.[27] in 1961, before the introduction of computed tomography (CT). The study included 180 patients, 91 assigned to the medical group and 89 to the surgical group. Patients with a rapid clinical recovery were excluded from the study. The two treatment groups were stratified according to level of consciousness, age, and the presence of hypertension. Open craniotomy with evacuation of the hematoma was performed within 48 hours in the majority of patients. Mortality rates were similar in both treatment groups: 51% for the medical group and 65% for the surgical group. Likewise, functional outcome on follow-up was not different for the two groups. In the medical group 11 patients returned to work, 20 were partially disabled, and 14 were totally disabled compared with 10, 8, and 13 patients in the surgical group, respectively. Patients with lobar hemorrhages had a better outcome than those with basal ganglia or thalamic hemorrhages, but in neither group did surgical treatment prove to be superior to medical treatment. The level of consciousness was found to be a good predictor of outcome: patients who initially were alert or drowsy did better than those who were stuporous or comatose, regardless of treatment modality used.

Subsequently, still prior to the introduction of CT, several uncontrolled surgical series reported on the outcome of surgery in supratentorial ICH. Some of these studies confirmed that the level of consciousness on presentation is an important indicator of outcome in patients with ICH,[28–31] and two reports[28,30] showed that patients with deeply located hematomas fared worse than those with lobar hematomas. The timing of surgical intervention was addressed by some studies with conflicting results. Cuatico et al.[28] and Paillas and Alliez[32] reported that the most beneficial outcome for surgery was in those patients who underwent craniotomy with hematoma evacuation several days after onset of the ICH (between day 4 and 7, and day 5 and 10, respectively). By contrast, Kaneko et al.[33] observed a remarkably low mortality (8%) in patients with surgical treatment within 7 hours of ICH onset.

The introduction of CT in 1973 provided a means for a more accurate diagnosis of ICH, and for a more precise delineation of the anatomic features of the hematoma. Subsequently, studies have been able to compare similar groups of patients in regard to the location and size of the hematoma.

With the exception of two,[34,35] most studies of surgical versus nonsurgical treatment of ICH in the past 15 years were not randomized or prospective. Kanaya et al.[36] analyzed the outcome of 410 surgically treated patients and 204 medically treated patients with putaminal hemorrhage. They found no difference in

functional outcome between surgical and nonsurgical patients who were 'alert or confused' or 'somnolent' on the one hand, and those who were in 'semicoma with herniation signs' or 'deep coma' on the other hand. However, both functional outcome and mortality in patients who were in 'stupor' or in 'semicoma without herniation signs' were better in the surgically treated group than in the medically treated group (mortality rates of 18% and 52%, respectively).

Kaneko et al.[37] reported encouraging results on early surgical treatment (within 7 hours of ICH onset) in 100 patients with putaminal hemorrhage, of which 10 were described as somnolent, 68 as stuporous, and 22 as semicomatose. Most patients had hematoma volumes greater than 20–30 ml with more than 5 mm of midline shift. The overall mortality was remarkably low at 7%, and 89% of the survivors were ambulatory 6 months after surgery. Similarly, the results of several retrospective clinical series have suggested a benefit of surgery in patients with mild-to-moderate depression of consciousness and intermediate-sizehematomas.[38–41]

The results of two prospective randomized controlled trials conducted in recent years have not been helpful in settling the issue of medical versus surgical treatment of ICH. The study of Batjer et al.[35] included only 21 patients, who were not stratified by either entry clinical status or hematoma volume. Poor results in all three treatment groups ('best medical management,' 'best medical management'+ICP measurement via ventriculostomy, and craniotomy with microsurgical hematoma evacuation) led to early termination of the trial. Juvela et al.[34] randomized 52 patients with spontaneous supratentorial ICH, 26 to surgical and 26 to medical treatment, within 48 hours of ICH onset. Patients were enrolled if they were 'unconscious and/or had severe hemiparesis or dysphasia'. The overall mortality rate at 6 months was similar in both treatment groups, although patients who were stuporous or semicomatose tended to do better in the surgically treated group.

Two small randomized, single-institution trials on the early surgical vs. non-surgical treatment of ICH have documented the feasibility of such a study.[41a,41b] Morgenstern et al.41a randomized 17 patients with putaminal or lobar ICH to surgery within 12 hours of onset vs. non-surgical treatment. They documented a non-significant trend toward lower mortality in the surgical group at 1 month, but the 6-month evaluation showed no such superiority for the surgically managed group. Similarly, Zuccarello et al.[41b] randomized 20 patients with lobar, thalamic or putaminal hemorrhage to surgery within 8 hours of ICH onset vs. non-surgical treatment. The results indicated a non-significant trend toward better outcome in the surgically-treated group at 3 months. In both instances, a potentially more robust benefit from surgery may have been missed by the small numbers of patients included in the studies.

In summary, the review of these clinical series suggests that surgery is not indicated in patients with small hematomas and minimally depressed level of consciousness, and in those with large hematomas and severely depressed level of consciousness. The former group has good outcome with medical treatment alone, and the latter has a very poor outcome regardless of the form of therapy used. Patients with intermediate-size hematomas and moderately depressed level of consciousness have a poor outcome with medical treatment alone and may benefit from surgical intervention. However, this hypothesis needs to be tested in a prospective controlled randomized clinical trial in which patients should be stratified according to their neurologic status on presentation and the features of the hematoma on imaging studies (size, location, mass effect, and ventricular extension). Other variables that may prove to be of importance and that should be included in the design are the surgical technique used (craniotomy, stereotactic aspiration with and without local thrombolysis, or stereotactic endoscopic aspiration), the timing of surgery, and the amount of hematoma removed.

SPECIAL SURGICAL SUBGROUPS

The theoretical benefits of surgical evacuation of an intracerebral hematoma are several:

1. evacuation of the ICH will improve perfusion of compromised brain parenchyma and prevent intracranial hypertension,
2. it may also enhance the clearance of blood breakdown products, hence preventing secondary brain edema and potential neurotoxicity.

The first 24 hours in patients with ICH are crucial, because this is the time of expansion of the hematoma and very early surgery can improve clinical outcome in some patients.[1–3] The volume of the hematoma is also consistently shown to be a powerful factor in making decisions regarding surgery. The 'ABC/2' method is a reliable bedside method for ICH volume measurement.[42] Some authors have advocated the use of ICP monitoring to determine which patients should be subjected to surgical drainage of the ICH,[43,44] based on the suggestion that patients who do not respond to maximum medical treatment may benefit from surgical treatment.

There are a number of situations in which it is current practice to contemplate some surgical options. These are summarized in Table 13.2.

PUTAMINAL HEMORRHAGE

The management of patients with putaminal hemorrhage is for the most part nonsurgical, as patients with small (γ20 ml) hematomas do well without surgery, whereas those at the other end of the size spectrum (>60 ml) do poorly regardless of the form of therapy employed.[45] Whether patients in the intermediate size group (hematoma volume of 30–60 ml) benefit from surgery remains to be determined, hopefully

Table 13.2 Current recommendations regarding surgical or nonsurgical treatment of intracerebral hemorrhage (modified from Minematsu and Yamaguchi, 1995[44a])

ICH location	Clinical/CT features	Treatment
Putamen	Alert, small ICH (<30 ml) Comatose, large ICH (>60 ml) Drowsy, intermediate ICH (30–60 ml)	Nonsurgical Nonsurgical Consider evacuation
Caudate	Alert or drowsy, with intraventricular hemorrhage and hydrocephalus	Consider ventriculostomy
Thalamus	Drowsy or lethargic, with blood in third ventricle and hydrocephalus	Consider ventriculostomy
Lobar white matter	Drowsy or lethargic, with intermediate ICH (20–60 ml), progressive decline in LOC	Consider evacuation
Pons, midbrain, medulla	–	Nonsurgical
Cerebellum	Noncomatose, with ICH>3 cm, and/or hydrocephalus, and/or effacement of quadrigeminal cistern.	Evacuation recommended, preceded by ventriculostomy if patient actively deteriorating

CT, computed tomography; ICH, intracerebral hemorrhage; LOC, level of consciousness

through the conduction of a randomized clinical trial of surgical versus nonsurgical treatment. In the absence of such data, patients in this intermediate clinical category are managed nonsurgically unless there

is progressive deterioration in the level of consciousness; in this event, patients with a worsening clinical course and enlarging hematoma by CT are often subjected to surgical drainage, a measure that intends to prevent death rather than expect an improved functional outcome. The latter should not be an indication for surgery in an otherwise clinically stable patient, as there is no evidence that surgical drainage of putaminal hemorrhage results in improved functional results.[46]

CAUDATE HEMORRHAGE

Patients with caudate hemorrhage present with generally small parenchymal hematomas but almost invariably with intraventricular hemorrhage.[47] In the event of having a large component of intraventricular hemorrhage, caudate hemorrhage is often associated with acute hydrocephalus and a deteriorating level of consciousness. In these instances, treatment with ventriculostomy should be considered, as the resolution of hydrocephalus is often followed by an improvement in the level of consciousness. In the absence of hydrocephalus, however, there is no evidence that the mere removal of ventricular blood has a beneficial impact on outcome, which is largely dependent on the magnitude of the parenchymal component of the hemorrhage, rather than the presence of ventricular blood.[48]

THALAMIC HEMORRHAGE

In thalamic hemorrhage, similar to the situation in caudate hemorrhage, the patient experiences the effects of both the parenchymal hematoma and the commonly associated intraventricular extension of the hemorrhage, generally through the third ventricle. In contrast to caudate hemorrhage, thalamic hemorrhage tends to produce more neurologic compromise, with hemiparesis, hemisensory loss and oculomotor—pupillary changes, resulting from the thalamic—capsular location of the hematoma and its pressure effects on the midbrain tectum.[49] In addition, ventricular extension and hydrocephalus add to the clinical picture by producing further compromise of the level of consciousness and, often, worsening oculomotor deficits which can be reversed, at times dramatically, by ventriculostomy.[50] Direct surgical drainage of thalamic hemorrhages is not a consideration in view of the deep location of the hemorrhage, which would entail substantial surgical trauma in gaining access to the hematoma. Computed tomography-guided stereotactic needle aspiration with or without local thrombolysis may have a role in the future treatment of such deep hematomas. Such a recommendation is awaiting further studies.[51]

LOBAR HEMORRHAGE

Patients with lobar hemorrhages have clinical presentations that differ markedly depending on the site and size of the hemorrhage. Small (<20 ml) hematomas in the frontal, temporal, or occipital lobe are generally well tolerated and can produce surprisingly few neurologic deficits, whereas large (>60 ml) hemorrhages in these locations and, especially, in the parietal lobe, can produce devastating combinations of sensory, motor, language, and visual deficits, often accompanied by drowsiness, lethargy, or coma.[52] In the latter instances, when lethargy or drowsiness evolve along with an enlarging hematoma by CT, surgical intervention is often considered a more reasonable option than in a patient with a putaminal hemorrhage of similar size and clinical presentation.[53] This results from the more superficial location of the lobar hematoma, making it more surgically accessible than the basal ganglionic variety, in which surgical trauma is considerably larger.

BRAINSTEM HEMORRHAGE

Hemorrhages in the brainstem (midbrain, pons, medulla) are nonsurgical, as the tissue destruc tion caused by the initial bleeding precludes any benefit from hematoma drainage. Instances of successful surgical treatment of hematomas located in the vicinities of the fourth ventricle[54–56] constitute neurosurgical rarities that, at this time, do not justify inclusion of these relatively rare hemorrhages in planned randomized trials of surgical versus nonsurgical treatment of ICH.

CEREBELLAR HEMORRHAGE

Patients with cerebellar hemorrhage constitute a special group in that the hemispheric cerebellar hematoma *per se* tends to damage structures (the cerebellar white matter and the dentate nucleus) that generally show surprising degrees of functional improvement with time, while at the same time having a notorious potential for producing abrupt and often fatal brainstem compression in the acute stage.[57] This combination of circumstances determines that surgical drainage of cerebellar hemorrhages is often a life-saving procedure, in which preventing death is followed by at times remarkable functional recovery, a situation that is not paralleled by deep, basal ganglionic (especially putaminal) hematomas. The surgical indication in cerebellar hemorrhage depends on the clinical presentation and CT features of the hemorrhage. It is generally accepted that the presence of signs of tegmental pontine compression (ipsilateral horizontal gaze palsy, peripheral facial palsy, trigeminal hypesthesia) should be strong indications for surgical drainage, as sometimes minor degrees of further pontine tegmental compression result in sudden fatal respiratory arrest.[58] In addition, a hematoma diameter of >3 cm[59] along with local mass effect (effacement of the quadrigeminal cistern),[60] and obstructive hydrocephalus are predictors of poor outcome if managed nonsurgically. By the time coma occurs, it is usually too late for surgical treatment to be beneficial. Based on the above data, the combination of clinical and CT criteria are accepted indications for urgent surgical treatment, which often starts with decompressive ventriculostomy followed immediately afterward by drainage of the cerebellar hematoma by suboccipital craniotomy. Ventriculostomy is indicated when the patient develops obstructive hydrocephalus in conjunction with a deteriorating level of alertness. Patients that are particularly at risk for the development of hydrocephalus are those with thalamic, cerebellar, and caudate hemorrhages, as the close proximity of the ICH to the ventricular system allows early ventricular extension of the hemorrhage. The main problems with intraventricular catheters are infection and hemorrhage. The occurrence of infection can be monitored by following the CSF glucose and the white cell count. Prophylactic antibiotics and catheter replacement every 5–7 days help reduce the risk of catheter-related infections. Rarely, a worsening in tissue shifts may occur as a result of a unilateral ventriculostomy.

NOVEL DEVELOPMENTS IN THE TREATMENT OF ICH

The mortality rate of patients with ICH continues to be high, ranging between 20% and 56%, and many ICH survivors remain severely incapacitated.[46] The development of modern surgical techniques and better understanding of the mechanism of ischemic brain damage in ICH have led to new treatment strategies that raise hope for improved survival and functional outcome.

NEW SURGICAL TECHNIQUES FOR INTRACRANIAL CLOT REMOVAL

With the objective to minimize surgical trauma associated with craniotomy and evacuation of intracerebral hematomas, several new surgical techniques have been proposed in recent years. These techniques may

prove to be particularly beneficial in the removal of deeply located hematomas, and in patients who are a high operative risk for conventional hematoma removal under general anesthesia.

Backlund and von Holst[61] described in 1978 the stereotactic removal of a large temporo parietal hematoma in a 55-year-old male using a rotating drill, after the principle of the Archimedean water screw. Through a burr hole, 70 ml of the 100 ml hematoma was aspirated. The patient made an excellent clinical recovery and was able to return to work 10 months after the surgery. Good results following clot evacuation by this technique were reported subsequently in two clinical series, including a total of 55 putaminal, 31 thalamic, and 4 subcortical hemorrhages with relatively small volumes of 5–34 ml.[62,63] In addition to this technique, a number of other devices have been developed over the years to break up and aspirate an intracranial clot;[64] however, prospective studies to assess their value in comparison with conventional craniotomy or nonsurgical treatment have not been performed.[65]

The safety and efficacy of using fibrinolytic agents in and around the brain have been studied in detail in animal models, and studies are being undertaken to assess their benefit and safety in humans with ICH, subarachnoid hemorrhage, and intraventricular hemorrhage. In patients with ICH, several groups have gained experience with liquefying the intracranial clot with thrombolytic agents (urokinase) prior to hematoma aspiration. A silicone tube was inserted in the center of the hematoma and, after initial aspiration with a syringe, urokinase (6000 U in 2–5 ml of saline) was administered through the tube, which was subsequently clipped. Aspiration and infusion of additional urokinase were repeated at fixed intervals of 6–24 hours until the bulk of the hematoma had been removed.[66,67] This technique was used to treat putaminal, thalamic, subcortical, and cerebellar hemorrhages. One of the main risks was rebleeding, reported in 2 of the 51 cases of Matsumoto and Hondo,[66] and in 7 of the 97 cases of Niizuma et al.[67] A comparison of 6-month postoperative outcome of stereotactic aspiration using urokinase with conventional craniotomy in 94 patients showed no difference in mortality between the two procedures, but the functional outcome was reported to be better in those treated with the stereotactic aspiration technique.[66]

Recently, and following the withdrawal of urokinase from the market, recombinant tissue plasminogen activator (rt-PA) has been tested for stereotactic hematoma lysis prior to aspiration.[68]

Intraventricular extension of the hematoma is a poor prognostic sign in patients with ICH. Mortality rates increase with the amount of blood in the ventricles, ranging from 32 to 91%.[69] The results of preliminary reports on the intraventricular infusion of urokinase or rt-PA in patients with extensive intraventricular hemorrhage (occupying the lateral, third, and fourth ventricles) are promising.[69,70] Rohde et al.69 reported a mortality of 5% in 20 patients who were treated with repeated intraventricular rt-PA infusions of 2–5 mg until ‘appreciable reduction of the hematoma volume in the lateral ventricles and clearance of the third and fourth ventricles were confirmed’ by CT.

Auer et al.[71] reported the evacuation of intracerebral hematomas by means of a ‘neuroendoscope.’ The device is introduced through a burr hole, guided by an ultrasound-assisted stereotactic technique. The hematoma cavity is continuously irrigated with artificial CSF, and aspirated at regular intervals through a separate channel of the endoscope. A miniature video camera provides direct visual feedback during the procedure, and a built-in laser is used to coagulate small blood vessels in the wall of the hematoma cavity. Patients with lobar, putaminal, and thalamic hematomas were treated with this technique, and their outcome was compared to medically treated patients with similar hem orrhages. The mortality rate at 6 months was significantly lower in the surgically treated group, except for patients over 60 years of age, in whom no differences between groups were observed. Benefit from surgical treatment was only seen in patients with lobar hemorrhages, in contrast to those with hematomas of the putamen and thalamus, who showed no difference in outcome in the two groups.

These new surgical techniques for hematoma evacuation offer an alternative to conventional craniotomy, and may be of particular benefit in selected subgroups of patients with ICH. However, their value can only be assessed by means of a prospective randomized trial.

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14.
Surgery for acute stroke

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INTRODUCTION

The treatment of patients in the acute stage of stroke remains a controversial issue despite expanding knowledge and improving technology in this field and despite the reduction of stroke and stroke-related death by 50% over the last three decades.[1] This chapter is intended to discuss emerging trends in the treatment of stroke in the acute stage from the surgical point of view. Surgical management of acute stroke especially intracerebral hematoma (ICH) and cerebral ischemia, is discussed (Fig. 14.1); a systematic approach to treatment, including neuroresuscitation in the neurointensive care unit, cannot be overemphasized in promoting a favorable outcome for those patients suffering from acute stroke.

HEMORRHAGIC STROKE

Spontaneous intracranial hemorrhage can be divided into epidural hematoma (EDH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH), intracerebal hematoma (ICH), and intraventricular hematoma (IVH), according to the location. Subdural hematoma is dealt with in Chapter 18.

Table 14.1 Causes of ICH (from Feldmann[2])

Cause	Percent
Hypertension	50
Cerebral amyloid angiopathy	12
Anticoagulants	10
Tumors	8
Prescription and street drugs	6
AVMs and aneurysms	5
Miscellaneous	9

AVMs, arteriovenous malformations, ICH, intracerebral hematoma.

INTRACEREBRAL HEMATOMA

Intracerebral hematoma accounts for 10-15% of stroke.[2,3] It should be noted that bleeding due to cerebral amyloid angiopathy (CAA) and anticoagulant therapy makes up a considerable share of ICH, aside from the large number of hypertensive hemorrhages (40-60%)[2] (Table 14.1).

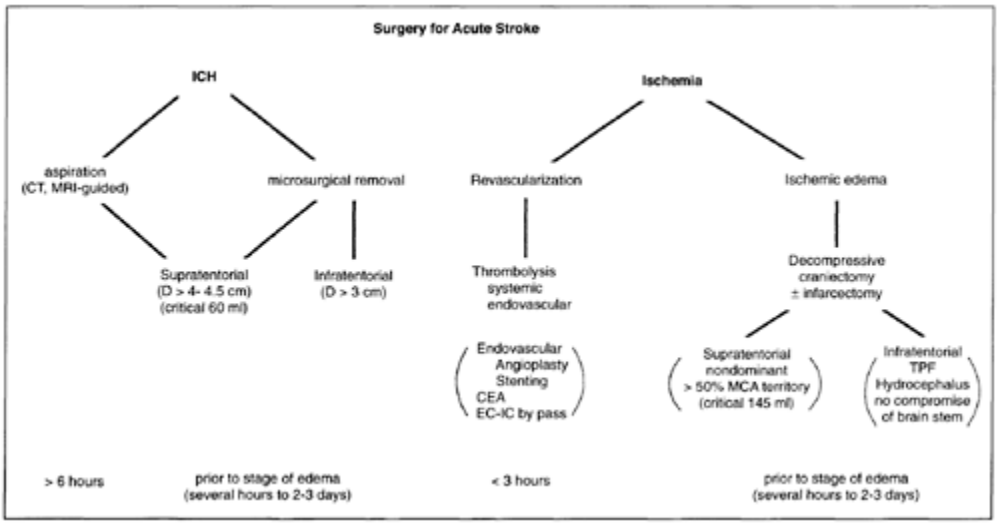

Figure 14.1 Schematic chart of surgical treatment of acute stroke.

For details see corresponding sections of this chapter.

The frequency of ICH due to rupture of aneurysms, arteriovenous malformations (AVMs) and other malformations is somewhat lower than that reported elsewhere and that of our department of consecutive 298 cases, which

Table 14.2 Causes of ICH (*n*=298) (modified from Fernandez[4])

Cause	No.	Percent
Structural ICH:	38	13
Aneurysm	7	2
AVM, AVF	23	7
Cavernous angioma	8	2
Non structural ICH:	260	87
Hypertension	145	49
Amyloid angiopathy	9	3
Vasculitis Hemorrhagic infarction	147	42
Anticoagulant	41	14
Others	3	1
Undetermined	40	13

AVF, arteriovenous fistula; AVM, arteriovenous malformation; ICH, intracerebral hematoma.

is approximately 10%[4] (Table 14.2). We are of the opinion that every patient with ICH should generally undergo cerebral angiography to obtain a definitive diagnosis, which can then be followed by optimal treatment, although we are aware of the technical development of magnetic resonance (MR) angiography

and three-dimensional computed tomography (3-D CT) angiography and of the inherent risk of angiography. We need clear and definite detailed findings that can direct the type and extent of surgical treatment.

HYPERTENSIVE INTRACEREBRAL HEMATOMA[5]

Hypertensive intracerebral hematoma accounts for 10% of cerebral stroke and causes 60% of death due to stroke. Around 60 years of age is the predilection. The male: female ratio is 2:1. Location of hemorrhage is basal ganglia-thalamus 60%, cortex-subcortex 20%, cerebellum 10%, and midbrain-pons 10%. Basal gangliathalamus hemorrhage can be divided into the lateral type (putaminal hemorrhage) and the medial type (thalamic hemorrhage), 1.5:1.0 (Fig. 14.2).

Although the symptomatology, diagnosis, and conservative treatment of this condition are discussed in other chapters in detail, they are mentioned here briefly in relation to their surgical treatment.

PUTAMINAL HEMORRHAGE

Hemiparesis is associated with sensory disturbance: stronger paresis in the upper extremity than in the lower extremity and in distal muscles than in proximal muscles. Consciousness is alert only in 10% of patients at the time of onset. Cases with consciousness disturbance are usually associated with conjugate deviation but with rare appearance rate of anisocoria.

Putaminal hemorrhage is considered to originate from rupture of the most lateral artery (A. apoplectica Charcot) of the lateral lenticulostriate arteries (see Fig. 14.7), although the concept of microaneurysms at this site has recently been called into quetion.[6] Putaminal hemorrage can be divided into three types:

1. localised at the putamen
2. progression from the putamen to the posterior limb of the internal capsule
3. further progression of the second type into the lateral ventricle.

THALAMIC HEMORRHAGE

Consciousness disturbance is usually less frequent than in cases of putaminal hemorrhage, also from the viewpoint of motor hemiparesis. Coordination disturbance, dysesthesia, and disturbance of position sense coined as thalamic syndrome are often recognized. Thalamic hand and Parinaud's sign may be present. Motor paresis is more prevalent in the lower extremity than in the upper extremity and in distal muscles than in proximal muscles. In cases of severe consciousness disturbance, eye ball position is abnormal—mostly one of upward gaze palsy combined with miotic unreactive pupils 'peering at the tip of the nose'.[7] Loss of pupillary reaction to light or anisocoria are observed more often than in cases of putaminal hemorrhage. These oculomotor findings are considered to be due to compression or extension of the hemorrhage into the midbrain tegmentum. Aphasia rarely takes place.

Thalamic hemorrhage can be divided into the following categories:

1. localised in the thalamus
2. progression to the posterior limb of the internal capsule
3. progression into the third ventricle
4. progression via the posterior limb of the internal capsule into the lateral ventricle
5. progression into the midbrain tegmentum.

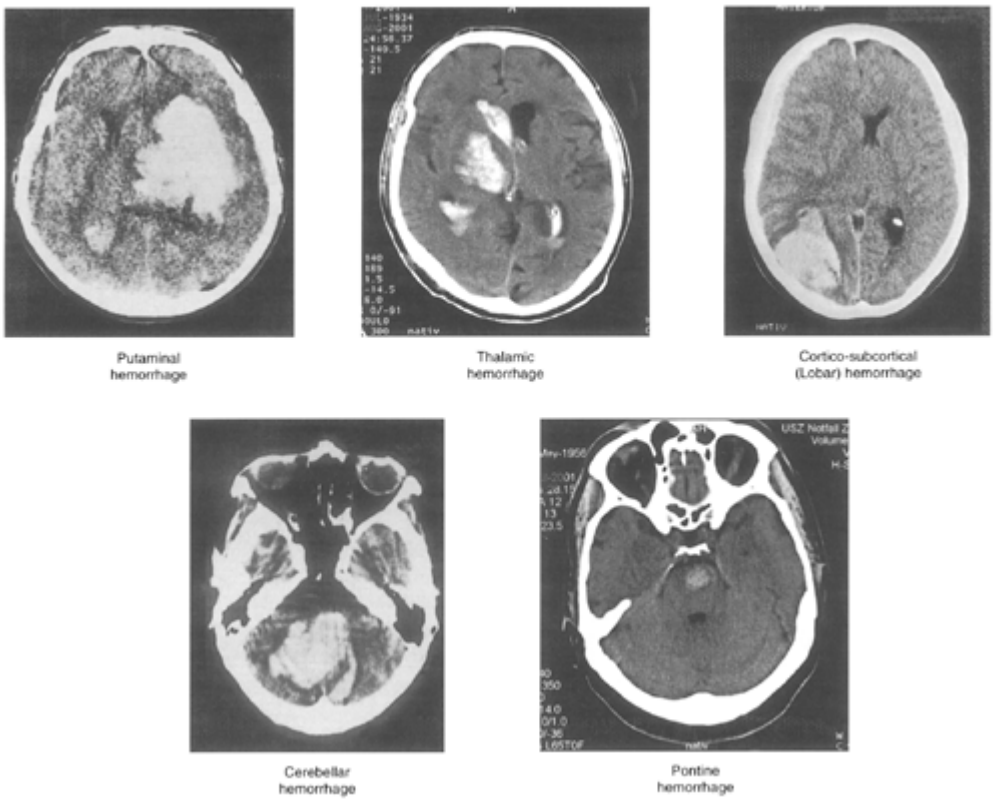

Figure 14.2 Typical intracerebral hematomas by location.

Thalamic hemorrhage is rarely indicated for surgical removal but ventricular drainage is often indicated to treat occlusive hydrocephalus, which takes place in about 20% of cases of thalamic hemorrhage.

CORTICO-SUBCORTICAL HEMORRHAGE (LOBAR HEMORRHAGE)

This hemorrhage usually takes place at the parietal lobe, temporal lobe, frontal lobe, and occipital lobe. Hemorrhage resulting from amyloid angiopathy or some other etiology, such as AVMs, aneurysms, or cavernous angioma, should be differentiated.

About one-quarter of cortico-subcortical hemorrhages have been reported to have some etiology other than hypertension.

Symptomatology and signs depend upon the location and size of the hematoma, so that hemiparesis is not necessarily observed.

Cortico-subcortical hematoma is indicated for surgical removal, as mentioned below.

PONTINE HEMORRHAGE

Pontine hemorrhage is associated with severe consciousness disturbance and frequently with tetraplegia or with Millard-Gubler syndrome (hemiparesis with contralateral peripheral facial nerve palsy). Disturbances of the autonomic nervous system is also frequent, with signs such as hyperthermia; hyperhydrosis, pinpoint pupil, but having normal reaction to light; and respiratory disturbance. Eye balls are fixed to the midpoint; ocular bobbing is encountered sometimes, but skew deviation is rare.

The hemorrhage is caused by rupture of a paramedian branch of the basilar artery. Pontine hemorrhage is out of surgical indication.

Midbrain hemorrhage is rare and mostly results from cavernous angiomas.

CEREBELLAR HEMORRHAGE

Severe dizziness is the initial symptomatology in 80% of cases, followed by headache and vomiting. The patient becomes unable to walk or stand. Consciousness disturbance or loss of consciousness develops in the course of hours, and is considered to be related to occlusive hydrocephalus. Two important prognostic factors are the size of the hematoma and perforation into the fourth ventricle. Nystagmus, coordination disturbance and equilibrium disturbance are observed in most cases when the patient is still alert.

Rupture of the arterial branch to the dentate nucleus is considered to be most frequent cause of the hemorrhage.

Cerebellar hemorrhage is one of the best indications of surgical removal.

CEREBRAL AMYLOID ANGIOPATHY

Cerebral amyloid angiopathy is characterized by deposition of beta-amyloid protein within the wall of small meningeal and cortical vessels. Intracerebral hematoma due to amyloid angiopathy was once considered rather rare, but with progress in diagnostic knowledge and technology, together with the increase of the aged population, it is now known to be more common than previously supposed. Cerebral amyloid angiopathy presents some diagnostic and therapeutic difficulties. A definitive diagnosis cannot be made without biopsy or autopsy, although lobar hemorrhage or repeated hemorrhage in a normotensive, elderly patient with dementia is a clue to the diagnosis. A consensus once existed that surgical removal, or even biopsy, was contraindicated because of the risk of a hemorrhagic complication. We agree, however, with the contention made in recent reports that large, life-threatening hematomata should be removed surgically; this would also help in obtaining a definitive diagnosis (Fig. 14.3).[8,9]

There is currently no effective treatment for CAA itself, although basic research is underway, including the elucidation of immune reactions.[10]

ANTICOAGULANT THERAPY

Intracranial hemorrhage has been reported to occur as a complication in 1% of anticoagulated patients per year. These patients are becoming more numerous because of the increase of the aged population and better detection of the disease. Anticoagulation reportedly accounts for 10% of cases of spontaneous intracranial hemorrhage; most of these (70%), in turn, are intracerebral.[11] The preferred sites of ICH due to anticoagulation are reportedly similar to those of hypertensive hemorrhage. The mortality is approximately 60%. Diminished consciousness, intraventricular hematoma, location in posterior fossa, and diameter >5 cm (hematoma volume > 60 ml) are factors predicting poor prognosis. Studies reported on a possible

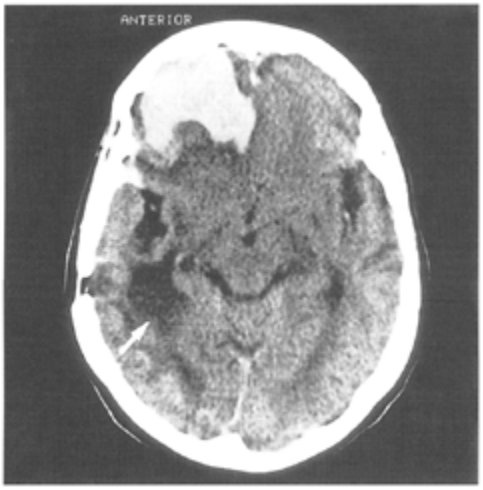

Figure 14.3 A 72-year-old man with an acute right frontal intracerebral hematoma (ICH) and a temporoparietal defect from a previously evacuated ICH 2 years previously (white arrow).

The right frontal ICH was evacuated and the histologic examination of hematoma walls revealed amyloid angiopathy.

correlation between the hematoma size and the INR (international normalized ratio) value found on admission, although INR measured on admission has been reported not to influence either functional outcome or inhospital mortality.[12] Emergency reversal of anticoagulation is very important to prevent hematoma enlargement, which takes place over 12–24 hours,[13] and also to prepare for cerebral angiography or hematoma removal, for which we require a prothrombine time of more than 30–50%. Surgical management has been reported to be undertaken in 10–20% of cases. We resume anticoagulation with low-dose heparin 24 hours after surgery. Full anticoagulation can be restored within several days, as has been stated in other reports.

DRUG-INDUCED ICH

A number of drugs, especially sympathomimetics (including cocaine, amphetamine, and phenylpropanolamine), have reported associations with ICH. Hypertension and/or vasculitis are considered to be the pathophysiologic mechanisms. These hemorrhages tend to occur in the subcortical white matter.[14,15]

The recent common use of thrombolytic agents, especially urokinase and tissue plasminogen activator (t-PA), for the treatment of coronary artery thrombosis has been associated with a small increased risk (about 1%) of ICH.[16]

ANEURYSMS AND AVMS

Intracerebral hematomas of this type account for about 10% in our series (Table 14.2), although the percentage might be lower in other reports (Table 14.1). Intracerebral hematoma formation has been observed in 15–20% of ruptured aneurysms, most frequently aneurysms of the middle cerebral artery followed by aneurysms of the anterior cerebral artery. Intracerebral hematoma is a manifestation of 60% of cases

with bleeding AVM. These hematomas should be removed surgically on an emergency basis, when the size is large and the progression is rapid, as mentioned below. Bleeding aneurysms and AVMs are also brought into order by clipping or microsurgical removal in the same session when possible.

ARTERIOVENOUS MALFORMATION

The treatment of AVM-associated bleeding in its acute stage has limited interest compared with that of aneurysmal rupture, as its frequency is one-tenth of that of aneurysmal rupture, it is usually not fatal and not associated with vasospasm, and rebleeding occurs months or years after the initial bleed. A general discussion of the pathophysiology and treatment of AVMs is beyond the scope of this chapter.

Although microsurgical elimination is the gold standard in the treatment of AVMs, it has been reported that about 30% of these cases cannot be treated by microsurgical methods alone. Endovascular embolization procedures and radiosurgery have gradually gained their place in this field as well. Single or repeated embolization with interventional endovascular techniques has been reported to occlude AVMs completely in 5–30% of cases.[17] Fatal complication takes place in 2% of endovascular embolization which are due to hemorrhagic as well as ischemic complications.[18]

Radiosurgical treatment of small AVMs (less than 3 cm) has been reported to yield an occlusion rate of more than 70% within one year.[19] Repeated embolization procedures and gradual occlusion with radiosurgery are always associated with a risk of rebleeding of approximately 1–20% per year until the completion of the treatment, which is usually not far from the 3–4% per year bleeding rate expected from the natural history.[19,20] Therefore, interdisciplinary discussion about the appropriate treatment or combination of treatments has become mandatory. Table 14.3 presents a comparison of each treatment, showing characteristics of advantages, disadvantages, complications, and indications of each of the therapeutic modalities.

Table 14.3 Comparison of microsurgery, endovascular embolization and radiosurgery in treatment of cerebral AVM

	Microsurgery	**Endovascular embolization**	**Radiosurgery**
Invasiveness	high	low	low
Accessibility	sometimes difficult in deep seated AVMs	relatively easy	easy
Effect on adjacent brain	larger	smaller	smaller
Functional evaluation of the adjacent brain	difficult	possible (superselective Amytal testing)	difficult
Complete cure	usually possible	rare (10–20%)	85–90% in small AVMs
NPPB	sometimes occurs (especially in large, high flow AVMs)	rare	none
Hemorrhagic complications	rare	2–5%	none
Ischemic complications	rare	2–10%	rare
Radiation dose	0	1000–2000 cGy	2000–3000 cGy (marginal dose)
Adverse effect of radiation	none	rare	2–10%

	Microsurgery	Endovascular embolization	Radiosurgery
Length of hospitalization	1–2 weeks	3–7 days	2–3 days

* NPPB, normal perfusion pressure breakthrough.

It is clear that a symptomatic, small AVM in a non-eloquent area should be extirpated surgically with or without the help of endovascular embolization methods. Surgical removal in an eloquent area will sometimes require preoperative functional mapping of the area with magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning, so that vital cortical zones may be spared. Cortical electrical stimulation and even surgery under local anesthesia have been reported to be necessary in this situation.

Special mention should be made in this section about ICH acutely induced by endovascular embolization of AVM as its treatment (Fig 14.4). From our experience around 1.5% of this intervention (a far lower complication rate than the reported 5–10%) has this type of complication. It is important therefore to know that every postinterventional neurologic deterioration should be checked with a CT scan. Surgical removal of ICH (mean hematoma size 5 cm in diameter on preoperative CT scan) along with embolized AVM on an emergency basis has brought us a good outcome (Glasgow outcome scale GOS 4 and 5) in 72% (18 cases). All patients showed a severe clinical presentation with Glasgow Coma Scale (GCS) 4.2 on average and mostly with anisocoria preoperatively. An important factor for the favorable outcome is considered to be the short time interval between the onset of symptoms of hemorrhage and the surgical hematoma evacuation: surgery was usually done in less than 3 hours. The role of perioperative neuroprotective measures in the neurointensive care unit for the good outcome cannot be overemphasized.

CAVERNOUS ANGIOMA

In Table 14.1, there is no mention of ICH resulting from cavernous angioma (cavernoma). It is our opinion that this angioma should draw more attention. The diagnosis of cavernous angioma has become more and more frequent since the introduction of MRI. This angioma is quite often associated with a developmental venous anomaly (DVA), previously termed as venous angioma. Hemorrhage from a cavernous angioma tends not to be large enough to be fatal, but rather to remain localized, so that it may be subclinical or manifest itself as a focal epileptic seizure. The bleeding rate of cavernous angiomata without previous bleeding has been reported to be up to 1% per year. In contrast, rebleeding of angiomata that have bled occurs far more frequently. Cavernous angiomata of the brainstem that have bled have been shown to rebleed at a rate as high as 21% per year and to be more symptomatic than other types of cavernous angioma,[21,22] although a far more benign natural history (bleeding rate 2.5% per year, rebleeding rate 5.1% per year and little effect of bleeding on the neurologic findings) has also been reported, recommending a rather conservative attitude toward its removal.[23]

The use of radiosurgery for cavernous angioma has been called into question.[19] The treatment of choice is surgical removal, of which some technical aspects should be pointed out:

1. The lesion may be difficult to find. Some technical preparation for its detection should be carried out, such as neuro-navigation, intraoperative ultrasound, etc., in order to minimize unnecessary injury of normal brain tissue.
2. Intraoperative neurophysiological monitoring of the facial nerve, the abducens nerve, and the lower cranial nerves, as well as somatosensory-evoked potentials (SEP) and brainstemevoked potentials (BEP),

may help prevent neurologic deterioration after microsurgical removal. A case of cavernous angioma of the brainstem located in the collicular region and extending to the thalamus and the superior cerebellar peduncle is illustrated in Fig. 14.5.

3. Epileptic seizures have been reported to stop after removal of a cavernoma in about 75% of patients who present with seizures. It is problematic whether the hemosiderin-containing tissue of the hematoma cavity should be extirpated in order to reduce or prevent further seizures. Its removal has been recommended in the case of a supratentorial lesion, but not an infratentorial lesion.[24]
4. Associated DVAs should be strictly preserved in order to avoid venous infarction. Cavernous angioma is sometimes categorized into the group of angiographically occult vascular malformations (AOVMs) together with cryptic AVMs,[25] as they are not opacified on angiography. But they should be differentiated from each other, as the disease entity (hence pathophysiology) is completely different.

SURGICAL REMOVAL OF INTRACEREBRAL HEMATOMA

Surgery in primary intracerebral hemorrhage is still controversial, as has been pointed out recently by Fernandes et al. analysing 7 randomized trials from 1966 (McKissok et al.) to 1999. Meta-analysis of all trials shows a trend toward a higher chance of death and dependency after surgery, while meta-analysis when two trials are excluded because of their biases or unclearness in the method suggests benefit from surgery.[26]

The STICH trial (surgical trial in intracerebral hemorrhage)—funded by the Medical Research Council of the UK—is ongoing, intending to enrol 1000 cases of randomization based on their analysis.[27]

Surgical removal of ICH has the following theoretical backgrounds:

1. Lowering of raised intracranial pressure (ICP) —hence, an increase of cerebral blood flow (CBF) in general, as well as of the regional cerebral blood flow (rCBF) of the surrounding brain tissue—through the elimination of direct compression of the microvasculature.[27,28]
2. Elimination of toxic substances, such as coagulation cascade derived from the clot, which are considered to be neurotoxic and/or to generate edema.[29–31,93]

Indicators for microsurgical removal of hematoma are given in Fig. 14.1.

We are of the opinion that not only cerebellar hemorrhage but also ICH in the basal ganglia and lobar hematoma should be taken into consideration for surgical removal. Removal of a hematoma is better performed by the microsurgical method, by craniotomy (Fig. 14.6), because it is radical, because of the completeness of the hemostasis, and also because the definite etiology of the bleeding is known. Removal of an ICH is, therefore, indicated under the following conditions:

1. A supratentorial hematoma more than 4–4.5 cm in diameter is considered to increase ICP and, thereby, to decrease overall CBF. It is reasonable to evacuate the hematoma before its space-occupying effect becomes augmented by the surrounding edema that will develop in the following days, clinically manifested by deterioration of consciousness and new focal neurologic findings.[32]
2. A posterior fossa hematoma more than 3 cm in diameter should be considered for removal, as it is large enough (alone or in combination with surrounding edema) to compress the brainstem, to produce tonsilar herniation or upward herniation, and to produce occlusive hydrocephalus.[33,34] Furthermore, tight posterior fossa (TPF)— nonvisualization of the cisterns in the posterior fossa, enlargement of the third ventricle and lateral ventricle, and nonvisualization of the fourth ventricle—and GCS less than 13

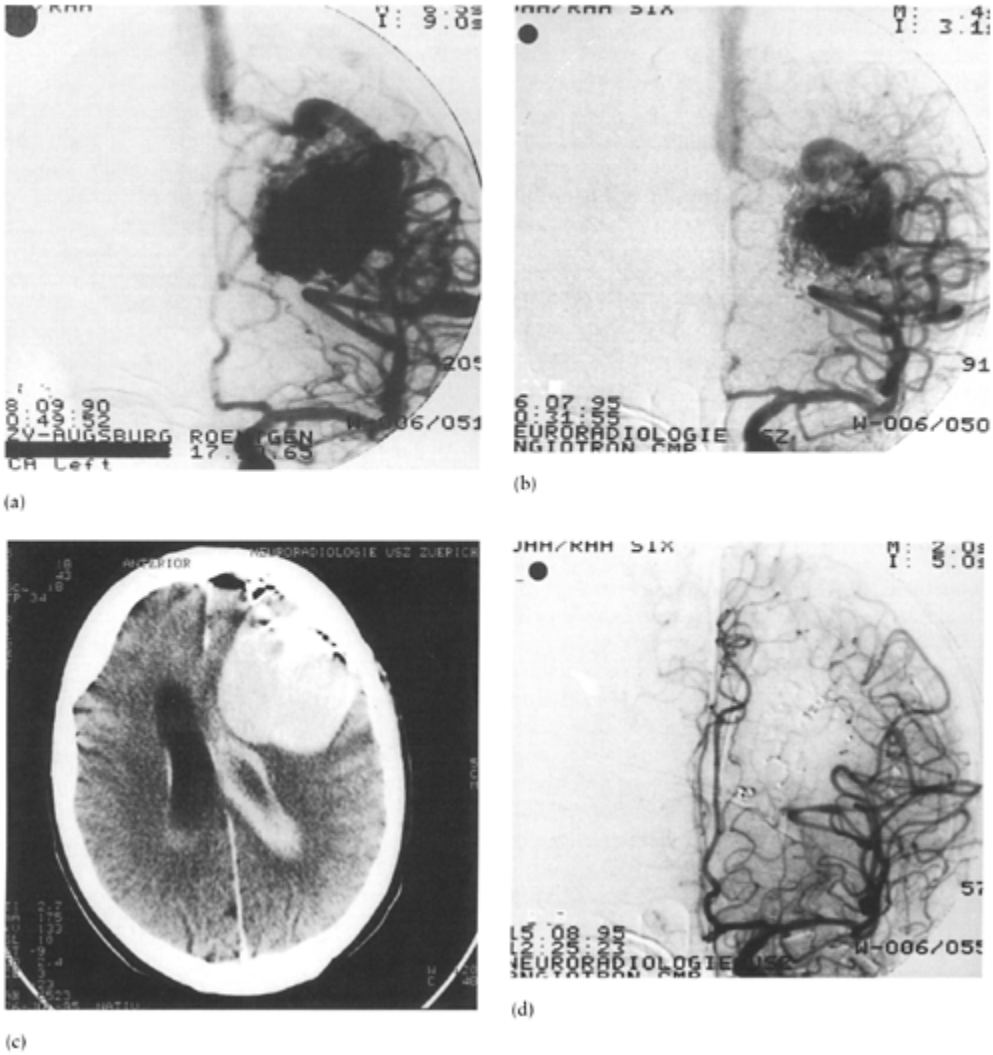

Figure 14.4 A 29-year-old right-handed man with a left frontoparietal large arteriovenous malformation (AVM).

He had received two embolization procedures before the last admission. (a) Pre-embolization left internal carotid angiogram revealed a large AVM in the left frontoparietal region. (b) Left carotid angiogram obtained just after the last embolization procedure confirmed significant reduction in filling the AVM. (c) Three hours after the last embolization procedure, he developed right hemiparesis and became obtunded. A computed tomography (CT) scan showed a large left frontal hematoma with intraventricular extension. He was taken immediately to the operating room; a large frontal hematoma and the subtotally embolized AVM were then removed. (d) The follow-up left carotid angiogram documented complete AVM removal. He returned to his previous work 5 months after the last procedure.

also are considered to be criteria indicating surgery. Smaller vermis hematoma should be considered for surgical removal as it is nearer to the brainstem and the CSF pathways than the hemispheric hematoma.[35,36]

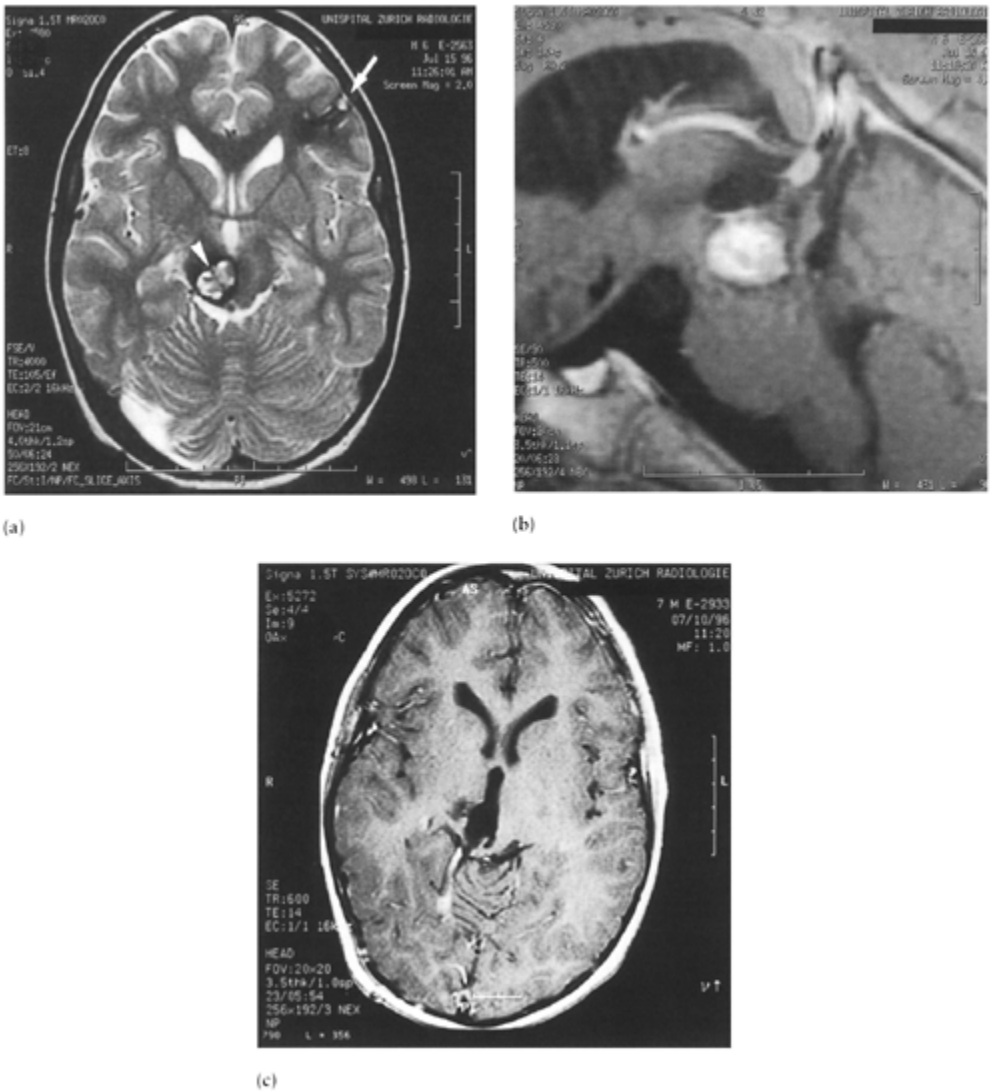

Figure 14.5 A 6-year-old boy with vertical gaze paresis and incomplete right ptosis.

He had received, two times, hematoma evacuation in the midbrain. (a) Axial T2-weighted magnetic resonance imaging (MRI) showed subacute mixed-intensity hemorrhage with low-intensity rim in the the tectum mesencephali (arrowhead) concomitant with a left frontal subacute hemorrhage (arrow). (b) Sagittal T1-weighted MRI revealed a hyperintense lesion along with some defect above it in the midbrain. (c) A T1-weighted MRI obtained after the extirpation of hematomas and abnormal vasculatures demonstrated the complete removal of the hematoma. Pathological evaluation of the extirpated specimens confirmed the diagnosis of cavernous angioma.

Sign of extravasation (angiographically or on the CT scan) was once considered to be sine qua non of hematoma removal but has turned out to be observed conservatively carefully at first, when the size of hematoma is smaller than that mentioned above (Fig. 14.7).

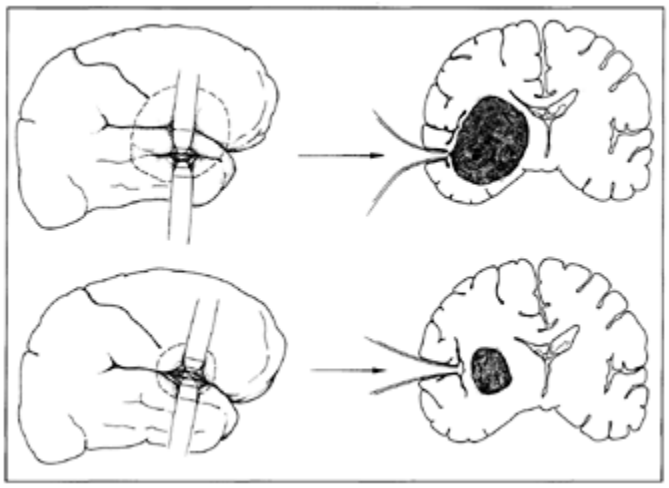

Figure 14.6 Microsurgical removal of hematomas.

A small hematoma at the basal ganglia is better approached by the trans-Sylvian insular route (lower line), whereas a large hematoma does not need this and can be accessed by the usual transcortical route (upper line).

COMPUTED TOMOGRAPHY, MAGNETIC RESONANCE GUIDED ASPIRATION OF HEMATOMA

As an alternative to microsurgical hematoma evacuation by craniotomy, CT-guided stereotactic hematoma evacuation deserves attention. With this needle aspiration technique, it has been reported that 60–70% of the hematoma can be evacuated at the time of the initial aspiration and up to 80% can be evacuated during subsequent drainage for several days with or without the use of a thrombolytic agent such as urokinase.[37,38] A combination of stereotaxy with endoscopy has also been reported, but without any further development. Stereotactic hematoma removal with interventional MRI has enabled us semireal time imaging of hematoma removal of what is important for completeness of removal and for detection of rebleeding[39] (Fig. 14.8). The rate of rebleeding after stereotactic hematoma aspiration has been reported to be approximately 10%.

Stereotactic hematoma aspiration is considered to be contraindicated during the first 6 hours after the initial bleed for fear of rebleeding.[37] Considering this time factor alone, while the result of microsurgical hematoma removal has been reported to be the ‘earlier the better’,[40,41] a mixture of direct microsurgical removal and aspiration method hematoma removal makes no sense as a study design for a randomized study.

VENTRICULAR DRAINAGE

Hydrocephalus complicating ICH has been reported to be a predictor of mortality in supratentorial ICH, in thalamic hemorrhage, putaminal hemorrhage, and in lobar and brainstem hemorrhage,[42–44] so that an external drainage along with hematoma removal in such patients has to be taken into consideration when deliberating the whole situation of a patient with ICH.

Intraventricular hematoma has been reported to complicate 40% of patients with ICH and to be one of the poor prognostic factors of the latter.[45] In addition to external ventricular drainage, the use of urokinase

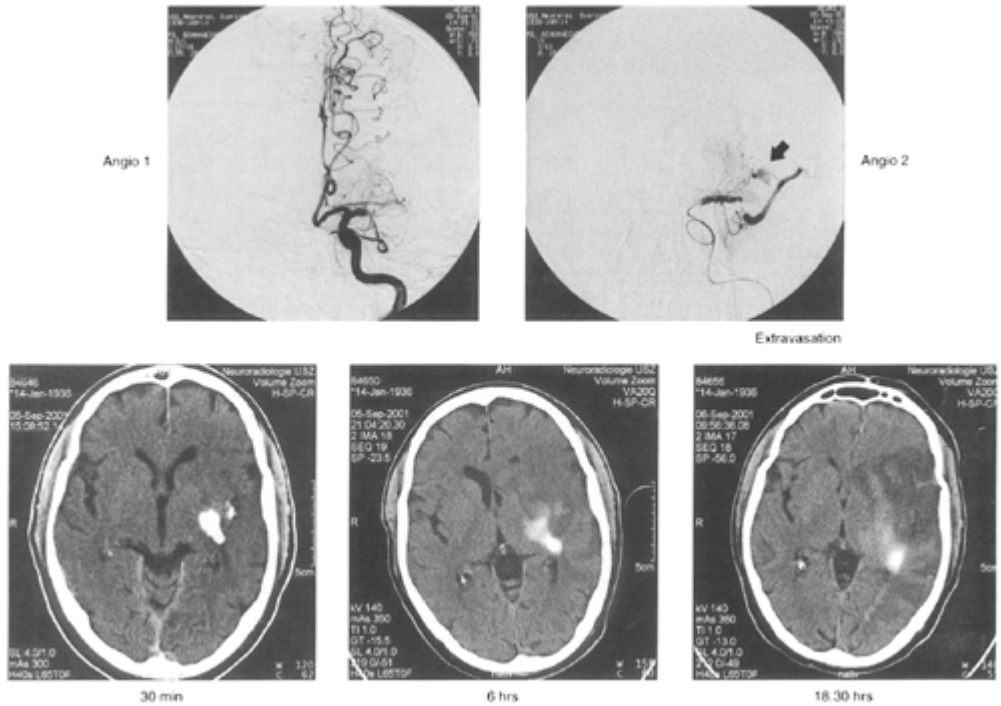

Figure 14.7 A 65-year-old female suffered from an occlusion of the left middle cerebral artery with the sudden onset of aphasia and hemiparesis on the right side: 12 hours later, endovascular thrombolysis was performed with partial recanalization of the middle cerebral artery.

Extravasation (arrow) from the most lateral lenticulostriate artery forced us to stop the procedure. The time course of the computed tomography (CT) scan after the procedure clearly showed only slight enlargement of the hematoma along with the development of infarction at the territory. No surgical intervention was necessary in this case. (Courtesy of Dr. Schuknecht.)

(5000–25 000 IU) through a ventricular catheter for thrombolysis of IVH has been reported to contribute to improvement of 30-day survival.[45]

EPIDURAL AND SUBDURAL HEMATOMA[46]

Stroke in the type of epidural hematoma (EDH) is very rare. It may be caused by rupture of an arteriovenous fistula between the middle meningeal artery and an extradural vein (Fig. 14.9). Spontaneous EDH has been sporadically reported due to hemorrhage from nasal polypoid mucosa or due to neighborhood infection such as chronic otitis media, frontal sinusitis, or orbital cellulitis. It has been reported as a complication of anticoagulant therapy or fibrinolytic therapy.

Acute subdural hematoma (ASDH) has been reported to occur in 0.5–8% of cases (3% in autopsy) with aneurysm rupture. Most of the patients are admitted with severe neurologic deficits, presenting with disturbance of consciousness, anisocoria, and hemiparesis. The aneurysm is most frequently located on the internal carotid artery (ICA), 40–70% (Fig. 14.10), followed by the middle cerebral artery (MCA), 20–30%, and the anterior cerebral artery (ACA), 20–25%. Very rarely, aneurysm ruptures only into the subdural space. Acute subdural hematoma can be caused by spontaneous rupture of a cortical artery with more than

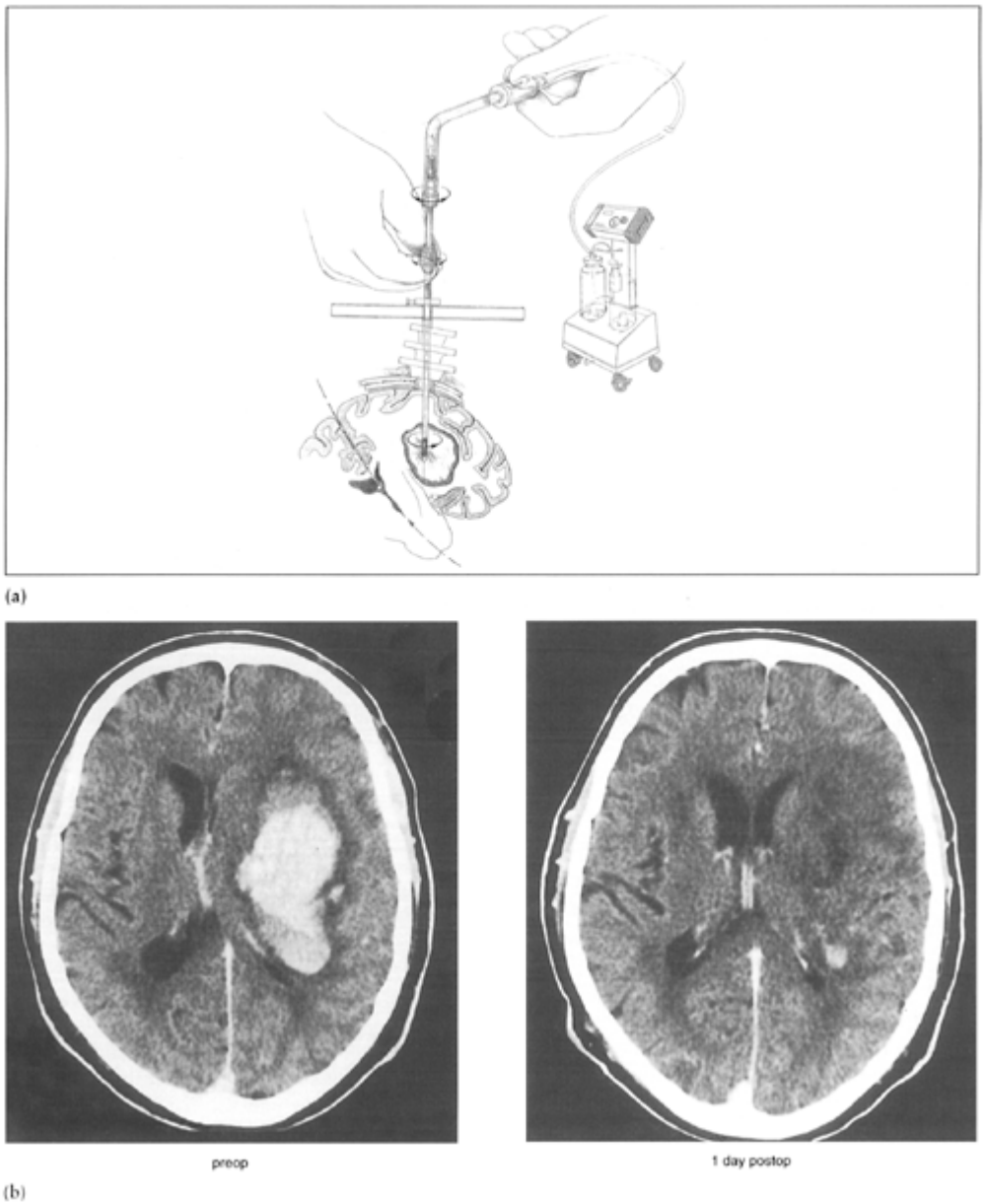

Figure 14.8 An MR-guided stereotactic aspiration of an ICH of basal ganglia.[39]

(a) Method of aspiration; (b) typical case of radical hematoma aspiration.

20 cases reported to date. A very rare case of chronic subdural hematoma (CSDH) due to rupture of MCA aneurysms has also been reported.

Acute subdural hematoma has been sporadically described in patients with AVMs. This may exceptionally occur in patients with Moyamoya disease, presumably resulting from rupture of a transdural

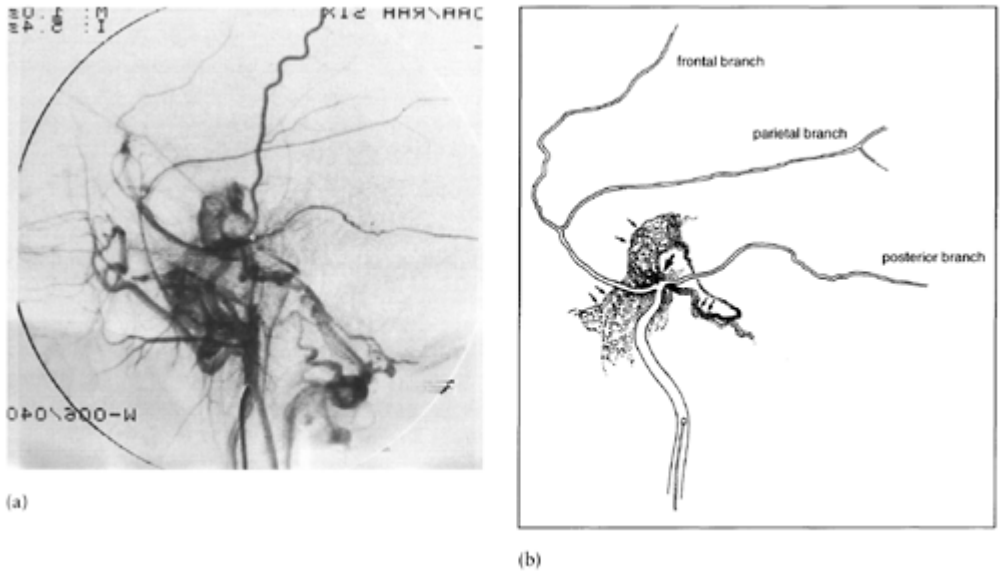

Figure 14.9 Angiographic appearance of an arteriovenous fistula of the middle meningial artery, which can induce a spontaneous epidural hematoma. (Courtesy of Professor Valavanis.)

anastomosis. Other causes of ASDH include metastatic tumors to the dura, cocaine, lumbar puncture, ventriculoperitoneal shunt, extracranial-intracranial (EC-IC) bypass, and anticoagulant therapy.

Acute subdural hematoma should be removed through a large craniotomy as soon as the diagnosis is made. The bone flap may be removed for decompression. Pathological processes causing ASDH such as AVMs or aneurysms should be brought into order at the time of hematoma removal. Half of patients with spontaneous ASDH do not survive, although their prognosis is definitely dependent on the preoperative neurologic condition.

ISCHEMIC STROKE

In the Framingham study, the two etiologies of completed ischemic stroke were atherothrombosis (65%) and embolism (35%).[1] Mention should be made, however, of arterial dissection and venous occlusion, because recent advances in diagnostic tools and in the understanding of stroke has made their diagnoses easier and more reliable. Venous occlusion, which induces ischemia as well as hemorrhage, is dealt with in Chapter 15.

DISSECTION OF CEREBRAL ARTERIES

Arterial dissection causes either extravasation of blood-subarachnoid hemorrhage—or ischemia secondary to arterial occlusion or embolism, depending on the site of dissection of the arterial wall. Aside from dissection of the extracranial portions of the carotid and vertebral arteries, more attention has been paid recently to dissections of the intracranial vertebrobasilar artery, internal carotid artery, middle cerebral artery, and anterior cerebral artery. Dissection of the vertebrobasilar artery frequently presents with subarachnoid hemorrhage. In contrast, dissection of the middle cerebral artery or the anterior cerebral artery tends to present with cerebral ischemia.[47–49]

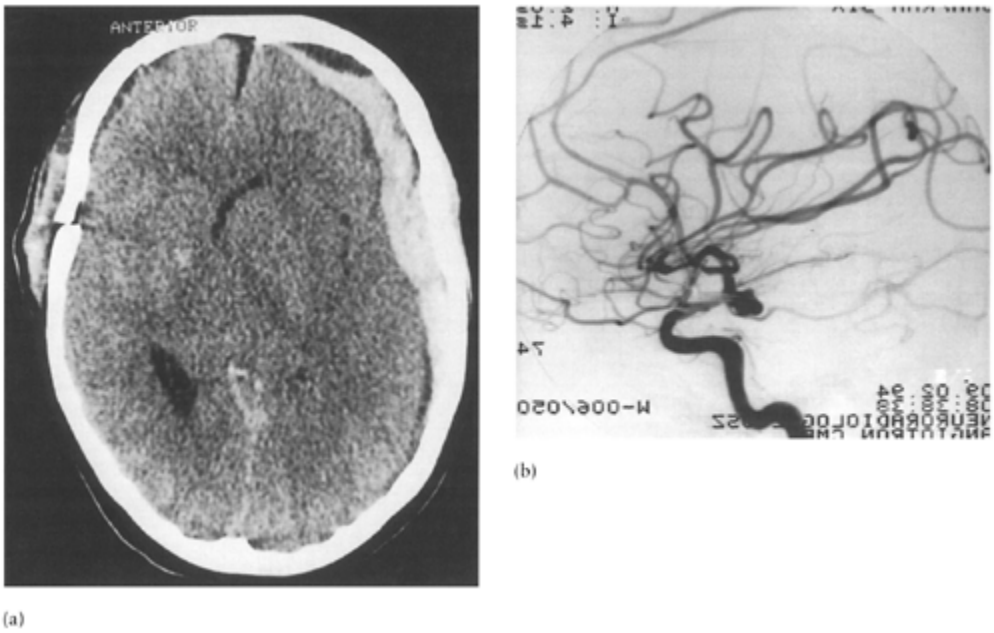

Figure 14.10 Acute subdural hematoma (ASDH) caused by rupture of an aneurysm of the internal carotid (ICA)—posterior communicating artery, occurring 3 days after emergency clipping of a right-sided ICA aneurysm.

(a) Typical ASDH with high density on the left cerebral hemisphere. (b) Carotid angiography showing a saccular aneurysm of the left ICA-posterior communicating artery.

For the diagnosis of arterial dissection, careful interpretation of the cerebral angiogram is mandatory. Serial angiography and follow-up angiography are essential to confirm the diagnosis and to guide therapeutic decisions. Several characteristic signs, such as the 'beads on a string sign,' the 'double lumen sign,' and the 'rosette sign,' are of diagnostic importance.[47] The etiology is unknown and seems largely unrelated to atherosclerosis; patients are usually relatively young males (under 50 years of age). Frequent combination with fibromuscular dysplasia (FMD) has also been reported.[50]

The treatment is still controversial. A dissection giving rise to SAH, particularly of the vertebrobasilar artery, should be treated surgically with parent artery occlusion, trapping, or with coating (Fig 14.11). Ischemic dissection has usually been treated conservatively with anticoagulant therapy or antiplatelet agents, and sporadically with an EC-IC bypass procedure, yielding relatively good results.[51] Successful treatment of arterial dissection with endovascular stenting has been sporadically reported,[52] although its timing, how to combine with anticoagulant therapy, and long-term follow-up results are to be elucidated.

From the surgical point of view, cerebral ischemia in the acute stage can generally be treated by:

1. a revascularization procedure within the time 'therapeutic window'
2. a decompressive procedure to protect against ischemic cerebral edema.

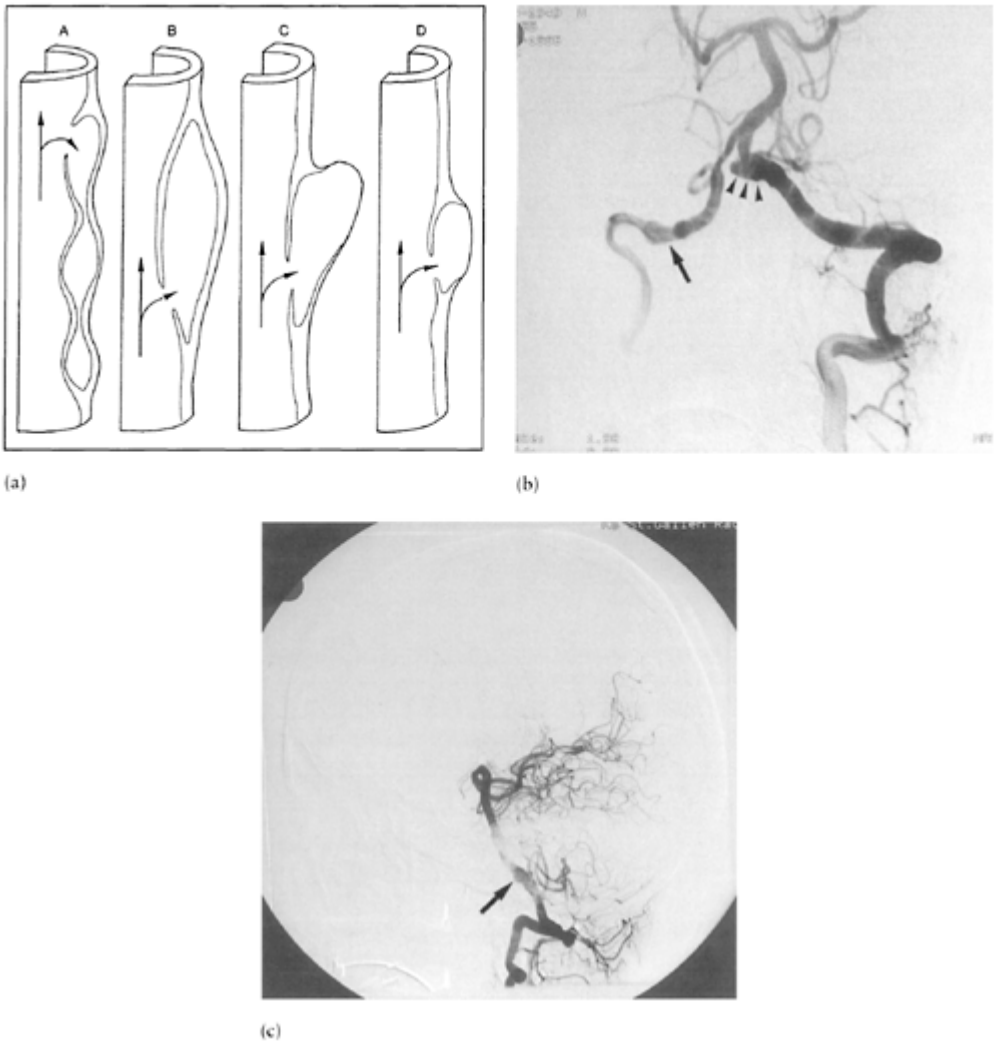

Figure 14.11 Arterial dissection.

(a) Typical configuration of arterial dissection. A represents a dissection extended toward the proximal direction. A typical angiographic finding of this type of arterial dissection is the double lumen or retention of contrast medium. B represents an arterial dissection between the intima and the media. A typical angiographic finding of this arterial dissection is the string sign. C represents an arterial dissection between the media and the adventitia. A typical angiographic finding of this type of arterial dissection is the proximal and/or distal dilatation. D represents an arterial dissection extended to directly outside. A typical angiographic finding of this type of arterial dissection is the blister aneurysm. (b) A case of dissecting aneurysm of type C (arrow heads) on the left side and wall irregularity (arrow) on the right side. (c) A lateral view of the dissecting aneurysm (arrow).

REVASCULARIZATION

The evaluation of surgical revascularization procedures such as carotid endarterectomy and EC-IC bypass in the chronic stage of cerebral ischemia has been settled by the NASCET study, the ECE study, and other

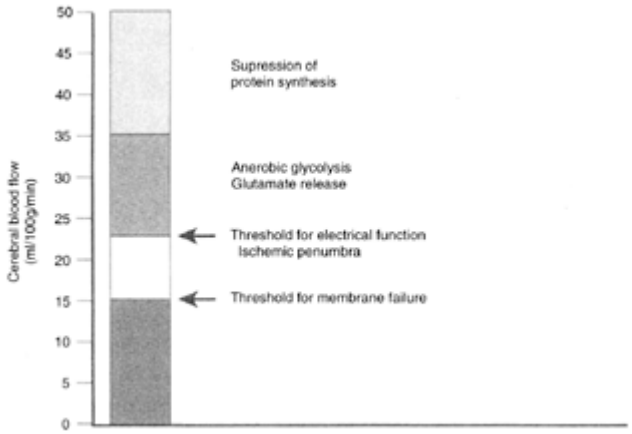

Figure 14.12 Electrophysiological and metabolic thresholds of ischemia.

international cooperative studies.

Experimental and clinical studies hitherto have led to a theoretical understanding of cerebral ischemia that underlies the approach to its treatment in the acute stage. Protein synthesis is suppressed when the CBF drops below a threshold of about 55 ml/100 mg/min. At a level of about 20 ml/100 mg/min, neurotransmitters are released and energy metabolism begins to be impaired. Anoxic depolarization takes place at flow rates of less than 15 ml/100 mg/min, and this level is considered to be the point at which potassium is released and membrane failure begins to occur (Fig. 14.12).[53] Reversible paralysis will take place when the CBF decreases to 23 ml/100 mg/min (ischemic penumbra), whereas a decrease below 10 ml/100 mg/min lasting for 2 hours, or 18 ml/100 mg/min for a longer period, will induce irreversible infarction.[54].

Enthusiasm for surgical revascularization in the acute stage of cerebral ischemia grew as a result of technical innovations such as microsurgery, CT and MRI (including magnetic resonance spectroscopy), and the measurement of CBF and cerebral metabolism. The purpose of revascularization procedures is to restore neurons in the ischemic penumbra. To prolong the time of 'therapeutic window,' until the restoration of CBF by revascularization, every effort is made: e.g., by improving collateral flow via artificial hypertension, the administration of brain-protective substances and/or the induction of a decrease in neuronal energy requirements by hypothermia and/or barbiturate coma.

In patients with stroke-in-evolution or peracute cerebral infarction, surgical treatments including emergency carotid endarterectomy, thromboembolectomy of the middle cerebral artery, and EC-IC bypass have yielded excellent results with acceptable morbidity and mortality.[51,55–58] Successful early carotid endarterectomy has been reported in selected cases after tissue plasminogen activator (t-PA) thrombolysis.[59] However, given the limited number of these successful reports and the absence of a controlled study, no solid indications can be stated for the routine use of these operations. Perhaps many of these patients would have obtained an equivalent benefit from endovascular rather than surgical recanalization. Endovascular methods of revascularization will be increasingly attractive because of their lesser invasiveness and the greater ease of carrying them out within a short time after the onset of ischemia (Fig. 14.13).

Intravenous and selective intra-arterial administration of fibrinolytic agents deserves mention here, although it is discussed in detail in Chapter 9. The US Food and Drug Administration (FDA) has approved the use of t-PA in the acute stage of ischemic stroke on the basis of the NINDS and ECASS studies, which concerned its intravenous use.[60,61] Fibrinolytic therapy has also been reported, as mentioned above,

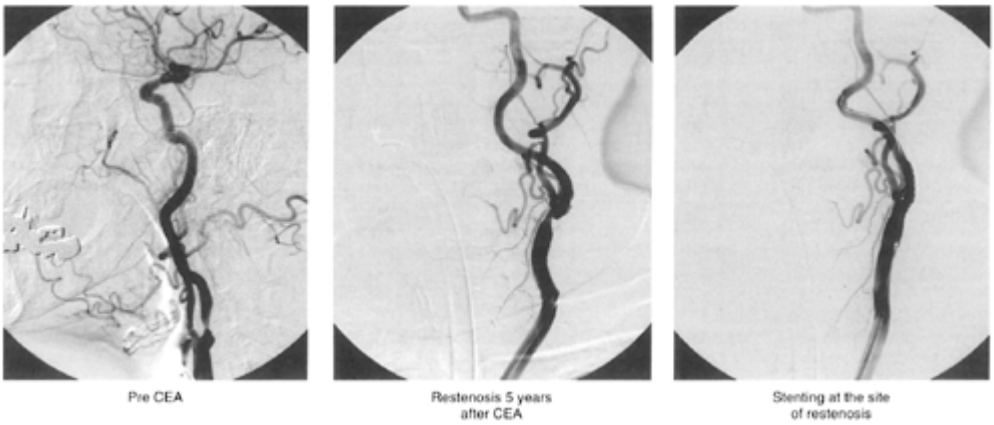

Figure 14.13 (a) A 62-year-old female underwent carotid endarterectomy because of the symptomatic severe stenosis of the left internal carotid artery.

(b) Five years later a severe restenosis was detected at the operated side on the occasion of regular check-up with Duplex sonography and angiography. (c) Stenting for the restenosis was successfully performed. (Courtesy of Professor Valavanis).

sporadically as a means of opening a therapeutic window to be followed by surgical or endovascular revascularization.[59,62]

Recanalization rates in recent studies have been consistently higher when selective intraarterial infusion was used. The recanalization rate with this method ranged from 44 to 100% (mean 64.5%), favorable outcomes were obtained in 33–94% (mean 51.5%), and hemorrhagic transformation occurred in 0–20% (mean 13.2%).[63–66] The risk of hemorrhagic transformation is considered to be higher when the pretherapeutic residual CBF is markedly reduced.[67]

Surely there are patients who will profit from the aggressive therapy shown in Fig. 14.13, although such an aggressive procedure as endovascular carotid angioplasty, with or without the use of a stent, has been viewed with great concern by stroke neurologists and neurosurgeons, because of its inherent risk of embolism and the lack of controlled studies and long-term follow-up.[68,69]

Thus, patient selection for any type of revascularization procedure should be done on an individual basis, taking into account the amount of residual blood flow and the elapsed time from the onset of ischemia, and the procedure should be performed by experienced hands (see Fig. 14.1).

DECOMPRESSIVE CRANIOTOMY

SPACE-OCCUPYING SUPRATENTORIAL INFARCTION

Life-threatening postischemic brain edema is reported to occur in approximately 10% of ischemic strokes.[70] The patients present clinically with severe hemispheric stroke syndrome, including hemiplegia, forced eye and head deviation, and progressive deterioration of consciousness within the first days after onset of stroke.[71] With conventional therapies up to 80% of these patients with complete MCA territory infarction (>145 ml in volume) die from transtentorial herniation because of increasing brain edema with space-occupying mass effect.[71]

In earlier years decompressive craniectomy was proposed as the treatment of choice for preservation of life.[70] The mortality of severe ischemic edema was reportedly reduced by onehalf with the surgical intervention, whereas the rate of disability mostly remained high.[72,73] Rieke et al.[74] showed that surgical decompression is correlated not only with a decreased mortality but with an improvement of functional outcome if patients are carefully selected. In a series limited to patients with nondominant hemispheric infarct, Carter et al.[75] had a favorable outcome in 72% of patients at 1 year (mild to moderate assistance at home and Barthel score greater than 60). With decompressive hemicraniectomy in 31 patients, early, within 21 hours, Schwab et al.[76] has reported a mortality rate of 27%: the Rankin scale revealed severe handicap in only 13% and the mean Barthel index was 69. Patients with nondominant hemispheric infarction, higher GCS score on admission and of younger age seem to have a better outcome.[75–77]

Decompressive hemicraniectomy early in the illness course may not only protect from transtentorial brain herniation but may also improve compromised microcirculation within the ischemic penumbra and may improve retrograde perfusion of leptomeningeal collateral vessels by decreasing the elevated intracranial pressure (ICP) caused by extensive ischemic edema.

Therefore, especially, younger patients with neuroradiological features of more than 50% MCA territory ischemia with increasing brain edema and neurological deterioration to somnolence and stupor should be considered for early or prophylactic surgical decompression (see Fig. 14.1). In these patients waiting for pupillary disturbances causes unnecessary delay, since allowing mesencephalic ischemia to occur may worsen functional outcome. Monitoring ICP to optimize the indication and time point for surgical decompression may be of disappointing sensitivity. Frank et al.[73] found that a large proportion of patients whose consciousness deteriorated to stupor did not have significantly increased ICP. Displacement of the brainstem from tissue shift due to a growing ischemic mass appears to correlate with the level of consciousness rather than with globally increased ICP.[78]

No controlled trials are available comparing decompressive hemicraniectomy with mild to moderate hypothermia in severe hemispheric infarction. Nevertheless, the first data indicate that decompressive surgery may be more effective.[76,79] In addition, the patients may be allowed to wake up immediately after the surgical intervention and the length of stay on the intensive care unit is documented to be low (7.4 days in mean).[76] On the other hand, hypothermia is associated with a high rate of major systemic complications such as nosocomial pneumonia.[80] Ventilator-related pneumonia is associated with a mortality rate of 30%.[81]

The decision for the surgical technique may depend on the differentiation of viable from non viable brain. External decompression, with removal of a large bone flap, may be the first choice, especially in patients with residual motor activity.[82] The need for a radical approach was documented by Rieke et al.,[74] who found that a few of their initial surgically treated patients harbored a bone defect that was too small—not providing adequate space for decompression. In the case of complete hemispheric infarction, the frontal, temporal, and parietal bones may be removed.[72,75,83] A dural expansion graft of pericranium,[75] homologous temporal fascia[74] or Silastic[83] expands the intracranial vault (Figs 14.14 and 14.15). Nevertheless, in patients with complete hemispheric infarction and rapidly developing massive edema, external decompression may not be sufficient alone to prevent brainstem herniation. In these patients, stable xenon-enhanced CT and diffusion/perfusion magnetic resonance may provide information concerning the extent of definite infarction.[84,85] Additional internal decompression with resection of parts of the infarcted tissue can be considered in several cases.

Because decompressive craniectomy may be a life-saving procedure in patients who will most likely survive with a significant neurologic deficit, the surgical intervention has important ethical and psychological implications.[85] With an altered level of consciousness, patients cannot provide consent by themselves. Detailed discussions with the patients' families have to be undertaken to clearly outline the

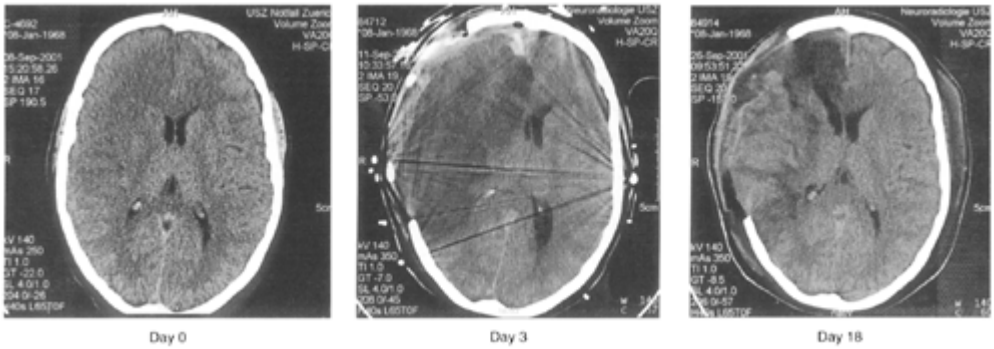

Figure 14.14 A 32-year-old female suffered from a severe right hemispheric infarction due to a dissection of the internal carotid artery combined with fibromascular dyplasia.

(a) Day 0:6 hours after the onset. (b) Day 3 showing a extensive decompressive craniotomy. Massive cerebral edema with definite infarction of the anterior cerebral artery (ACA) territory to be recognized. (c) Day 18 in which still some swelling to be observed. Cortical structure at the middle cerebral artery (MCA) territory is preserved while definite infarction at the ACA territory. Hypothermia and the barbiturate therapy were combined with decompressive craniotomy.

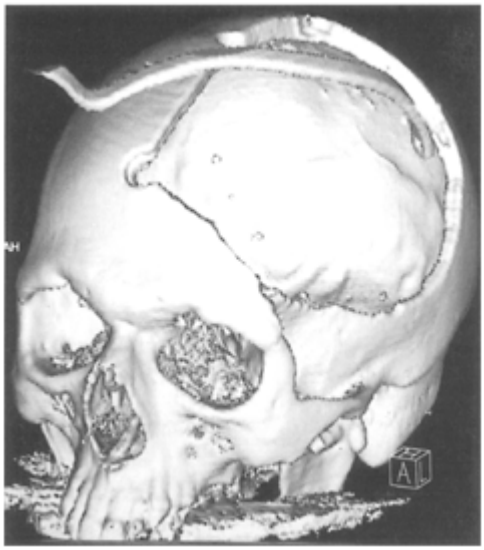

Figure 14.15 A three-dimensional reconstruction of a computed tomography (CT) scan, indicating an external decompression with removal of a large bone flap and duraplasty over the infarcted area.

A subdural probe for intracranial pressure (ICP) monitoring is to be observed. (Courtesy of Dr. Harms.)

potential benefits of the procedure and the certain accompanying morbidity. In the series of Carter et al[75] 4 of 11 patients after right-sided hemispheric stroke suffered severe depressive symptoms. When asked if they would have chosen to undergo the operation given the choice, for 6 patients the response was definitely yes, 3 patients were uncertain, and 2 would have declined the operation. In further studies, not only the

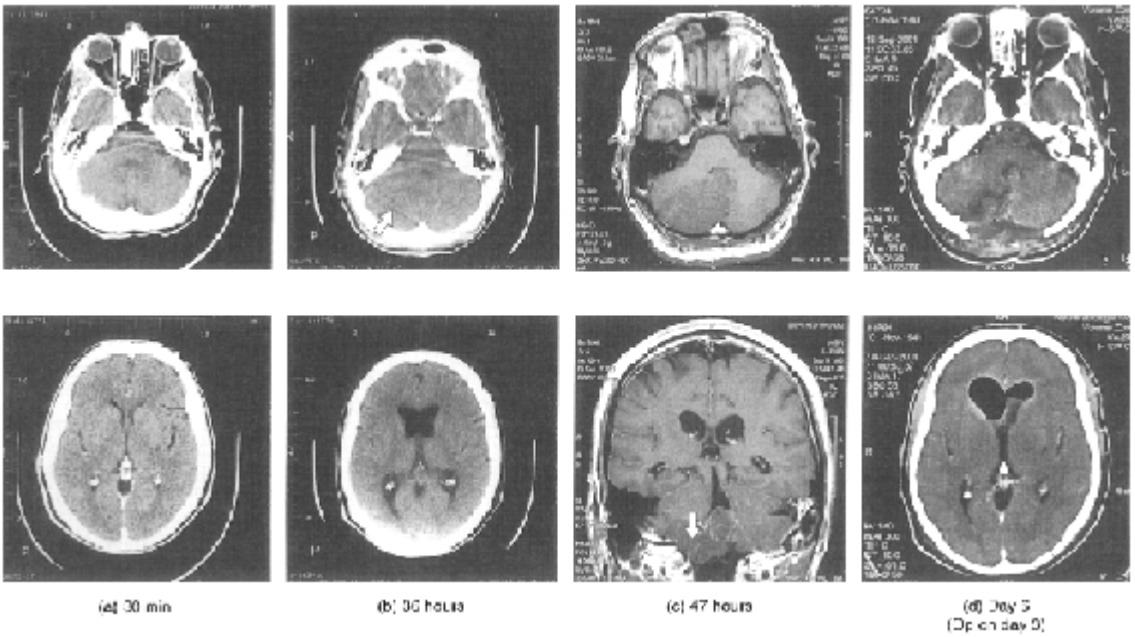

Figure 14.16 A 58-year-old male suffered from a cerebellar infarction treated ischemia with decompressive craniotomy and infarctectomy.

(a) At 30 min after the onset. (b) At 36 hours after the onset: space occupying at the right cerebellar hemisphere (arrow) associated with compression of the fourth ventricle and with occlusive hydrocephalus. (c) At 47 hours after the onset. Magnetic resonance imaging (MRI) indicates remarkable ischemic edema, with hemorrhagic component along with tonsillar herniation (arrow) and occlusion of the fourth ventricle. (d) Day 6:3 days after the decompressive craniectomy and infarctectomy. Computed tomography (CT) scans showing no space-occupying lesion with normal midline structure.

indications and timing for the surgical procedure but also the overall level of satisfaction in survivors should be investigated.

SPACE-OCCUPYING CEREBELLAR INFARCTION

Patients with extensive areas of cerebellar hypodensity on CT—e.g. expanding to two-thirds of the posterior inferior cerebellar artery territory are at risk for subsequent neurologic deterioration.[86,87] Disturbance of consciousness and secondary brainstem signs occur in 11–25% of all cerebellar infarcts.[87,88] Deterioration results from space-occupying effects of cerebellar edema in the posterior fossa with brainstem compression and the risk of occlusive hydrocephalus. Ventricular drainage alone in this condition is mostly insufficient and can even be dangerous, as it may lead to upward transtentorial herniation of the cerebellum.[89,90]

Numerous case series provide convincing evidence that decompressive suboccipital craniectomy is the treatment of choice for massive cerebellar infarction causing impairment of consciousness or progressive brainstem signs.[86,91,92]

Decompressive surgery has to be performed as a large craniotomy over the infarct, duraplasty, and resection of the posterior atlas arch if tonsillar herniation is apparent. Resection of the infarcted tissue may

be mandatory. The procedure prevents herniation, brainstem compression, and secondary fourth ventricular obstruction resulting in occlusive hydrocephalus (see Fig. 14.1).[79,93]

Timing of decompressive surgery in spaceoccupying cerebellar infarction should be early enough (Fig. 14.16). The functional outcome may be worse for patients operated in the late stage.[92] Decompression must be considered in patients with CT-proven cerebellar infarction early in case of deterioration of consciousness, if evoked potentials tend to be pathological, or with increasing neuroradiological signs of brainstem compression.[81] If the patients are already comatose and posturing, decompressive surgery should still be considered. In the series of Hornig et al.[91] 38% of the surgically treated comatose patients were nondisabled at hospital discharge. Advanced age and signs of a concomitant primary brainstem infarction are associated with poor functional prognosis and may restrict the decision for surgical intervention in a late clinical stage.[91,92]

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15.
New management trends in aneurysmal subarachnoid hemorrhage

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INTRODUCTION

Both the medical and surgical management of aneurysmal subarachnoid hemorrhage (SAH) has markedly changed in the past few decades. New surgical techniques, including the development of the operative microscope, have significantly improved the morbidity and mortality of acute repair of ruptured aneurysms: this has largely shifted the emphasis from late to early surgery for this condition. In addition, surgical interventions in some of the traditionally more complex aneurysmal locations, such as the posterior circulation, have been largely supplanted by endovascular techniques.

The shift toward early surgical repair has allowed for the further use and delineation of new medical techniques designed to increase cerebral blood flow (CBF). Perhaps in no other area of medicine has treatment changed so radically. Prior to 1980 the medical management of SAH included fluid restriction, aggressive blood pressure reduction, and sedation. Newer medical strategies have focused on volume replacement and techniques designed to augment hemodynamics.[1–4]

However, several management issues remain unresolved. The best approach to a particular aneurysm, the optimal means to augment CBF in cerebral vasospasm, the recognition of familial aneurysmal SAH, and the management of unruptured aneurysms will undoubtedly be clarified in future studies. This chapter focuses on the medical management of aneurysmal SAH and provides some insight into continuing trials and future avenues of treatment. A recent Stroke Council statement should be consulted as well.[5]

SCOPE OF THE PROBLEM

Subarachnoid hemorrhage due to ruptured cerebral aneurysms remains a significant problem, with an annual prevalence of approximately 30 000 cases per year in the United States alone. The annual incidence varies between 6 and 19 per 100 000, based upon the population under study. These numbers have remained relatively constant over the last several decades.[6]

The incidence of SAH is highest in the fifth and sixth decades of life, with a 3:2 female to male predominance. Below this age group, the incidence slightly favors a male predominance. SAH in children is rare.[7]

The natural history of SAH is devastating. An observational study in the early 1960s documented a progressive mortality of 75% in 2 years following SAH. Roughly 15% of patients died at each of the following time periods after SAH: before reaching the hospital, within 24 hours of admission, between 24 hours and 2 weeks after admission, between 2 weeks and 2 months, and between 2 months and 2 years after

SAH. Mortality could be attributed to the initial effects of the hemorrhage, rebleeding, vasospasm, medical complications, and long-term medical issues related to disability, respectively.[8]

Despite medical and surgical advances, morbidity and mortality due to this disease remain problematic. Two population studies have suggested that only one-third of all patients will make a full recovery. The remaining patients either die or were significantly disabled.[9,10] Most large hospitals should expect that approximately one-third of patients admitted for SAH will present moribund and will have an increased morbidity and mortality beyond that listed above.[11]

Table 15.1 Hunt and Hess grading system: classification of patients with intracranial aneurysms according to surgical risk

Categorya	Criteria
Grade I	Asymptomatic, or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

[a] Serious systemic disease, such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography, result in placement of the patient in the next less favorable category.

Numerous clinical prognostic indicators have been developed for SAH but, generally, outcome can be predicted based upon the initial presentation of the patient. Several grading systems were initially developed but the Hunt and Hess classification of patients was generally the most popular (Table 15.1).[12] To clarify some of the subjectivity of the Hunt and Hess and previous grading scales, a grading system for the classification of patients with SAH was recently proposed by the World Federation of Neurological Surgeons (Table 15.2).

In addition to predicting outcome, the above grading scales can be used to select which patients should undergo early surgical repair of their aneurysms. Distinction between patients in poor grade and those in good grade is arbitrary, but most neurosurgeons agree that early surgery is indicated in patients with grades I or II. The management of patients with grades III or IV is uncertain. Some centers prefer early neurosurgical intervention irrespective of grade, whereas others await further improvement in the level of consciousness with or without ventricular drainage before surgery is contemplated.

PRESURGICAL MANAGEMENT

Management for treatment of aneurysmal SAH can be divided into treatment before and after the aneurysm is secured. Treatment initated

Table 15.2 Grading system proposed by the World Federation of Neurological Surgeons (WFNS) for the classification of patients with subarachnoid hemorrhage

WFNS grade	Glasgow coma scale score	Focal deficit
I	15	Absent

WFNS grade	Glasgow coma scale score	Focal deficit
II	14–13	Absent
III	14–13	Present
IV	12–7	Present or absent
V	6–3	Present or absent

prior to aneurysm repair focuses on means to prevent aneurysm rebleeding. Treatment initiated after the aneurysm is secured is designed to prevent the neurologic complications of delayed cerebral vasospasm. Guidelines for the initial management of aneurysmal SAH are summarized in Table 15.3.

As with any critically ill patient, management of the airway in SAH has the highest priority. Reduced wakefulness often decreases the tone in the laryngeal muscles, allowing the tongue to obstruct the airway. In addition, patients with a Glasgow Coma Scale (GCS) score of <9 are at can be divided into treatment before and after lapsed airway, an examiner should secure the increased risk for aspiration pneumonia. Neurologists should thus be familiar with the principles of airway management. To open a colthe aneurysm is secured. Treatment initiated airway by tilting the head, holding thumb and

Table 15.3 Initial management in aneurysmal subarachnoid hemorrhage (revised from Wijdicks EFM. The clinical practice of critical care neurology. Philadelphia: Lippincott-Raven; 1997.)

Type of management	Details	
Airway management	•	Intubate with mechanical ventilation for aspiration, neurogenic pulmonary edema, or GCS score <9
	•	Avoid paralysis if possible
	•	Lidocaine (100 mg IV) to blunt cough and increase in ICP prior to intubation
	•	CPAP mode with 10 of pressure support or IMV mode (8–10 breaths/min) and PEEP of 5
	•	Assist-control mode if patient is moribund or has possible progression to brain death
	•	Consider pressure-controlled ventilation for significant aspiration or early ARDS
	•	Maintain normal pCO_2 33–40 torr
	•	FiO_2 to maintain oxygen saturation >93%
Fluid management	•	2–3 liters/day of 0.9% NaCl
Blood pressure management prior to	•	Systolic blood pressure <160 mmHg or MAP =100–110 mmHg
aneurysm repair	•	Medication options: labetalol, 10–20 mg IV q 15 min prn; hydralazine, 10–20 mg IV q 15 min prn; enalapril, 1–5 mg IV; or nicardipine or esmolol drips

Type of management	Details	
Nutrition management	•	Enteric nutrition with limited free water by continuous infusion on day 3
Additional measures	•	Nimodipine, po 60 mg q 4 hours or 30 mg q 2 hours
	•	Stool softener
	•	GI prophylaxis with H_2-blocker or proton pump inhibitor
	•	Pneumatic compression devices
	•	Acetaminophen with codeine or morphine, 1–2 mg, for pain management
	•	To consider prophylactic anticonvulsants
	•	Prn sedation
	•	Prn ventriculostomy

ARDS, adult respiratory distress syndrome; CPAP, continuous positive airway pressure; $Fi0_2$, fractional inspired oxygen concentration GCS, Glasgow Coma Scale; GI, gastrointestinal; ICP, intracranial pressure; IMV, intermittent mandatory ventilation; IV, intravenously; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; PS, pressure support; q, every; prn, as required; po, orally.

index finger on a mask, and placing the other three fingers behind the vertical part of the mandible and using them to lift the jaw upward. The thumb and index finger can tightly compress the ventilated mask to the face while the other hand squeezes the resuscitation bag.

Once adequate ventilation and oxygenation is attained, elective endotracheal intubation should follow. It is important that endotracheal intubation in a patient with an unsecured aneurysm occurs in a controlled fashion. Adequate intravenous (IV) access and monitoring of blood pressure and oxygenation should be assured prior to any attempt. Lidocaine (100 mg) can be given prophylactically as an IV push to suppress the cough reflex and avoid the potential large fluctuations in blood pressure and intracranial pressure (ICP) that can occur during intubation. The sedative used for intubation is a matter of choice; however, both propofol and etomidate are short-acting effective agents that do not affect CBF. If using etomidate, one must be aware of the associated fasciculations that can occur and muscular paralysis should be avoided.

After endotracheal intubation, most patients are often misinterpreted as seizures. If possible, are able to breathe on their own. Under these circumstances, airway control is generally all that is needed and adequate ventilation can be attained with continuous positive airway pressure (CPAP) support. Intermittent mandatory ventilation (IMV) sometimes combined with a pressure support augmentation may be needed in some patients. In patients who are extremely combat ive and have sustained hyperventilation, brief sedation with propofol may be necessary to secure adequate oxygenation and gas exchange. It is important to recognize that patients with poor-grade SAH may have aspirated. In these circumstances more sophisticated modes of ventilation may be necessary to secure appropriate gas exchange—pressure control modes in association with positive end-expiratory pressure (PEEP) ventilation.

Fluid intake should begin with 2–3 liters/day of isotonic saline (0.9% sodium chloride), with an attempt to attain euvolemia. There is no rationale for glucose-containing IV fluids, which may increase the risk of inducing hyperglycemia, a state which is deleterious in animal stroke models. Mild hyperglycemia, however, may occur as a catecholamine-associated stress response. Similarly, elevated antidiuretic hormone

(ADH) levels occur early after SAH and may reflect a stress response to the hemorrhage itself or possibly a normal physiologic reaction to the accompanying pain and nausea. In either case, free water and hypotonic fluids are to be avoided in both the initial and delayed management of SAH.

The blood pressure management in an unsecured aneurysm is controversial. The International Cooperative Study of intracranial aneurysms and SAH found an increased incidence of aneurysmal rerupture in patients with sustained systolic blood pressures > 160 mmHg.[13] This number appears to be verified by a recent Japanese study.[14] However, overzealous control of blood pressure should be avoided. Many patients with SAH have increased blood pressure at the initial ictus, which subsequently returns to normal levels within 48 hours. One retrospective study indicated that aggressive blood pressure management may lead to an increased prevalence of delayed cerebral ischemia, most likely by reducing perfusion pressure.[3] Guidelines for blood pressure limits have not been established but a mean arterial blood pressure of 100–110 mmHg appears reasonable. Management of blood pressure is usually attained with shortacting beta-blockade. Labetalol can be given in 10–20 mg IV pulses every 15 min. If bradycardia limits the use of labetalol, hydralazine given in similar doses can be substituted. In patients with long-standing hypertension, angiotensin-converting enzyme (ACE) inhibitors such as enalapril (1 mg IV) can be considered as well. Sustained hypertension may require the use of an esmolol or nicardipine drip. Sublingual nifedipine is best avoided due to possible precipitous drops in blood pressure. Nipride is effective in controlling blood pressure but carries a theoretical risk of increasing ICP due to cerebral venodilation.

Most neurosurgeons initiate prophylactic anticonvulsant loading primarily due to concerns of the potential catastrophic consequences of a seizure in an unsecured aneurysm. The utility of this practice is unknown. A multicenter randomized controlled study is currently underway to study the efficacy of phenytoin prophylaxis in SAH. Nutrition should probably be deferred until after surgery to avoid aspiration. Unlike patients with severe closed head injury, patients with SAH are seldom catabolic or exhibit sympathetic storms. Nutrition can therefore be easily deferred for 1 or 2 days in those who have defective swallowing mechanisms associated with impaired consciousness. Alert patients, however, should be allowed to have a normal diet.

Additional measures in the patient with SAH include gastrointestinal (GI) prophylaxis with either an H_2-blocker or a proton pump inhibitor to prevent gastric stress ulcers. Sedation is used judiciously to avoid self-harm in the confused patient. Stool softeners or a mild laxative can be used to avoid blood pressure changes with Valsalva maneuvers. Mild analgesia, with a goal to relieve pain but not depress consciousness, is used. Pneumatic compression devices should be part of standard orders.

The use of antifibrinolytic drugs to prevent rebleeding has fallen into disfavor. Tranexamic acid or γ-aminocaproic acid has been used for years to prevent aneurysmal rebleeding by preventing clot dissolution around the aneurysm. While effective in preventing rehemorrhage, it also delays dissolution of blood in the basal cisterns, leading to an increase in the development of delayed cerebral vasospasm. In a study performed in the early 1980s using tranexamic acid for 4 weeks, the rate of rebleeding was reduced from 24% in the control group to 9% in the treated group, but overall outcome in terms of survival and disability in the two groups was similar. This result was entirely explained by a concomitant increase in the rate of ischemic complications of 50% in the control group but only 24% in the treated group.[15,16] These results were confirmed in the Cooperative Aneurysm Study.[13,17] An attempt to reduce the side effects of antifibrinolytic drugs by administration only in the first days (before the onset of delayed cerebral ischemia) did not reduce the rebleeding effect. The rate of rebleeding was as high as that expected in untreated patients and cerebral ischemia was as frequent as it was previously in patients with long-term treatment.[18] Therefore, there is currently no rationale for the use of antifibrinolytic treatment. The use of antifibrinolytic agents in patients in poor clinical condition who are not candidates for surgery in an attempt to reduce the risk of fatal rebleeding should be discouraged.

Poor-grade patients or those with evidence for hydrocephalus are candidates for ventriculostomy placement.

Prophylactic measures are important. While initially controversial, the use of nimodipine in SAH has gained wide acceptance. This has been based upon several studies suggesting that oral nimodipine significantly reduces delayed cerebral ischemia and improves outcome.[19–26] Recent analysis of all published randomized trials confirmed a better outcome with the use of nimodipine (Fig. 15.l).[19] The exact mechanism by which nimodipine improves outcome in SAH is unknown.

POSTSURGICAL OR INTERVENTIONAL MANAGEMENT

Management of the immediate postoperative neurosurgical patient is the same as for all postoperative patients, including frequent examinations and monitoring of all vital signs. Patients may have received large volumes of fluid intraoperatively and may begin to mobilize these fluids with a brisk diuresis. If normal saline was used for intraoperative fluid support, a hyperchloremic metabolic acidosis may exist immediately postoperatively. This will typically resolve with diureses. Lactated Ringer's solution is hypotonic and should be switched to normal saline postoperatively.

No formal extubation criteria have been established but, in general, patients are extubated when they are awake and following commands.

Once an aneurysm is secured, the management of patients with SAH focuses on monitoring medical and neurologic issues, which includes neurologic monitoring for hydrocephalus and cerebral vasospasm.

Hydrocephalus after SAH presents in three forms, presumably through different mechanisms:

- an acute form occurs at the time of rupture due to a rapid increase in pressure in the subarachnoid space that overwhelms the ability of the cerebraspinal fluid (CSF) drainage system
- a delayed form occurs a few days after SAH due to the breakdown products of hemoglobin inhibiting CSF absorption
- finally, a chronic form can occur a few weeks post-SAH due to scarring of the arachnoid granulations.

Treatment is the same, with ventricular drainage typically being required.[27]

One of the main purposes of intensive car unit (ICU) management in patients with SAH is to identify and manage cerebral vasospasm. Cerebral vasospasm is a pathological narrowing of the cerebral arteries that occurs after SAH and is one of the leading causes of morbidity and mortality in this population. Pathologically, changes are seen in the intima and media of the vessel wall with involved vessels displaying myonecrosis, smooth muscle proliferation and contraction, collagen remodeling, and a monocellular infiltrate.[28] Despite extensive work, the exact process by which these changes occur is incompletely understood. It is generally believed that oxyhemoglobin initiates a series of events leading to the formation of superoxide radicals causing vascular damage. The role of nitric oxide in the process of vasospasm has been recently explored.[29] The process is self-limited, starting approximately 4 days after SAH and rarely lasts longer than 2 weeks post-SAH. The location and severity of vasospasm appears to be related to the amount of subarachnoid blood found on a 24-hour post-SAH computed tomography (CT) scan, as first noted retrospectively by Fisher et al.[30] and later prospectively verified by Kistler et al.[31] Patients at highest risk for developing vasospasm are those patients with thick clots in the basal cisterns (Table 15.4).

Clinically, vasospasm can present in a single primary artery or be more diffuse, occurring in secondary and tertiary vessels. Early symptoms may be nonspecific and include alterations in consciousness, agitation, confusion, headache,

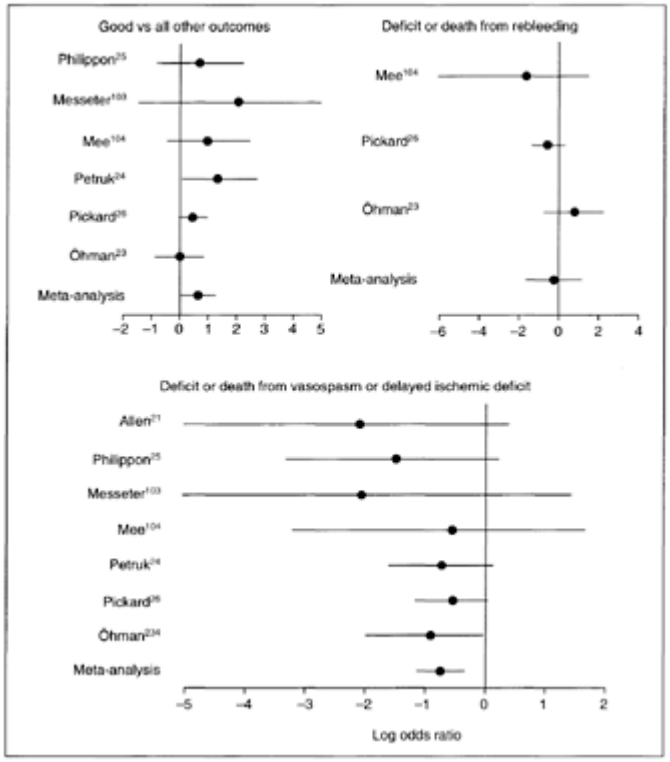

Figure 15.1 Comparison of results of trials testing the effects of prophylactic administration of nimodipine.

The horizontal line depicts the results of analysis of raw data from individual studies. The central black dot indicates the estimated treatment effect of nimodipine for each study; a 99% confidence interval is shown by the extent of the horizontal lines. When the line does not overlap the vertical line at the origin, there is a significant difference between nimodipine and placebo at p <0.01 level.[19,21,23–26,103,104]

Table 15.4 The Fisher scale

Group 1: No detectable blood on CT

Group 2: Diffuse blood that did not appear dense enough to represent a large, thick homogenous clot

Group 3: Dense collection of blood that appeared to represent a clot greater than 1 mm thick in the vertical plane or greater than 5×3 mm in longitudinal and transverse dimensions in the horizontal plane; severe spasm predicted

Group 4: Intracerebral or intraventricular clots but with only diffuse blood or no blood in the basal cisterns

CT, computed tomography.

and malaise. Physical signs may include fever, tachycardia, and hypertension.[32] Specific neurologic syndromes depend on the vessels involved. When severe, vessel narrowing leads to stroke. In rare cases, diffuse cerebral ischemia is fatal.

TREATMENT FOR CEREBRAL VASOSPASM

HYPONATREMIA

Our understanding of the fluid, volume, and electrolyte alterations that occur with SAH have changed dramatically over the past few decades. Hyponatremia has been known to occur since the 1940s; however, the etiology was not known. Initially, hyponatremia was attributed to the development of the syndrome of inappropriate antidiuretic hormone (SIADH), which soon became documented in a variety of neurologic and neurosurgical disorders. Elevated ADH levels were similarly documented in SAH and fluid restriction for hyponatremia became the standard of care.

Maroon and Nelson were the first to suggest that this treatment may be in error. In a small group of patients with SAH they were able to document decreased blood volume and a negative sodium balance. They recommended volume repletion in place of fluid restriction.[33] Wijdicks verified this work and noted that fluid restriction exacerbated an underlying volume depletion and worsened outcomes.[4]

Accumulating evidence suggests that the release of atrial natriuretic factor (ANF) is important to the development of volume depletion and salt wasting seen with SAH. ANF is a 28 amino acid peptide which is released by the cardiac atrium in response to volumetric stretch. Release of ANF results in a 30-fold increase in urinary sodium and a 10-fold increase in urinary volume.

Initial attempts to link ANF levels with sodium concentration in patients with SAH were unsuccessful.[34,35] More recently, ANF has been subclassified into three groups: a, b, and c. Atrial natriuretic factor a (ANFa) is found in the cardiac atrium and is released with stretch. Atrial natriuretic factor b (ANFb) is found in both the hypothalamus and the cardiac ventricle and may be released due to cerebral ischemia. Atrial natruretic factor c (ANFc) is found in the vascular endothelium and is unrelated to sodium homeostasis. The release of ANFb may be the stimulus that leads to salt wasting and volume contraction in SAH. Support for this concept was provided by Sviri et al.,[36] who were able to demonstrate increased ANFb levels that paralleled the development of cerebral vasospasm in patients with SAH. Hyponatremia after SAH, however, is more complex than identifying a single responsible substance. The exact etiology of hyponatremia in any individual patient with SAH may be difficult to ascertain. Elevated ADH levels and cerebral salt wasting (CSW) may coexist simultaneously. It has been postulated that elevations in ADH levels occur early post-SAH, whereas CSW is a later cause of hyponatremia.[37]

VOLUME EXPANSION

The concept that CSW leads to volume depletion and worsening cerebral vasospasm has altered how we treat patients with SAH. Patients are now treated with salt and volume replacement. Normal saline is given in moderate to large volumes to maintain volume repletion. If hyponatremia develops, increased concentrations of sodium are given to combat the aggressive sodium natriuresis that occurs with CSW. Sodium can be given as small amounts of 3% normal saline or in larger amounts as 1.5% normal saline (NS +100 mEq NaCl). The advantage to using 1.5% NS is that it can be run at large volumes (1–300 ml/h) through a peripheral line. Higher sodium concentrated IV fluids require central access. Sodium can be given orally as salt tablets, but the amount that can be given is limited by GI upset. Fludrocortisone (Florinef), 0.2 mg orally twice a day, has also been shown in a recent study to be useful.[38]

The value of using colloids over crystalloids for volume expansion is debatable. Colloids appear to be better at initial volume expansion but no different in maintaining intravascular volume. Mayer et al.[39] had advocated using colloids to avoid the induced natriuresis that can develop from too rapid a volume

expansion but, to date, no conclusive evidence supports use of one over the other. Albumin use may be limited by the risk and expense of using large amounts of blood products. Dextrose-containing solutions are generally avoided in neurosurgery due to concerns of bleeding: however, these concerns are probably overstated. Packed red blood cells may be an alternative means of volume expansion.

Free water in all forms is avoided post-SAH. Both elevated ADH and ANF levels will lead to hyponatremia, which will be exacerbated by free water intake. Tube feeds should be as concentrated as possible and oral intake of water should be limited. It should be emphasized that water restriction does not mean volume restriction. Volume is encouraged, water is limited.

Monitoring of a patient's volume status can be challenging. Ins and outs should be followed closely as well as daily weights and blood urea nitrogen (BUN) to creatinine ratios. Central venous pressure (CVP) alone is a poor measure of volume status in this population and correlates poorly with pulmonary capillary wedge pressures[40] but can be used in conjunction with the above measures.

Hypervolemia is the traditional term used to describe the volume status needed in this population; however, the goal of volume repletion is *euvolemia*. The terminology of hypervolemia probably originated from the large amount of fluid that may be needed to maintain euvolemia. Additionally, pulmonary capillary wedge pressures used to maximize cardiac indexes in some studies were above normal values.[40] Hypervolemia, however, by definition, requires a pathologic state—ascites, congestive heart failure (CHF) and should be avoided to avoid unnecessary iatrogenesis. Support for this concept has been provided by Lennihan et al.,[41] who demonstrated no increase in CBF with hypervolemia compared with euvolemia in an SAH population.

Evidence that volume repletion is helpful after SAH has been provided in both animal and human CBF studies.[42–44] The largest study to date has been a retrospective review that has shown a significant improvement of outcome in patients with SAH treated with volume repletion compared with historical controls.[45]

HEMODYNAMIC AUGMENTATION

Previously referred to as 'triple H' therapy or hyperdynamic therapy, hemodynamic augmentation is probably the more precise description of the therapies involved to augment cerebral blood flow. Triple H therapy instituted the therapies of hypervolemia, hemodilution, and induced hypertension. As previously noted, there is no role for aggressive volume repletion beyond maintenance of euvolemia. Hemodilution has been of considerable interest. It is well known that decreasing blood viscosity increases CBF. This effect, however, is limited by decreasing cerebral oxygencarrying capacity. Multiple CBF studies have clearly revealed that cerebral oxygen delivery is maintained over a wide range of hematocrits. In addition, brain tissue oxygenation is maintained until the hematocrit drops below 30%.[46] It thus appears that hemodilution itself has a very limited role in treating cerebral vasospasm.

The best means to increase cerebral perfusion in cerebral vasospasm is somewhat debatable. Cerebral autoregulation is disturbed after SAH, with coupling between CBF and cerebral metabolism disrupted for greater than 1 week.[47] Vasospasm can extend this uncoupling.[48] Early CBF studies revealed a reversal of neurologic deficits secondary to cerebral vasospasm with induced hypertension using either phenylephrine or dopamine as pressors.[49–51] Intravascular volume expansion and induced hypertension have thus been suggested to treat symptomatic cerebral vasospasm.[52–56] The first large patient series, reported by Kassell et al.[54] showed that combined induced hypertension and volume expansion reversed neurologic deficits in the vast majority of patients (47 of 58 patients; 81%). In addition, in 16 patients who had a response to this

treatment, neurologic deficit recurred when blood pressure transiently decreased but again resolved with an increase in blood pressure.[54]

Other authors have demonstrated and emphasized the importance of increasing cardiac output as a means of increasing CBF after SAH.[40,57,58] Unfortunately, these studies did not control for changes in blood pressure that occurred with the use of dobutamine.

A direct comparison between increased cardiac index or induced hypertension has not been performed. Currently, additional CBF studies are underway to evaluate relative changes in CBF with each measure.

INTRA-ARTERIAL PAPAVERINE

Papaverine, an alkaloid of the opium group, is a vasodilator that may be useful as an additional treatment for patients with severe cerebral vasospasm. Its exact mechanism is unknown; however, cyclic adenosine monophosphate (cAMP) inhibition has been postulated to block intracellular calcium influx.[59,60]

Small series of anecdotal reports have reported the reversal of neurologic deficits with its use. A decreased mean circulation time, which correlates with an increased CBF, has also been demonstrated with the use of papaverine.[61] Animal studies suggest that this effect is less significant when vasospasm has existed for several days. Thus, secondary histological change in the vessel wall may reduce the vasodilatory effect of papaverine.[62]

Intra-arterial administration of papaverine involves infusion in doses of approximately 300 mg for 20 min to 1 hour. More rapid infusion may cause increased ICP or significant blood pressure changes. The effect of papaverine is generally limited to 4–8 hours but may last as long as 1 day. This may be just enough time to overcome the most severe period of cerebral vasospasm. Intra-arterial papaverine is often combined with angioplasty; therefore, its effect alone on angiographic cerebral vasospasm is not clear. Approximately 50% of patients have a noticeable change in vessel diameter. Clinical improvement, however, is much less impressive and it is more likely that only 1 out of 4 patients has a reduction of neurologic deficit. The only retrospective review of patients treated with papaverine for cerebral vasospasm revealed no difference in Glasgow outcome scores at 3 months.[63]

CEREBRAL ANGIOPLASTY

A relatively new technique is the use of balloon catheters to dilate cerebral arteries. This treatment is commonly used when neurologic manifestations of delayed cerebral ischemia cannot be reversed by optimal medical therapy. With this technique, the distal internal carotid and proximal middle cerebral arteries, distal and proximal vertebral arteries, and the entire basilar artery can be dilated. It is probably not safe to go beyond the proximal portions of the anterior middle and posterior cerebral arteries. The technique, is contraindicated when CT scans show early infarction, but the selection criteria are not well established: it has been utilized by neuroradiologists with a specific accreditation. In this procedure, a silicone balloon is inflated at low pressure (1–4 atm) to reduce the risk of endothelial damage and the risk of rupture. This results in the deformation and elongation of the collagen fibers in the adventitia and media of the vessel wall. Complication rates vary between 0 and 30%; however, the initial results with angioplasty for delayed cerebral ischemia are very encouraging. In the Seattle series of 60 patients treated with combined angioplasty and papaverine infusion, 66% had sustained improvement, defined as a two-point increase in the GCS score within 48 hours of treatment.[64] More recent studies have seemed to corroborate this. A retrospective review of 50 patients treated with angioplasty reported a 61% sustained reversal of neurologic deficits.[65]

ENDOVASCULAR OCCLUSION

Endovascular treatment of aneurysms has been significantly advanced by electrolytically detachable coils.[66–68] Follow-up angiograms showed persistent occlusion in 91% of patients and clinical results at up to 3 years of follow-up were excellent. This coil system can be detached electrothrombotically by applying a direct electrocurrent of 1 mA. Several coils are necessary to occlude the aneurysmal sac. Experience in treating basilar tip aneurysms is good at many institutions. In a recent study[69] of 71 patients in whom these coils were placed, 1 patient had a further hemorrhage 6 months later but no patients suffered direct or indirect permanent morbidity as a consequence of placement of the coils. Nonetheless, long-term follow-up is mandatory before placement of coils can be claimed to be an alternative to clipping of the aneurysm. However, patients who are difficult to treat surgically, who have associated medical comorbidity, or who have a poor grade of SAH may be specifically suitable for this approach.

STRATEGIES FOR IMPLEMENTING TREATMENTS

Volume loading generally begins once a ruptured cerebral aneurysm has been secured through either clipping or coil embolization. Adjusting to a normovolemic state remains the first priority. This may require a large amount of fluid if CSW has already developed. In general, aggressive volume repletion is started in patients who are at significant risk for delayed cerebral ischemia. Patients with a history of cardiovascular disease and patients with echocardiographic or clinical evidence of left ventricular dysfunction may need placement of a Swan-Ganz catheter to monitor intravascular volume.

The timing of the institution of hemodynamic augmentation is controversial. The institution of hemodynamic augmentation carries a 3–25% complication rate characterized by difficulties with CHF, myocardial infarction, and peripheral vasoconstriction.[55,70] However, 33% of patients who develop a neurologic deficit due to vasospasm will already have evidence for a cerebral infarction on cerebral imaging. Given the above difficulties, strategies have been developed in an attempt to individually tailor therapies to those patients at high risk for developing ischemic deficits secondary to vasospasm. These include the use of transcranial Doppler ultrasound (TCD) or some direct measure of CBF.

Transcranial Doppler ultrasound represents a noninvasive means of measuring flow velocities in the cerebral arteries. It uses a lowfrequency pulsed wave to insonate through the temporal bone: through this and other Doppler sites or ‘windows,’ a map of the cerebral vasculature can be obtained. Aaslid et al.[71] were able to document an excellent correlation between elevated middle cerebral artery (MCA) flow velocities and narrowed angiographic vessel diameters. In addition, early studies suggested that rising TCD flow velocities could be used to determine which patients would develop ischemic deficits secondary to cerebral vasospasm.[72]

Later studies suggested that the correlation between elevated TCD velocities and the development of ischemic deficits may not be so precise. Although able to document vessel narrowing, the predictive value of elevated TCD velocities may be limited by a number of theoretical and technical limitations. Rapid elevations, testing of cerebrovascular reserve, and cerebral autoregulation have met with varying success in their ability to predict neurologic deficits.[73] The latest retrospective study of TCD flow velocities suggested that the positive predictive value of elevated flow velocities in predicting neurologic deficits is only significant at flow velocities greater than 200 cm/s.[74]

Despite significant limitations, TCD flow velocities may have a significant role in monitoring patients after SAH. Some authors have advocated using elevations in TCD velocities to select patients for confirmatory CBF studies.[75] Others have suggested that angiography could be limited in those patients with

normal flow velocities. In addition, rising TCD flow velocities may be able to focus the neurologic examination on the vascular distribution at risk.

Monitoring of CBF using either SPECT (single-photon emission computed tomography) or xenon CT may be the optimal means to predict cerebral hypoperfusion in cerebral vasospasm but remains limited to a relatively small number of medical centers. One study has suggested continuous electroencephalographic (EEG) monitoring may be useful in predicting which patients will develop neurologic deficits.[76]

Due to the limitations of several monitoring techniques, manipulation of cerebral vasospasm, when demonstrated by any of the new diagnostic techniques, may not, therefore, improve patient outcome. Most institutions treat delayed cerebral ischemia when patients become symptomatic. Any antihypertensive diuretic therapy is discontinued to optimize hemodynamic manipulation. If hemodynamic therapy fails, cerebral angiography is performed, followed by angioplasty or intra-arterial papaverine infusion. One approach is summarized in Table 15.5.

PREVENTION OF CEREBRAL VASOSPASM

Numerous compounds have been hypothesized to initiate or propagate the development of cerebral vasospasm. One strategy designed to prevent the development of cerebral vasospasm has been to dissolve or wash away the offending subarachnoid blood prior to its breakdown. Intracisternal fibrinolysis with recombinant tissue plasminogen activator (rt-PA) or urokinase has been tried in a

Table 15.5 Guidelines for management of cerebral vasospasm (adapted from wijdicks EFM. The clinical practice of critical care neurology. Philadelphia: Lippincott-Raven; 1997.)

- Discontinue any antihypertensive or diuretic agent
- Ensure volume replacement with normal saline (NS) or hypertonic saline
- NaCl+100 mEq NaCl (1.5% NS) as maintenance IVF or 3% NaCl, 50 ml t.i.d., in patients at risk for cerebral vasospasm
- Fludrocortisone acetate (0.4 mg in 200 ml of glucose 5% b.i.d.) if hyponatremia is present
- Follow TCD flow velocities
- If acute increases in flow velocities, consider verification with angiography of CBF measures
- If TCD flow velocities > 200 cm/s, angiographic or CBF evidence for cerebral vasospasm, or neurologic deterioration, start induced hypertension with phenylephrine, dopamine, or norepinephrine
- If no clinical improvement in 4–6 hours, place Swan-Ganz catheter and start dobutamine 5–15 mg/kg/min to maximize cardiac output
- If no improvement in 4–6 hours, consider cerebral angiography with the use of papaverine or cerebral angioplasty

CBF, cerebral blood flow; IVF, intravenous fluid; TCD, transcranial Doppler ultrasound; b.i.d., twice per day; t.i.d., three times per day; IVF, intravenous fluid.

number of studies with varying success.[77–79] In general, fibrinolysis has been shown to decrease the incidence of angiographic vessel narrowing but has failed to be of proven clinical benefit.[80]

A variety of antioxidants and free radical scavengers have been tried to prevent lipid peroxidation, an event that appears important to the development of vessel narrowing. The use of free radical-induced lipid peroxidation with the 21-amino steroid tirilazad was initially found to improve outcome in a randomized, double-blind study in Europe, Australia, and New Zealand[81] but could not be verified in a subsequent North American trial.[82]

Some pathological studies have reported a cellular infiltrate in the vasospastic vessel wall, raising the possibility that immunosuppression could be utilized as a treatment strategy.[83] However, Manno et al.[84] found cyclosporin ineffective in preventing vasospasm. Corticosteroids, in one small series, were found to be effective in preventing vasospasm[85] but have generally been avoided due to the development of medical complications.[86]

Perhaps the two compounds that have generated the most recent excitement about treating vasospasm have been endothelin antagonists and nitric oxide donors. Endothelin is a recently discovered potent vasoconstrictor that when blocked has been shown to reduce cerebral artery vasoconstriction in animals.[87,88] Nitric oxide, a known potent vasodilator, has been administered with success in a primate model and intrathecally in the form of nitroprusside in three patients successively.[89,90]

Several other strategies designed to prevent or treat vessel narrowing have been proposed and are listed in Table 15.6. A more thorough review of these compounds is provided in Ref 86.

FUTURE CLINICAL INVESTIGATIONS IN TREATING VASOSPASM

As noted above, a variety of compounds are being evaluated for efficacy in treating cerebral vasospasm and many look promising. However, future studies in SAH will need to focus on elucidating the exact means by which symptomatic cerebral vasospasm occurs. There appears to be convincing evidence that intravascular volume contributes importantly and hypovolemia develops from profound natriuresis. Further characterization of ANFb, and ADH levels in SAH, and their relationship to the development of cerebral vasospasm, may lead to the development and use of specific ANF and ADH antagonists to prevent the volume depletion that occurs with cerebral vasospasm.

Cerebral blood flow studies are currently underway and should elucidate the best means of hemodynamic augmentation to treat cerebral vasospasm. Once ‘best medical management’ for cerebral vasospasm is better delineated, randomized controlled trials should be developed: this, however, may be difficult to initiate.

Table 15.6 Additional classes of compounds under study for the prevention of cerebral vasospasm

Treatment	Mechanism of action	References
Nicaraven	Hydroxy free radical scavenger	91, 92
Ebselen	Lipid peroxidation inhibitor	93
Deferoxamine, U74389G	Free radical scavengers	94, 95
FUT-175	Serine protease inhibitor	96
Calcitonin gene-related peptide	Endothelial vasodilation	97–99
OKY-1581, Cataclot	Thromboxane-A_2 inhibitor	100, 101
Adrenomedullin	Vasodilation	102

CONCLUSION

The management of patients with subarachnoid hemorrhage has changed dramatically in the past several years. An improvement in surgical techniques and the development of new endovascular approaches has shifted the emphasis in treatment to early repair or protection of the ruptured cerebral aneurysm. This has provided protection against rebleeding and also allowed for the initiation of medical therapies designed to augment CBF in the event of the development of cerebral vasospasm. Medical strategies designed to

improve CBF have come under greater scrutiny, and elucidation of the best means to initiate this therapy should greatly improve outcomes. New basic research has provided insight into the mechanisms involved in the development of cerebral vasospasm, while new and exciting potential therapies continue to be explored.

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16.
Prevention of early recurrences in acute stroke

Ritu Saxena and Peter J Koudstaal

INTRODUCTION

One of the feared complications in the acute phase of ischemic stroke is early recurrence of stroke. The frequency of early recurrent stroke varies in different studies and is often believed to be higher in patients with a potential cardiac source of embolism. It has also been suggested that recurrent stroke is often more severe than the initial event and is associated with increased mortality and disability. The value of antithrombotic treatment, especially heparin and aspirin, has recently been addressed in several studies. This chapter aims to review the definition and epidemiology of early recurrent stroke and to focus on the benefits and risks of antithrombotic therapy in the prevention of this complication.

DEFINITION OF EARLY STROKE RECURRENCE

Although nearly all patients who survive an acute ischemic stroke eventually show some degree of clinical improvement, neurologic symptoms are often unstable during the early phase. Patients may show rapid deterioration ('progressive stroke'), fluctuations ('stuttering stroke'), or secondary deterioration after initial improvement ('recurrent stroke'). These various forms of worsening are difficult to define and often overlap. Several studies have shown that spontaneous fluctuations occur in about 20% of carotid territory ischemic stroke and in up to 50% of vertebrobasilar ischemia.[1–3] Systemic disorders, such as myocardial ischemia and metabolic disturbance, are thought to play a role in fluctuation and late deterioration. Surprisingly, the large majority of studies focusing on early recurrent stroke reviewed in this chapter have not addressed this diagnostic problem. In fact, this issue is briefly discussed in only one study[4] and very few studies have attempted to define recurrent stroke (see Table 16.1).[5–10] Some have included worsening of a preexisting deficit, while others have accepted only new deficits that occurred in a different anatomic or vascular territory or were of a different stroke subtype than the index stroke. It is obvious that the lack of a uniform definition of recurrent stroke strongly influences the existing data on the epidemiology and medical prevention of this complication.

INCIDENCE OF EARLY RECURRENCE

The frequency of early recurrence has recently been reported in several large acute stroke trials, in which the efficacy of aspirin and/or heparin was investigated. Table 16.2 summarizes the early stroke recurrence rate. Because of the inherent methodological drawbacks of retrospective, non-randomized, and uncontrolled studies only prospective, randomized, controlled studies, in which recurrent stroke was a predefined outcome

event are shown. Data for untreated groups are presented if available or otherwise data for patients treated with aspirin. Patients were randomized within 24–48 hours of stroke onset and the observation period varied between 7 and 28 days after the index stroke. The International Stroke Trial (IST),[11] the Chinese Acute Stroke Trial (CAST),[12] and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[13] and FISS[14] included all types of ischemic strokes. However, physicians were free to exclude patients whom they believed to require anticoagulation; e.g., patients with atrial fibrillation (AF) and a pre

Table 16.1 Definition of recurrent stroke in various studies

Author	Definition
CESG (1983)[5]	Clinical evidence of recurrent systemic or cerebral embolism (no further details)
Ramirez-Lassepas (1986)[6]	New infarct and no extension of index cerebral infarct (no further details)
Sacco (1989)[7]	A cerebrovascular event within 30 days after the index stroke that clearly resulted in a new deficit and occurred in a different anatomic or vascular territory or was of a different subtype than the index stroke
Sandercock (1992)[8]	Clear clinical evidence of the sudden onset of a new neurologic deficit, or an increase in an existing deficit, for which no explanation other than a recurrent stroke could be found
Hornig (1993)[9]	Sudden worsening of preexisting focal deficit, or new symptoms without other reasons, e.g. epileptic seizure
Berge (2000)[10]	A clinical sudden and persistent (>48 hours) deterioration occurring after the first 48 hours following stroke onset, which equals a loss of three or more points in the Scandinavian Stroke Scale (SSS), excluding cerebral hemorrhage, intercurrent illness, and effect of medication
Petty (2000)[17]	A new neurologic deficit fitting the definitions of ischemic or hemorrhagic stroke, occurring after a period of unequivocal neurologic stability or improvement lasting γ24 hours and not attributable to edema, mass effect, brain shift syndrome, or hemorrhagic transformation of the incident cerebral infarction
Over 40 other publications on the subject	Not explicitly stated

sumed high risk recurrence. in the Heparin in Acute Embolic Stroke Trial (HAEST) only patients with acute ischemic stroke and AF were randomized.[10] Table 16.2 shows that the risk of early recurrence varies between 0.09% per day in CAST patients (7% AF) and 0.68% per day in the small CESG trial. In the HAEST study the recurrence risk was also high (0.53% per day). In that study, recurrent ischemic stroke was a primary outcome event and patients were assessed for neurologic deterioration every day during the first week and every other day during the second week. Another important factor is the time between stroke onset and inclusion in studies. In IST and CAST, patients could be randomized up to 48 hours after onset of symptoms, so some very early recurrences may have been missed.

Since patients from clinical trials in general represent a selected group, information from stroke data banks and population-based studies are important. These are also summarized in Table 16.2. The disadvantage of some of these studies is, however, that they were retrospective, leading to potential underreporting of recurrent stroke and to uncertainty regarding dose, duration and the clinical grounds of antithrombotic therapy. The observation period in all these studies was 30 days.

Sacco et al. studied 1273 patients with acute ischemic stroke who were entered into the NINDS-Stroke Data Bank, a prospective, observational study.[7] The risk of early recurrence was 3.3% in 30 days.

Gustafsson followed 276 consecutive patients admitted to a population-based stroke unit in Stockholm:[15] within 1 month, 2.9% had a recurrent stroke. In the Rochester Epidemiology Project (REP), 1382 patients with first-ever cerebral infarction between 1960 and 1984 were tracked.[16] The recurrence risk within 30 days was 2.0%. In a second report, 442 patients between 1985 and 1989 were studied retrospectively and the 30 day recurrence rate was 4.8%.[17] In the Oxfordshire Community Stroke

Table 16.2 Risk of early stroke recurrence in untreated or aspirin-treated patients from randomized, controlled acute stroke trials and patients from stroke data banks and community studies, with unspecified treatment

Study	Patients (*n*)	Observation period (days)	Recurrence rates (%)		
			During observation	Per day	Time to inclusion (hours)
Clinical trials					
CESG (1983)[5]	21	14	9.5	0.68	48
FISS (1995)[14]	105	10	5.7	0.57	48
IST (1997)[11]	9718[a]	14	3.8	0.27	48
CAST (1997)[12]	10552	28	2.5	0.09	48
TOAST (1998)[13]	631	7	1.4	0.20	24
HAEST (2000)[10]	225[b]	14	7.5	0.53	30
Stroke data banks and community studiesc					
NINDS-SDB (1989)[7]	1273	30	3.3	0.11	Unknown
Gustafsson (1991)[15]	276	30	2.9	0.10	Unknown
REP 1960–84 (1992)[16]	1382	30	2.0	0.07	Unknown
OCSP (1992)[8]	545	30	3.5	0.12	Unknown
REP 1985–89 (2000)[17]	442	30	4.8[c]	0.16[c]	Unknown

[a] Half were treated with aspirin.
[b] All were treated with aspirin.
[c] Procedure-related strokes were excluded.

Project (OCSP), 545 patients with first-ever ischemic stroke were followed.[8] The risk of early recurrence within 30 days was 3.5%. However, some recurrences may have occurred unnoticed as many of these patients stayed at home and were not carefully studied in the acute phase.

In conclusion, the risk of recurrent strokeseems to be higher in patients entered in clinical trials than in population-based studies or stroke data banks. Patients in trials were randomized early after stroke onset and probably followed more carefully. On the other hand, they probably represent a selected group of high-risk patients.

RISK FACTORS FOR EARLY RECURRENCE

All of the abovementioned population studies have also tried to identify risk factors for early stroke recurrence. Some authors have compared the recurrence rate for specific etiological stroke subtypes. Sacco et al. prospectively studied determinants of early recurrence in 1273 patients with ischemic stroke from

various causes.[7] A total of 40 patients (3.3%) had a recurrence within 30 days. Procedure-related strokes were not included. Patients with atherothrombotic infarction (ATH) had the highest risk of very early recurrence (7.9%), followed by patients with presumed cardioembolic stroke (CES, 4.3%), infarction of undetermined cause (IUC, 3.0%), and lacunar infarcts (LAC, 2.2%). Petty et al. reviewed records of 442 patients with first-ever ischemic stroke from the Rochester Epidemiology Project and used the same etiological subclassification.[17] Twenty-five patients (5.6%) had a recurrent ischemic stroke within 30 days and there was a significant difference between stroke mechanisms and the recurrence rate: ATH, 18.5%; CES, 5.3%; IUC, 3.3%, and LAC, 1.4%. Procedurerelated strokes were included and it is noteworthy that 4 of the 13 recurrences in the ATH group were iatrogenic (angiography, carotid endarterectomy).

As the early recurrence rate is often believed to be higher in patients with a potential cardiac source of embolism, data for patients with presumed cardioembolic stroke, compared with those without cardioembolic stroke are shown in Table 16.3. In IST, 3169 (17%) of 18 451 acute stroke patients had AF at study entry.[11] Patients with AF had a higher risk of early death, which could be explained by older age and larger initial strokes in AF patients, but not by a higher risk of early recurrent ischemic stroke, although slightly more patients with AF died from a fatal recurrent stroke of ischemic or unknown type :1.3% vs 0. 9%; odds ratio (OR) 1.7, 95% confidence interval (CI) 1.2–2.4.[18] Three-quarters of IST patients received heparin and/or aspirin and one-quarter no antithrombotic therapy. The rate of early recurrent stroke was equally frequent in both groups (3.9% in AF vs 3.3% in SR; OR 1.2, 95% CI 1.0–1.5) when all treatment groups were combined. The IST data are potentially weakened by the possibility of selection bias, since patients with AF and a high risk may have been treated with anticoagulants and not have been entered into the study. On the other hand, the frequency of AF of 17%, which is very similar or even higher than that found in other series of stroke patients, does not point in that direction. The data for the patients who did not receive heparin are given in Table 16.3. In these patients (half received no antithrombotic treatment and the others received aspirin), the risk of stroke recurrence was somewhat higher than in patients without AF.

In the TOAST trial no difference between patients with and without CES was found.[13] The HAEST and CESG studies are not mentioned in Table 16.3, as all patients had a cardioembolic stroke. In the HAEST study all patients had AF and the recurrence rate was high (7.5% per 14 days).[10] Furthermore, recurrent stroke was a primary outcome event in this trial and patients were rigorously checked for recurrences. In CESG, 2 of 21 patients (9.5%) had a recurrence.[5] In CAST,[12] 7% of patients had AF and in FISS,[14] 13% had a CES, but recurrence rates were not reported separately for these groups.

Epidemiological studies have also focused on differences in the risk of early recurrence

Table 16.3 Risk of early stroke recurrence in patients with or without cardioembolic stroke (CES or non-CES) in untreated patients or aspirin-treated patients from randomized, controlled trials and patients from stroke data banks and community studies, with unspecified treatment

				Recurrence rate (%)				
				CES		Non-CES		
Study	**CES *(n)***	**Non-CES *(n)***	**Observation period (days)**	**During observation**	**Per day**	**During observation**	**Per day**	**OR (95% CI)[a]**
Clinical trials								
IST (1997)[11]	1612 (all AF)	8105[b]	14	4.9	0.35	3.6	0.26	1.38 (1.06–1.79)
TOAST (1998)[13]	123 (52 AF)	508	7	1.6	0.23	1.4	0.20	1.18 (0.26–6.25)

Study	CES *(n)*	Non-CES *(n)*	Observation period (days)	Recurrence rate (%)				
				CES		Non-CES		
				During observation	Per day	During observation	Per day	OR (95% CI)[a]
Stroke data banks and community studiesc								
NINDS-SDB (1989)[7]	246	958	30	4.1	0.14	3.1	0.10	1.31 (0.59–2.84)
Gustafsson (1991)[15]	88 (all AF)	188	30	4.5	0.15	2.1	0.07	2.2(0.46–10.94)
REP 1960–84 (1992)[16]	318	1064	30	2.0	0.07	2.0	0.07	0.96(0.34–2.5)
OCSP (1992)[8]	76 (all AF)	448	30	1.0	0.03	4.0	0.13	0.25(0.02–1.7)
REP 1985–89 (2000)[17]	132	310	30	4.85[c]	0.16[c]	5.2[c]	0.17[c]	0.91 (0.34–2.56)

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio.
[a] CES vs non-CES.
[b] Half were treated with aspirin.
[c] Procedure-related strokes were excluded.

between patients with presumed cardioembolic stroke and those with a likely vascular cause (see Table 16.3). Two population studies discussed earlier, OCSP and REP, showed no clear evidence of a higher risk in patients with a cardiac cause.[7,17] In the Oxfordshire Community Stroke Project, the prevalence of AF was 98 (18%) among 545 patients with first-ever stroke.[8] Twenty-one patients with AF received anticoagulants at some time after the stroke. The risk of early recurrence within 30 days was 1% in AF patients against 4% in patients with sinus rhythm. A potential weakness of the study is that cardiac screening was very rarely performed, which may have led to an underestimation of the prevalence of cardiac disease. Furthermore, some recurrences might have been missed, as many patients stayed at home and were not carefully studied in the acute phase.

In the first study from the Rochester Epidemiology Project, 318 (23%) of 1382 patients with first-ever cerebral infarction had at least one major potential cardiac source of emboli.[16] AF was present in 19% of all cases. The recurrence risk within 30 days was 2%, both in patients with or without a cardiac abnormality. Details on antithrombotic treatment were known only in the subgroup of patients who survived the first week. Slightly less than half of them were treated with heparin, warfarin, or both within the first 7 days. The 30-day stroke recurrence rate was 3% for treated vs 2% in untreated patients. Gustafsson also did not find a significant difference in the 14-day recurrence rate: 4/88 in AF patients versus 4/188 in patients with sinus rhythm.[15]

There may also be differences in the recurrence rate between various types of underlying cardiac disease, but the available data are insufficient to determine major differences with the possible exception of rheumatic heart disease, which carries a higher risk, and atrial fibrillation, which is more benign.[19] Yasaka and colleagues studied risk factors for early recurrence in 227 patients with cardioembolic stroke, none of whom were treated with anticoagulants:[20] One-quarter of the study population had rheumatic heart disease; recurrent brain or systemic embolization within 14 days occurred in 31 (13.7%) and 19 (8.4%) patients,

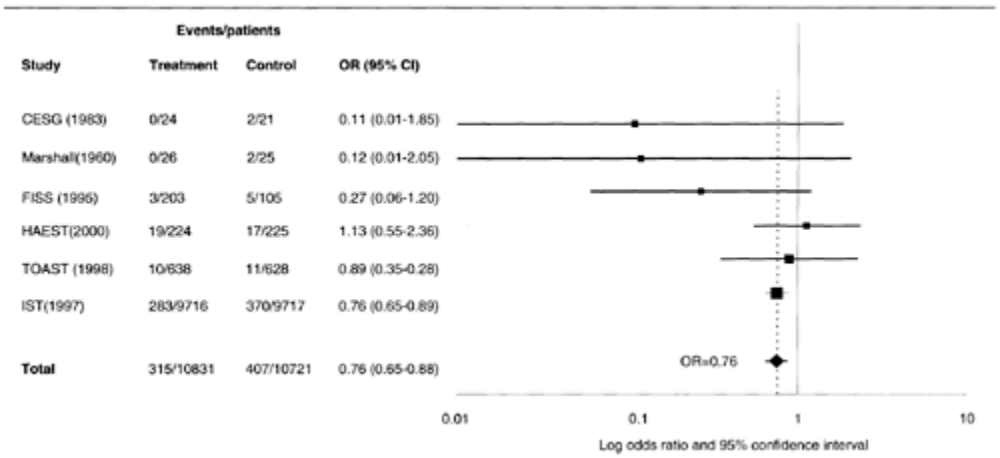

Figure 16.1 The efficacy of anticoagulant treatment in the prevention of early recurrent stroke in patients with acute ischemic stroke.

respectively, and was associated with a higher mortality. The presence of rheumatic heart disease, prosthetic valves, and intracardiac thrombi were associated with recurrent emboli. The incidence of rheumatic heart disease, however, has strongly declined in the Western world. In the Rochester Epidemiology Project 1960–84, cardiac valve disease and congestive heart failure (but not AF) were independent predictors of recurrent stroke.[16]

In conclusion, there is contradictory evidence whether a cardiac source of embolism, especially AF, is associated with a higher risk of early stroke recurrence. The main disadvantage of clinical trials is that they represent a selected group, whereas the potential impact of antithrombotic treatment is an uncertain factor in epidemiological studies.

Some other factors have been found to be associated with the risk of early recurrence. Sacco found that a history of hypertension and diabetes mellitus as well as diastolic hypertension and an elevated blood sugar on admission and increased weakness scores were associated with early recurrence in a logistic regression analysis.[7] Yasaka also reported low plasma levels of antithrombin III and dehydration to be associated with recurrent stroke.[20] Studies concentrating on late stroke recurrence have found that a history of hypertension, ischemic heart disease, diabetes, and previous thromboembolism were associated with a higher risk.[21–23] These data suggest that risk factors for early and late recurrence are strikingly similar.

PREVENTION OF EARLY RECURRENCE

Immediate use of antithrombotic therapy might reduce the risk of early recurrent stroke, but may also increase the risk of intra- and extracranial hemorrhage. Older clinical trials, mostly nonrandomized and retrospective, have suggested a reduction of the absolute risk of early recurrence by anticoagulants from 15% to 5% during the first month.[19] We shall concentrate on prospective, randomized, controlled trials addressing the safety and efficacy of antithrombotic treatment in acute stroke, in which recurrent stroke and intracranial hemorrhage were predefined endpoints and patients were randomized within 3 days of stroke onset. The results are summarized in Figs 16.1–16.3.

In 1960, Marshall and Shaw published a clinical trial of 51 patients with a clinical diagnosis of ischemic stroke of less than 72 hours' duration and without a potential source of embolism in the heart.[24] Patients

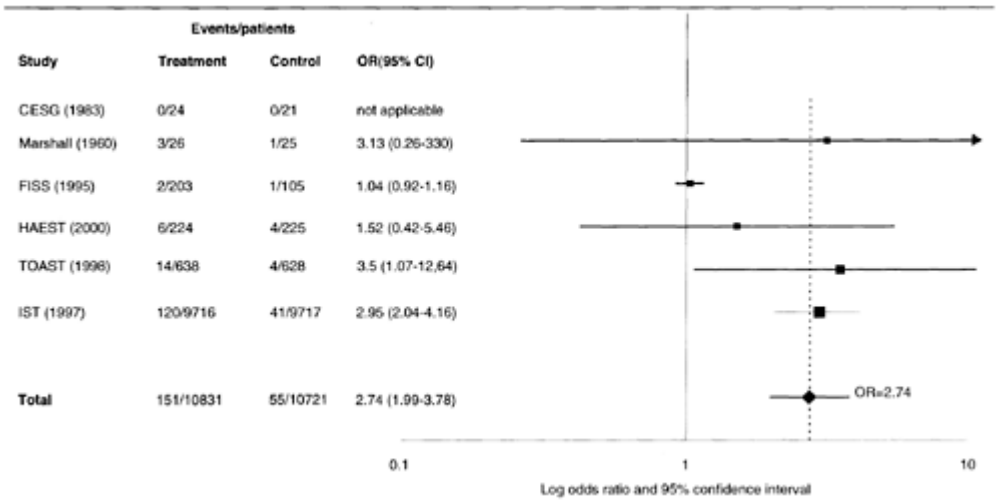

Figure 16.2 Number of symptomatic intracranial hemorrhages in patients with acute ischemic stroke and anticoagulant treatment.

were randomized to openlabel treatment with three doses of 12 500 units unfractionated heparin plus the oral anticoagulant phenindione twice daily, aiming at PT ratio between 2 and 3, or to no treatment. Two patients in the control group and none in the anticoagulants group had an early recurrent event within 6 weeks after randomization. Three treated patients died of cerebral hemorrhage vs 1 untreated patient.

Low-molecular-weight heparins (LMWHs) were tested in the FISS[14], TOAST[13] and FISS-bis study.[25] In 1995, Kay et al. published the double-blind, placebo-controlled FISS trial in which 312 Chinese patients with acute ischemic stroke were treated with subcutaneous LMWH, either low dose or high dose, or placebo within 48 hours of stroke onset.[14] Patients were younger than 80 years and did not have valvular heart disease necessitating anticoagulant therapy. Treatment lasted 10 days. The main measure of outcome, clinical condition at 6 months, was significantly improved in both actively treated groups. Early recurrent

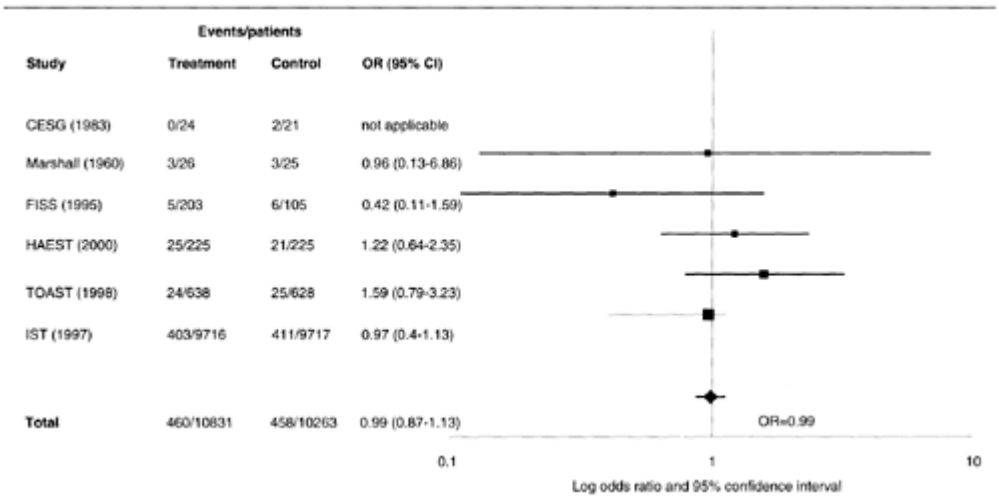

Figure 16.3 Number of recurrent ischemic strokes and symptomatic intracranial hemorrhages in patients with acute ischemic stroke and anticoagulant treatment.

stroke during the treatment period occurred in 1 patient receiving the high dose, 2 at the low dose, and 5 in the placebo group. Early hemorrhagic transformation was found in 5 patients in the high-dose group, 7 in the low-dose, group, and 9 of the placebo patients. Symptomatic hemorrhagic transformation occurred in, respectively 0, 2 and 1 patients.

In an attempt to reproduce the results of FISS, a replication study with a larger number of patients (placebo: n=250; low-dose LMWH: n=271; high-dose LMWH: n=245) was undertaken.[25] In 1998 FISS-bis was published and there was no overall benefit of either heparin dose on clinical condition at 6 months. Recurrent stroke was not a specified outcome event and was not reported in the publication.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the LMWH danaparoid among 1281 patients with ischemic stroke treated within 24 hours of stroke onset.[13] Danaparoid was given intravenously and treatment was continued for 7 days. The primary measures were the Glasgow outcome scale and the Barthel index at 3 months. Within 10 days of onset of treatment, the risk of recurrent ischemic stroke was similar in both groups (10/638 vs 11/628 in controls). Serious intracranial bleeding events occurred in 14 patients given ORG 10172 (15 events) and in 4 placebo-treated patients (5 events, p=0.05). Treatment with ORG 10172 was not associated with an improvement in favorable outcome at 3 months.

The efficacy of antithrombotic treatment in the long-term prevention of stroke recurrence has been firmly established in patients with AF by the European Atrial Fibrillation Trial.[26] Only two trials have studied the value of heparin in the acute treatment of CES. In 1983, the Cerebral Embolism Study Group published the results of a small open randomized trial in 45 patients with acute cardioembolic stroke of less than 48 hours' duration.[5] The trial was primarily designed to assess the safety, and not efficacy, of early treatment with continuous intravenous heparin activated partial thromboplastin time (APTT) ratio 1.5–2.5—compared with no treatment during 10 days. Early recurrent stroke occurred in 2/21 control patients and none of the 24 treated patients. Symptomatic intracranial hemorrhage did not occur, but intracranial bleeding on a control computed tomography (CT) scan was found in 2 control patients. The recently published HAEST trial randomized 449 patients with acute ischemic stroke (within 30 hours after onset) and AF to treatment with

aspirin, 160 mg/day, or a high dose of the LMWH dalteparin, 100 IU/kg subcutaneously (sc), twice a day (bid). No difference in the frequency of early recurrent ischemic stroke or cerebral hemorrhage was detected.[10]

By far the largest trial to date is the IST, which involved 19 435 patients with acute stroke, randomized in 467 hospitals.[11] Three-quarters of the patients were randomized to antithrombotic therapy—i.e. to one of the three regimens, aspirin, subcutaneous unfractionated heparin (low dose or medium dose), or the combination —and one-quarter to control. Patients with mild, moderate, and severe deficits, presenting within 48 hours of the onset of suspected acute ischemic stroke, were eligible for the study. Duration of treatment was 14 days. Nearly all patients had a CT scan either before or after randomization. The primary outcomes were death within 14 days and death or dependency at 6 months.

Symptomatic intracranial hemorrhage and recurrent ischemic stroke within 14 days were protocol-specified secondary outcome events. Patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs 3.8%) but this was completely offset by an increase in hemorrhagic strokes (1.2% vs 0.4%). A total of 3169 (17%) patients were in AF, 784 of whom were allocated to 12 500 IU heparin (sc bid), 773–5000 IU heparin (sc bid), and 1612 to avoid heparin. The proportion of AF patients with further fatal or nonfatal events within 14 days allocated to 12 500 IU heparin, 5000 IU heparin, and to avoid heparin were, respectively, ischemic stroke 2.3%, 3.4%, 4.9% (p for trend=0.001); hemorrhagic stroke 2.8%, 1.3%, 0.4% ($p<0.0001$); and any stroke or death 18.8%, 19.4% and 20.7% ($p=0.3$). No effect of heparin dose on the proportion of patients who were dead or dependent at 6 months was found.[18]

In acute ischemic stroke, a majority of patients show evidence of in-vivo platelet activation, which can be inhibited by aspirin.[27,28] The only antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke is aspirin. In CAST, aspirin treatment, 160 mg/day, was started within 48 hours of the onset of suspected acute ischemic stroke and continued in hospital for up to 4 weeks.[12] In total, 20 000 patients were randomized. The primary outcome events were death from any cause during the 4-week treatment period and death or dependence at discharge, the secondary fatal or nonfatal recurrent hemorrhagic or ischemic stroke. There was a significant 14% (SD 7) proportional reduction in mortality during the scheduled treatment period: 343 (3.3%) deaths among aspirin-allocated patients vs 398 (3.9%) deaths among placebo-allocated patients; $2p=0.04$. Significantly fewer recurrent ischemic strokes occurred in the aspirin-allocated than in the placebo-allocated group (167 [1.6%] vs 215 [2.1%]; $2p=0.01$) but slightly more hemorrhagic strokes (115 [1.1%] vs 93 [0.9%]; $2p>0.1$). In IST, aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs 3.9%) with no significant excess of hemorrhagic strokes (0.9% vs 0.8%), resulting in a significant reduction in death or nonfatal recurrent stroke with aspirin (11.3% vs 12.4%).[11]

With the results of IST and CAST combined, aspirin produces a small reduction of about 10 early deaths or recurrent strokes per 1000 patients treated. Both trials suggest that aspirin should be started as soon as possible after the onset of all subtypes of ischemic stroke.

SUMMARY

The diagnosis of early recurrent stroke is not always easy in patients with acute ischemic stroke, since up to 20% of patients show spontaneous fluctuations, some of which may be caused by repeated embolism, but many have other causes, including systemic disorders. The risk of recurrent stroke seems to be higher in patients entered in clinical trials than in population-based studies or stroke data banks. The aggregate results of randomized clinical trials of heparin in acute ischemic stroke suggest that this treatment reduces the risk of early recurrence by about onequarter, but also that this benefit is completely offset by an equal risk of hemorrhage. Present data neither suggest a clear subgroup, in particular those with cardioembolic stroke,

with a higher risk of early recurrence, nor one that specifically benefits from early treatment with anticoagulants. Findings from two large trials show that aspirin is effective in reducing death and early recurrence (10 events prevented per 1000 treated) and is safe.

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17.
Published guidelines: update and synthesis

Risto O Roine and Markku Kaste

INTRODUCTION

Evidence-based guidelines are rapidly becoming the gold standard in every field of medicine, and the management of stroke is not an exception to this rule. The goal of such guidelines is to provide high quality and uniform level of care, irrespective of time and place. Guidelines have been written for local, national, and international scientific societies and health authorities, including local, institutional, national and international, political, legislative, and scientific organizations, each of which have their distinct characteristics and scope. Finland was one of the first countries to publish national guidelines,[1] updated in 1989.[2] Some national guidelines have reached a global reference status, especially the American Heart Association guidelines for the management of patients with acute ischemic stroke published 1994.[3]

Guidelines have also been written by international organizations such as the European Federation of Neurological Societies (EFNS), which published its guidelines for acute stroke care in 1997.[4] Some national guidelines effectively provide a reliable source of evidence-based information on different aspects of stroke management. The British guidelines published in 2000 are a good example of this.[5]

Furthermore, extensive and detailed guidelines have been produced as the joint effort of more than one scientific society, such as European Stroke Initiative (EUSI) recommendations for stroke management, published in 2000.[6,7] The EUSI is a joint venture of three societies—the European Stroke Council, the European Neurological Society, and the European Federation of Neurological Societies— to provide evidence-based recommendations for the management of stroke. Finally, guidelines may also serve to increase the awareness of the importance of stroke care: one example was the WHO consensus meeting on stroke management, held in Helsingborg, Sweden in 1995.[8]

Although guidelines and recommendations are generally welcomed by clinicians treating stroke patients, too many different guidelines with sometimes conflicting recommendations may be a problem. Due to the large number of published stroke guidelines, this review will be mainly limited to acute care of ischemic stroke but some references to other aspects of stroke care will be included.

THE NEED FOR COMPARISON OF GUIDELINES

Probably the best known and most influential guidelines are those issued by the American Heart Association. The AHA has published separate guidelines for prevention of stroke, management of ischemic stroke, spontaneous intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack (TIA), carotid endarterectomy, and stroke outcome classification, respectively. The guidelines on acute ischemic stroke, published in 1994, were amended in 1996 after the US Food and Drug Administration (FDA) had

approved thrombolytic therapy in ischemic stroke. The three main American guidelines are those of the American Heart Association, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Stroke Association (NSA).[3,9,10] The Recommendations for the Establishment of Primary Stroke Centers by the Brain Attack Coalition are considered together with the NSA recommendations, although produced as a joint venture.[11] Although the American Heart Association is often considered as the opinion leader, ordinary clinicians might find it difficult to decide which recommendations to follow. The availability of updates might have an impact on the decision. The situation is quite similar in Europe. A European clinician may use the American guidelines or choose between a variety of national and international guidelines. He or she might rely on international guidelines (WHO, Regional Office for Europe 1995,[12] EFNS 1997,[4] EUSI 2000[6]) or on national guidelines such as the guidelines of the Royal College of Physicians[5] or the local guidelines of individual hospitals. For instance, a physician working in Scotland may prefer local guidelines such as those of the Royal College of Physicians of Edinburgh (2000). As a result of the increasing number of guidelines, there is an obvious need for critical evaluation of available guidelines. The scope, coverage, content, and feasibility of six major guidelines—three from the United States and three from Europe—will be critically evaluated in this chapter in order to make it easier for a clinician to decide which one to follow in daily practice.

AMERICAN AND EUROPEAN GUIDELINES

Although an individual physician treating stroke patients may not pay attention to organizational aspects of stroke care, these factors have a major influence on the outcome of a stroke patient. It makes a difference if a patient is treated at home, as still often happens in the United Kingdom, or is transferred fast to an emergency room capable of providing early thrombolysis, if the patient is eligible for this treatment. Thrombolysis is part of routine care in the United States, Canada, and Germany but also in well-organized stroke centers in some other European countries. In order to safely and effectively provide thrombolysis for stroke patients, the hospital organization must be able to provide efficient prehospital and inhospital services, critical pathways including emergency computed tomography (CT) imaging, and laboratory services 24 hours with minimum delays. However, even in the United States, only a minority of patients will receive thrombolysis[13] but all stroke patients benefit from a well-organized acute care, which includes stroke unit services.[14] In Table 17.1, the three US and three European stroke guidelines/recommendations on organizational aspects of stroke services are compared. As can be seen, none of them touches all the organizational aspects of stroke management. The UK guidelines do not say anything about time windows, prehospital services, or emergency room, while all three US guidelines cover these aspects well but seem to neglect stroke units, the use of which is highly evidence-based medicine[14] and an essential feature of effective stroke care. The EUSI guidelines cover all of the above issues, emphasizing the importance of rehabilitation as well as the role of outcome and quality assessment. The same holds true for the British guidelines, while the US guidelines seem to pay less attention to these aspects.

There are a few multicenter randomized placebo-controlled trials evaluating thrombolysis in ischemic stroke, one of which led to the approval of the treatment by the FDA.[15] Many more such trials have studied neuroprotective agents in acute ischemic stroke, but all of them were either terminated prematurely or ended with a negative result. There are no randomized controlled trials on how to treat blood pressure, blood glucose, oxygenation and ventilation, or temperature in acute ischemic stroke, yet these basic aspects of acute stroke care are probably among the key elements for the success or failure of acute stroke care as also are prevention of aspiration pneumonia, pulmonary embolism, bed sores, contractures, depression, and other common complications of stroke. These points may look scientifically less challenging, although for

most stroke patients the outcome is predicted by how well these aspects are taken care of. The recommendations for these cornerstones of stroke care in the six guidelines are presented in Table 17.2. The three American and the EUSI guidelines underline the importance of thrombolysis. The British guidelines also mention it, but only the EUSI recommendations stress all the key elements of good

Table 17.1 Comparison of US and European stroke guidelines: organization of stroke care

Service	AHA	NSA	NINDS	EUSI	WHO	UK
Stroke awareness	++	++	+++	++	+	-
Time windows	+	+	++	+	+	-
Prehospital	++	++	+++	++	+	-
Emergency room	++	++	++	+++	-	-
Critical pathways	+	+	++	+	-	-
Stroke unit	-	-	-	+++	+	++
Stroke center	-	+	++	++	+	-
Stroke team	-	+	+	-	-	-
Brain imaging	++	++	+	+	+	+
Ultrasound	+	+	-	+	+	+
Laboratory	+	++	+	+	-	-
Other resources	-	-	++	-	-	-
Stroke team	-	+	+	-	-	-
Rehabilitation	+	+	-	+++	+	+++
Personal aids & appliances	-	-	-	-	-	+
Outcome and quality assessment	+	+	++	+++	++	++
Caregivers and families	+	-	-	+	+	++
Patient organizations	-	-	-	-	+	++
Guidelines	+	+	+	+	-	+
Education	+	+	++	+	+	+
Research	+	+	+	+	++	-

AHA, American Heart Association; NSA, National Stroke Association; NINDS, National Institute for Neurological Disorders and Stroke; EUSI, European Stroke Initiative; WHO, World Health Organization; UK, United Kingdom.

-=not mentioned; += mentioned; ++=recommendation given; +++=recommendation enforced/emphasis.

stroke care. These include diagnosis, vital functions, blood pressure, ventilation, myocardial ischemia, arrhythmias, infections, continence, prevention of thrombosis, and swallowing. The British guidelines stress some of these aspects and are a good source for references in these topics. It is obvious that more research is

needed to establish evidence-based guidelines for these basic aspects of stroke care, which now rely more on opinions than evidence. As long as there is no contrasting evidence, it seems sound to keep physiological parameters within normal range for optimal care of a stroke patient. We don't know yet whether this is true, however. According to all guidelines and general opinion, only extremely high blood pressure should be lowered in acute ischemic stroke, or in case there are additional indications to do so, such as congestive heart failure or signs of hypertensive encephalopathy. Despite increasing evidence of the harmfulness of hyperglycemia and hyperthermia, an aggressive approach to these problems does not yet seem to be very common, although adopted in some guidelines.

While the guidelines of acute care are based on opinions in many key points of the care, the situation is totally different in stroke prevention. Both primary and secondary prevention of stroke are based on evidence more than on any other part of stroke management. Accordingly, the guidelines of primary and secondary prevention of stroke in Table 17.3 are mainly evidencebased. For this reason, the recommendations for prevention are more similar than those for organization of stroke services or acute stroke care. Yet there are some differences between the guidelines. The role of treating arterial hypertension is more heavily underlined in the AHA, NSA, and EUSI guidelines than in the British guidelines and the same holds true for treating

Table 17.2 Comparison of US and European guidelines: acute care

Factor	AHA	NSA	NINDS	EUSI	WHO	UK
Diagnosis	+	+	+	+++	+	+
Monitoring	+	-	++	++	+	-
Vital functions	+	+	+	++	+	-
Blood pressure	+	+	++	+++	+	-
Temperature	+	+	-	+++	-	+
Blood glucose	+	+	-	+++	-	+
Oxygen and ventilation	+	-	+	++	-	-
Intracranial pressure control	-	+	-	+++	-	-
Myocardial ischemia	+	-	+	++	-	-
Arrhythmias	+	-	-	++	-	-
Infection	+	-	-	++	-	-
Thrombosis prophylaxis	+	-	-	++	-	++
Swallowing, nutrition	+	-	-	++	-	++
Continence	-	-	-	+	-	++
Mood	-	-	-	+	+	+
Other complications	++	+	-	+	-	-
Thrombolysis	+++	++	+++	+++	-	+

Factor	AHA	NSA	NINDS	EUSI	WHO	UK
Antithrombotics	++	++	-	++	+	+
Anticoagulants	+	++	-	+++	-	-
Other drugs	++	+	-	++	+	-
Surgery	++	+	-	++	+	-
Research	-	-	-	+	++	-

AHA, American Heart Association; NSA, National Stroke Association; NINDS, National Institute for Neurological Disorders and Stroke; EUSI, European Stroke Initiative; WHO, World Health Organization; UK, United Kingdom.
-=not mentioned; += mentioned; ++=recommendation given; +++=recommendation enforced/emphasis.

atrial fibrillation with anticoagulants. Also the weight of antithrombotic therapy in stroke prevention is emphasized in the same two US and EUSI guidelines and less in the WHO and British guidelines. The NINDS guidelines do not contain recommendations for secondary prevention of stroke, including carotid endarterectomy, neither do the British guidelines include strong recommendations in any aspects of stroke prevention. The WHO guidelines are the only ones which underline the need for future research.

DISCUSSION

ADVANTAGES

The ultimate goal of all national and international stroke guidelines and recommendations is to guarantee an appropriate care for all stroke care might have decreased case fatality stroke patients, irrespective of time and place. The use of automated routines will facilitate care and increase safety by eliminating complications. The guidelines include indirectly an assumption that a good care is also cost-effective, which is probably true, although the cost-effectiveness of stroke care has barely been studied at all. Stroke is not only a financial burden but causes more quality-adjusted life years (QALY) lost than any other disease.[16] Accordingly, the guidelines have a very important role in improving the outcome of stroke patients. Since the early 1990s, written standard operating procedures have been followed in many well-organized stroke centers, including Helsinki. It has been suggested that improved of stroke.[17] Organized stroke unit care has been reported to result in lower case fatality, less dependency, and less need for institutional care,[4,18] supporting the idea that well-organized

Table 17.3 A Comparison of US and European stroke guidelines: Primary and secondary prevention of stroke

	AHA	NSA	NINDS	EUSI	WHO	UK
Hypertension	++	++	-	+++	+	+
Coronary heart disease	-	++	-	-	-	-
AF	+	+++	-	+++	-	-
Diabetes	+	++	-	-	+	-
Lipids	++	+	-	+++	+	+
Diet	+	+	-	-	-	-

	AHA	NSA	NINDS	EUSI	WHO	UK
Obesity	+	+	-	-	-	-
Physical activity	+	+	-	+	-	-
Smoking	+	+	-	+	+	-
Alcohol	+	+	-	+	+	-
Lifestyle	+	+	-	+	+	+
Anticoagulants	++	++	-	++	+	+
Antithrombotics	++	++	-	++	+	+
Statins	+	++	-	+	-	-
ACE inhibitors	++	-	-	++	-	-
Estrogen	+	-	-	+	-	-
Carotid surgery	++	++	-	+	+	+
Research	-	-	-	-	++	-

ACE, angiotension-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; NSA, National Stroke Association; NINDS, National Institute for Neurological Disorders and Stroke; EUSI, European Stroke Initiative; WHO, World Health Organization; UK, United Kingdom.
-=not mentioned; += mentioned; ++=recommendation given; +++=recommendation enforced/emphasis.

stroke care not only reduces human suffering but is also cost-effective.

PROBLEMS AND WEAKNESSES

The strength of the recommendations in the guidelines can be graded depending on the level of evidence. The most widely used grading scale for recommendations is the one developed by the AHA in 1994 (Table 17.4).

Although evidence-based data is rapidly evolving as a result of well-controlled randomized clinical trials, only a small percentage of all everyday clinical decisions in stroke management can be based on Level 1 evidence. Many important areas of care, including control of blood pressure, temperature, and blood glucose in acute ischemic stroke, are not yet covered by any evidence-based data. Equally problematic is the fact that in some points the guidelines are unequivocal or even contradictory. An example of this is whether to use standard or low-molecular-weight heparin in acute anticoagulation and, also, whether these drugs have a role in prevention of deep vein thrombosis in stroke patients. The AHA recommendations support the use of heparin or low-molecular-weight heparinoids in prevention of deep vein thrombosis, whereas the British guidelines do not.[19]

Due to differences in local health care resources, it is not possible to follow some recommendations. For example, due to lack of CT facilities or magnetic resonance imaging (MRI) facilities, laboratory blood tests, or non-invasive monitoring methods for 24 hours day, such guidelines, which underline radiological and laboratory diagnostic work-up on admission, cannot be followed in all hospitals treating stroke patients. Detailed guidelines help the clinician most but must be frequently updated, otherwise they will lose their

credibility and may be even harmful in providing outdated information. Obviously, no guidelines can be completely valid for more than a year or two

Table 17.4 Guideline strength: level of evidence and grade of recommendation by the AHA

Level of evidence	Type of evidence	Strength of recommendation
I	Date from randomized controlled trials (RCTs) with low false-positive (alpha) and low false-negative (beta) errors	A
II	Data from RCTs with high false-positive (alpha) or high negative (beta) errors	B
III	Data from nonrandomized concurrent cohort studies	C
IV	Data from nonrandomized cohort studies using historical controls	C
V	Data from anecdotal case series	C

due to the rapid development in stroke care. The EUSI guidelines were published in 2000, but there will soon be an updated version available. Some recommendations are too general to be helpful for everyday clinical decision making, such as the WHO consensus statement, which underlines the need for each stroke patient to receive immediate inhospital evaluation and care at a stroke unit but does not provide detailed instructions on how to care for stroke.

AVAILABILITY

To have a true impact on stroke care, the guidelines must be rapidly available and accessible, when needed. The world wide web (www) is the optimal media for the publication and distribution of guidelines, offering the possibility for more frequent updates than printed copies. The AHA Scientific Statements for stroke care are available on the AHA web site *www.american-heart.org*. The NSA guidelines can be found on the NSA web site *www.stroke.org*. The EUSI guidelines are available at *www.eusi-stroke.com/recommendations/rc*. The web is likely to be the main channel for the distribution of stroke guidelines in the foreseeable future.

It is often necessary to translate the guidelines into different languages at the same time as they are approved by national scientific organizations: this will ensure their wider use. The EUSI guidelines originally published in English have already been translated into German, French, Danish, and Polish; Spanish, Italian and Russian translations are on their way and will soon to be found at the EUSI web site. Accurate translations of guidelines into native languages is a great challenge but seems necessary for their widespread use and should also minimize the possibility of error and misunderstanding, especially in those countries where English is not generally spoken.

RELIABILITY

Published guidelines should preferably undergo a similar peer review process as original research manuscripts do in all major medical journals, and most scientific organizations have followed this principle. An exception to this rule may be the consensus statements of scientific workshops, which cannot be revised after the consensus has been reached.[20] The need for disclosure of possible conflicts of interest is obvious for anyone preparing sponsored guidelines and recommendations. Obviously, sponsorship may not under any circumstances have an impact on the content of any treatment guidelines. Unrestricted grant is the only acceptable sponsorship for the production of such guidelines. Independent scientific societies, health

authorities, and governmental agencies should preferably organize and fund the preparation and publication of guidelines, the quality and content of which should be ensured by peer review.

CONCLUSIONS

No matter whether the existing stroke guidelines and recommendations are evidence-based medicine at its best or just consensus opinions of experts, they probably have already improved the level of stroke care Most of the time, the principles of stroke guidelines can be applied without major investment in stroke centers. Conversely, no stroke patients should be treated in a hospital where the key principles of stroke care cannot be followed. Future stroke guidelines will most likely be more uniform than they are now, irrespective of their scope, authorship, or funding. Although the current guidelines differ in their scope and priority, they already provide a solid basis for the management of stroke.

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THE MAJOR GUIDELINES FOR MANAGEMENT OF STROKE PATIENTS CAN BE FOUND AT THE FOLLOWING WEB SITES:

National Institute for Neurological Disorders and Stroke (NINDS)
Acute Stroke Treatment Guidelines (1997)
http://www.ninds.nih.gov/health
European Stroke Initiative (EUSI)
The EUSI Recommendations
http://www.eusi-stroke.com/recommendations/rc
American Heart Association (AHA)
American Heart Association—Medical and Scientific Statements.
http://www.americanheart.org
Royal College of Physicians, UK
National Clinical Guidelines for Stroke (2000)
http://www.rcplondon.ac.uk/pubs/books/stroke/in dex.htm
Royal College of Physicians of Edinburgh, UK
Consensus Conference on Stroke Treatment and Service Delivery (2000)
http://www.rcpe.ac.uk/esd/consensus/stroke2000.html
3rd Karolinska Stroke Update
Stroke Consensus Statements (2000)
http://192.38.241.20
National Stroke Association (NSA)
http://www.stroke.org

18.
Experimental findings with important clinical implications for stroke treatment

Turgay Dalkara, Lorenz Hirt and Michael A Moskowitz

INTRODUCTION

Cerebral ischemia triggers a plethora of cellular and molecular events that promote cell death and tissue infarction. Mechanisms such as free radical production and lipid peroxidation, excitotoxicity and Ca^{2+} overload have become important therapeutic targets based on the results of preclinical pharmacology and two decades of stroke research using in-vivo and in-vitro models.[1–4] Each mechanism appears interrelated in a complex way. Programmed cell death, a genetic event of importance to ischemia, provides an additional and alternative mechanism to necrotic cell death and, until recently, was not considered relevant to neuronal loss in ischemia.[5–12]

Concepts concerning the feasibility of therapeutic intervention in acute stroke have evolved over the past 20 years. We now know that a subset of ischemic tissue (i.e., penumbra) can be salvaged by interventions aimed at either restoring blood flow and/or delivering neuroprotective agents.[13,14]Our concepts about the vulnerability of brain to ischemia have also significantly changed. We now know that the brain is especially prone to excitotoxicity and free radical damage because of the ubiquitousness of gluta-matergic synaptic transmission and the high rate of oxidative metabolism.[1–4] Demand unmatched by substrate supply seems to provide only one explanation for the exquisite vulnerability of brain tissue; it is well accepted that neurons continue to die several days after successful restoration of blood flow to ischemic tissue (delayed neuronal death).[15,16] Considerable effort has therefore been expended to discover the mechanisms by which restoration of blood flow during recirculation promotes cellular injury. In view of the recent success of thrombolysis in acute stroke, prevention of reperfusion injury has become an especially hot topic in drug research.[17]

In the past decade, several drugs affording neuroprotection were developed based on targets defined by cell culture, tissue slices, and whole animals: e.g., *N*-methyl-D-aspartate (NMDA) receptors, free radicals, and growth factors. However, the most difficult of all challenges still remains; i.e., the successful transfer of preclinical treatments to improve neurologic outcome in patients. This may not be achieved easily, as evidenced by negative results in numerous clinical trials to date.[18] The problems are multiple, including shortcomings of the drug, the drug target, the preclinical testing, and the clinical trial design. To achieve success, each must be modified to achieve a seamless transition. For example, the clinical trial design should observe the time window measured in experimental studies. Patients with delayed stroke onset were recruited for clinical trials based on the premise that ischemic lesions evolve over many hours. Although ischemic lesions evolve over many hours, NMDA receptor antagonists all have a very short post-occlusion time window in animal models. Moreover, there is no experimental or clinical evidence showing that NMDA receptors remain overactive during these extended time periods. More importantly, patients were not

selected based on imaging criteria showing the presence of salvageable tissue at the time of drug administration. Enrolling patients after establishing the presence and extent of rescuable tissue may decrease the number of subjects required and reduce the cost and increase the success of these trials.

MECHANISMS OF ISCHEMIC CELL DEATH

It is generally accepted that whereas some cells readily die by excitotoxic swelling, osmotic disruption, and necrosis at the onset of focal ischemia, others die by apoptosis, and yet still others die by a combination of apoptosis and necrosis. Recent evidence suggests that the apoptotic and necrotic death pathways are not entirely independent.[19,20,20a] Early phases of cell death may involve a common pathway and, when energy levels are severely compromised, cells dying by apoptosis may divert to necrosis. It has been proposed that mitochondria play a role in choosing between the apoptotic and necrotic pathways, depending on the severity of insult.[21] Following moderate but irreversible injury, mitochondria can retain their membrane potential (at least initially) so they can continue ATP synthesis but release cytochrome c and other pro-apoptotic factors to initiate the caspase cascade. Severe injury leads to loss of mitochondrial membrane potential, swelling, and rupture of the mitochondrial membrane and collapse of oxidative phosphorylation and, hence, necrosis. It is thought that opening of the mitochondrial permeability transition pore plays a role in both cell death types by releasing mitochondrial macromolecules into cytoplasm and by the loss of homeostasis and intramitochondrial milieu, although not mandatory for apoptosis.[21]

Linnik et al.[6] provided early pharmacological evidence based on the ability of the protein synthesis inhibitor cycloheximide to reduce brain injury. Cellular features of apoptosis have been documented after focal and global ischemia including cytoplasmic shrinkage, chromatin condensation, nuclear segmentation, and apoptotic bodies,[10,22–24] although electron microscopic studies indicate that ischemic neuronal death is characterized by a mixture of apoptotic and necrotic ultrastructural changes.[25–27] Nevertheless, a substantial reduction in infarct volume after treatment by caspase inhibitors strongly suggests that apoptotic cascade is activated in injured surviving cells.[28,29]

DNA laddering, a hallmark of apoptotic cell death, was also shown by gel electrophoresis along with terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL) staining.[5–9] Several characteristic biochemical markers such as cleavage and activation of caspase-1 and caspase-3 and cleavage products of gelsolin and actin (cytoplasmic substrates of caspase-3) as well as upregulation of Bax/Bcl-2 ratio were found in ischemic brains of experimental animals.[10,12,23,30–32] However, some biochemical markers conventionally thought to indicate necrosis (e.g., cathepsins, calpain) are also found to be activated in ischemic cells and inhibition of them also confers resistance to ischemic injury, suggesting a complex interplay between apoptotic and necrotic death pathways in cerebral ischemia.[33]

It should also be noted that the cell death phenotype may vary significantly, depending on the species, age, cell type, triggering factors, and coexisting conditions in the tissue. Therefore, the biochemical characteristics of apoptosis in humans after ischemia, as has been demonstrated for several neurodegenerative diseases and after spinal cord injury, remain to be elucidated in future studies. Several factors have been identified that can trigger either death forms after an ischemic injury. A brief overview of those neurotoxic mechanisms, which have been well characterized in the past two decades, is now given.

EXCITOTOXICITY

Olney and Sharpe[34] first proposed that high amounts of excitatory amino acid glutamate may be toxic to neurons; they coined the term excitotoxicity in 1969. It is now well established that excessive amounts of

excitatory amino acids and their analogs cause neurodegeneration both under in-vitro and in-vivo experimental conditions.[35,36] Demonstration of high extracellular levels of glutamate and aspartate during ischemia led to the suggestion that excitotoxicity may play a significant role in cerebral ischemia.[37] Although our knowledge of excitotoxicity in cerebral ischemia still remains incomplete, a reduction in infarct volume can be achieved by administering NMDA- and non-NMDA-type glutamate receptor antagonists in experimental animals.[18] Inhibition of expression of NMDA receptor NR1 subunit by antisense oligodeoxynucleotides in the rat[38] or knocking out the gene encoding the NR2 subunit of the NMDA receptor in the mouse[39] also leads to smaller infarcts after middle cerebral artery (MCA) occlusion.

A brief but intense exposure to glutamate can cause delayed cell death through NMDA receptor-mediated mechanisms.[40] Delayed death of neurons results from excessive Ca^{2+} influx through the NMDA receptors.[1,2] Activation of several Ca^{2+}-dependent enzymes such as phospholipase A2 and calpain plus free radical generation may promote delayed neuronal death. Since a generalized increase in intracellular Ca^{2+} does not necessarily lead to cell death, it is proposed that a localized increase in Ca^{2+} in the vicinity of NMDA receptors is critical for activation of lethal processes such as the nitric oxide (NO)—generating enzyme, nitric oxide synthase (NOS).[41] There is substantial evidence that about half of the NMDA-mediated neuronal toxicity can be blocked by NOS inhibitors, and neurons lacking expression of neuronal type NOS (nNOS) are more resistant to NMDA toxicity.[42,43] One of the submembrane proteins involved in receptor clustering, PSD-95, is required for efficient coupling of NMDA receptor activity to NO synthesis as suggested by the resistance of PSD-95 mutant neurons to NMDA toxicity.[44] Mitochondria take up large amounts of Ca^{2+} during exposure to excitotoxins.[45,46] There is now considerable evidence suggesting that mitochondrial Ca^{2+} uptake can trigger excitotoxic neuronal death[46–48] by causing energy depletion, cytochrome *c* release, and increased generation of superoxide.[49] Cytochrome *c* may initiate the apoptotic cascade. Activation of caspase-3 after exposure to glutamate has been demonstrated in some but not all studies.[50–52] It may depend upon the duration and intensity of glutamate exposure.[53] Activation of non-apoptotic protease calpain is *readily* detectable after exposure to NMDA. It has been proposed that calpain I may inhibit the ability of cytochrome *c* to activate the caspase cascade, since inhibition of calpain activity restored a caspase-3-like protease activity in the hippocampal neuron cultures after NMDA exposure.[52]

Rapid swelling caused by excitatory amino acids and their analogs is attributed to Na^{+} and accompanying water and Cl- influx through activation of non-NMDA and NMDA receptors.[35] Contrary to NMDA receptor-mediated mechanisms of cell death, non-NMDA (AMPA/kainate) receptors require prolonged stimulation for neuronal death to occur.[54] This process may also involve Ca^{2+}, which may enter neurons through nearby voltage-gated calcium channels activated by membrane depolarization and, in some brain regions, through AMPA/kainate receptors that lack the GluR2 subunit.[55,56] Consistently, mice that overexpressed the AMPAR subunit (GluR2flip) sustain increased cerebral injury after focal ischemia.[57] As loss of immunoreactivity of the microtubule-associated protein-2 indicates, localized swelling of dendrites upon glutamate exposure may disrupt the cytoskeleton, which is inhibited by non-NMDA as well as NMDA receptor antagonists, and may induce apoptosis.[58] Increased acidity during ischemia may inhibit NMDA receptor overactivity, although ischemiainduced glutamate release and depolarization provides a favorable milieu for NMDA receptor activation.[59] Rapid loss of NMDA currents during in-vitro and in-vivo ischemia has been demonstrated.[60–62] However, initial exposure to excess glutamate before inactivation of NMDA receptors may be sufficient to trigger the processes that are sustained under energy compromised conditions and lead to cell death. Moreover, favorable conditions for NMDA receptor overstimulation may be prolonged in the penumbra.[63]

Perhaps for these reasons, NMDA-type receptor antagonists or channel blockers reduce the size of focal ischemia in many animal models. They seem less effective in models of global ischemia where severe

acidity prevails.[14] It was also proposed that recurrent spreading depression occurring in the peri-infarct zones exposes the tissue to repeated excitotoxic and other metabolic stresses.[63] The fact that brief glutamate exposure can trigger the cell death cascade suggests that inhibiting events following ligandreceptor binding may be more efficacious than receptor antagonists during ischemia. In that regard, calpain inhibitors may be promising neuroprotective agents.[64]

Ca^{2+} CYTOTOXICITY

Ischemia leads to a rapid rise in intraneuronal free Ca^{2+} (from approximately 100 nmol/1 to 30 μmol/1) and an associated decrease in extracellular Ca^{2+}.[65,66] NMDA receptor ion channel and voltage-gated Ca^{2+} channels have been proposed as putative pathways for Ca^{2+} entry because both channels can be activated by ischemia-induced depolarization.[1,67] Na^+/Ca^{2+} exchanger may also transport Ca^{2+} inside while it attempts to extrude intracellular Na^+ accumulated by failure of Na^+/K^+ ATPase. The latter mechanism seems to be particularly important in axons, because an inhibitor of Na^+/Ca^{2+} exchanger is reportedly protective against optic nerve ischemia, and axons lack NMDA or voltage-sensitive Ca^{2+} channels.[68] However, a significant component of Ca^{2+} rise comes from intracellular stores and, in line with this, dantrolene, which blocks Ca^{2+} release from the endoplasmic reticulum, decreases infarct size in experimental models of focal ischemia.[69] Like NMDA receptors, voltage-gated Ca^{2+} channels may be inhibited during the course of ischemia,[60,62,72] yet the initial Ca2+ rise in the vicinity of these channels may be critically involved in the subsequent cascade of events leading to cell death.

Cells can tolerate large increases in intracellular Ca^{2+} under physiological conditions by extruding or sequestering excess Ca^{2+}. For example, during spreading depression neurons become heavily loaded with Ca^{2+} without any detrimental consequences.[71] Similarly, if mitochondria are depolarized and loaded with Ca^{2+} without depleting cytoplasmic ATP, survival of the granule cells is greatly enhanced.[46] However, under energy compromised conditions, pumps and sequestration mechanisms fail and a sustained rise in intracellular Ca^{2+} may trigger neuronal death by activating lipases, proteases, and endonucleases, and by increasing free radical production.[3] Free radical production, in turn, can inhibit Ca^{2+} sequestration to generate a vicious cycle. It has also been proposed that excess cycling of Ca^{2+} across mitochondrial membranes may further disrupt already jeopardized mitochondrial function, deepening energy failure and enhancing free radical formation.[72] Although the Ca^{2+}-induced cell death hypothesis remains most attractive and was put forward more than 20 years ago, a causal relationship between intracellular Ca^{2+} rise and cell death and the cascade of events leading to cell death has not been established unequivocally. Increasing evidence suggests that rather than a generalized increase in intracellular Ca^{2+} (Ca^{2+} load hypothesis), increases around the macromolecules involved in Ca^{2+} signaling pathways (source specificity hypothesis) are more critical to Ca^{2+} neurotoxicity.[41] Moreover, cytoplasmic Ca^{2+} may also stimulate expression of specific genes as well as activation of some enzymes that provide cytoprotection.[73] The actin filament-severing protein gelsolin negatively modulates Ca^{2+} influx through NMDA receptors and voltage-gated Ca^{2+} channels. Hence, gelsolin-null neurons have enhanced cell death and rapid, sustained elevation of Ca^{2+} levels following glucose/oxygen deprivation, and larger infarcts develop in gelsolin-null mice after reversible MCA occlusion.[74]

FREE RADICALS

Oxygen free radicals (e.g., hydroxyl radical, superoxide anion) are highly reactive species that avidly bind and damage nucleic acids, lipids, carbohydrates, and proteins. Mitochondria, a free radical generator, DNA

repair enzymes, and some transcription factors can also be a target for free radical damage.[4] Under basal conditions, oxygen radicals can act as cell signaling messengers. Excessive amounts and/or a decrease in the efficiency of detoxification mechanisms are required for acute cell injury. Release of bound iron from tissue stores may significantly increase free radical generation. Levels of endogenous free radical scavenging enzymes and oxidized glutathione drop during ischemia, whereas free radical production increases during reperfusion. High levels of oxygen radicals can be generated by cyclooxygenases, phospholipase A_2, NO synthases, xanthine oxidase, xanthine dehydrogenase, NADPH oxidase, monoamine oxidase, Fenton and Haber-Weiss reactions, as well as by mitochondria in the endothelium, neurons, and glia during ischemia and particularly during reperfusion. There is evidence suggesting that free radical production contributes to breakdown of the blood-brain barrier and brain edema to movement of white cells into the ischemic zone and alterations in blood flow.[4,75] Inflammatory cells attached to the endothelium or invading the brain tissue are a rich source of oxygen radicals. Endothelial cells appear to be a primary target of free radical damage. A significant NO and superoxide generation and peroxynitrite formation in the endothelium has recently been demonstrated after cerebral ischemia/reperfusion and proposed as one of the major mediators of blood-brain barrier breakdown.[76,77]

Scavengers of free radicals and/or inhibitors of lipid peroxidation protect the brain after ischemia, particularly during reperfusion. In fact, mice overexpressing superoxide dismutase (SOD) are more resistant to neuronal death after transient cerebral ischemia associated with reperfusion injury[78] and, conversely, larger infarcts develop in mice deficient in SOD expression.[4] As might be anticipated, NADPH oxygenase knockouts or mice overexpressing glutha-tione peroxidase show increased resistance to ischemic brain damage.[4] The 21 amino-steroid tirilazad mesylate reduces stroke damage in models of transient ischemia.[4,79] Superoxide dismutase linked to polyethylene glycol (PEG-SOD) reduces stroke size in animal models in the presence of reperfusion.[80,81] 'Spin traps' and other free radical scavengers that readily penetrate into the brain might impart even greater brain protection than PEG-SOD or tirilazad, which work primarily within the vasculature.

NITRIC OXIDE

NOS-containing neurons are resistant to NMDA toxicity as well as to destruction in Huntington's disease and ischemia.[82,83] These neurons represent only 1–2% of all neurons in the cerebral cortex, corpus striatum, and hippocampus; however, they extensively branch and are thought to kill neighboring neurons when NO is produced in excessive amounts.[84,85] Activated leukocytes invading the brain may also be a source of NO generation. Contrary to transient NO pulses that serve various roles in cell signaling, high amounts of NO can cause cytotoxicity by inhibiting mitochondrial respiration, depressing glycolysis, and reducing intracellular glu-tathione levels. In addition to disrupting cellular metabolism, NO inhibits DNA synthesis by depressing ribonucleotide reductase activity.[86] NO also damages DNA structure in several possible ways, including DNA nitration, deamination, and oxidation.[86]

Formation of peroxynitrite anion (ONOO-) by reaction of NO with superoxide anion may be a major pathway through which NO mediates cell death.[87,88] Peroxynitrite is a strong oxidant and decomposes to highly reactive oxygen species, a hydroxyl radical-like product, and nitrogen dioxide. Peroxynitrite anion also facilitates S-nitrosylation of tyrosine residues in proteins. Especially in a superoxide-rich environment, NO may release intracellular iron, thereby triggering the Haber-Weiss reaction and formation of reactive oxygen species.[86] In summary, NO, a weak free radical, can readily be converted to more toxic oxygen species, especially under conditions of increased oxidant stress. Available evidence indicates that NO and peroxynitrite can trigger both apoptotic and necrotic cell death, depending on the severity of injury.[89]

It is believed that constitutive NOS activity increases during ischemia due to a rise in intracellular Ca^{2+}. Constitutive NOS is activated by intracellular calcium concentrations slightly above the resting level and is maximally stimulated at 0.5 μmol/1, suggesting that it is fully active during ischemia.[90,91] In line with this hypothesis, a striking increase in brain NO levels has been detected at the onset of MCA occlusion by several methods.[91,92] However, available evidence suggests that constitutive NOS activity decreases shortly after its activation at the onset of ischemia. A second wave of NO and peroxynitrite generation may take place during reperfusion when constitutive NOS is reactivated.[93,94] Although NO formation in endothelium may counteract clogging within microcirculation during reperfusion, recent evidence suggests that the net outcome is detrimental, due possibly to peroxynitrite-mediated blood-brain barrier disruption and edema formation.[77] A late, but sustained, increase in NO levels may also occur due to expression of inducible NOS within microglia and invading inflammatory cells 24–72 hours after the induction of reversible ischemia.[95] It is possible that NOS activity may differ between the core and penumbra. The penumbra, which has a residual oxygen supply, may be exposed to repeated surges of NO, especially during recurrent spreading depression.[96] However, even a short exposure to NO may have a detrimental effect on neuronal survival by further compromising cellular metabolism and/or DNA damage, similar to NMDA receptor-mediated neurotoxicity in ischemia as discussed above.[62]

During the immediate period following focal cerebral ischemia, NO production may improve blood flow and be neuroprotective. Indeed, infusion of L-arginine dilates pial vessels via an NO-dependent mechanism, increases regional cerebral blood flow (rCBF) in normal as well as in ischemic brain, and reduces infarct size.[97] L-arginine leads to electrocorticogram recovery if blood flow enhancement exceeds the functional flow threshold of approximately 30% of preischemic level.[98] Of importance, L-arginine infusion did not augment blood flow in endothelial nitric oxide synthase (eNOS) knockout mice." However, this favorable action of L-arginine is not sustained during ischemia, due to rapid inactivation of eNOS. In addition to its blood flow enhancing effect, endothelial NO production may also improve microcirculation by reducing platelet aggregation and leukocyte adhesion.[100,101] Sodium nitroprusside was shown to improve rCBF in ischemic brain areas and inhibit platelet aggregation and adhesion molecule expression in stroke patients.[102] Selective eNOS upregulation might also provide a useful treatment strategy to enhance vascular NO production. HMG-CoA reductase inhibitors (statins) have recently been shown to selectively upregulate NOS, with an action independent of their cholesterol-lowering effect, and confer protection in rodent stroke models.[103] Supporting this idea, a clinical trial (CARE study) demonstrated that stroke incidence decreased by 31% in 4159 subjects treated chronically with pravastatin.[104] Interestingly, a point mutation in the *eNOS* gene has recently been reported to be associated with coronary artery spasm.[105]

In line with this pharmacological evidence, larger infarcts developed in knockout mice that do not express the gene for endothelial NOS *(eNOS)* after 24-hour permanent MCA occlusion.[106] *eNOS* mutants developed more pronounced rCBF reductions in corresponding brain regions after MCA occlusion and exhibited pro-portionally lower rCBFs at reduced perfusion pressures during controlled hemorrhagic hypotension. These unfavorable alterations in blood flow regulation in *eNOS* knockouts plus a greater susceptibility to platelet and neutrophil damage may explain their sensitivity to ischemia. On the other hand, the neuronal *NOS* knockouts developed infarcts smaller than the wild-type mice when subjected to permanent or transient MCA occlusion.[107,108] Similar protection was also detected after global ischemia.[109] These data from mutant mice clearly demonstrate that lack of neuronal NO generation is associated with reduced ischemic damage after MCA occlusion.

In summary, data from NOS null mice indicate that NO possesses a dual role in focal cerebral ischemia. Neuronal NO overproduction may be neurotoxic, whereas endothelial NO may protect brain tissue by improving rCBF and other hemodynamic factors. However, during reperfusion, endothelial NO generation

and peroxynitrite formation may cause blood-brain barrier damage.[77] These findings are consistent with published dose-dependent effects of NOS inhibitors[110] and emphasize the need to develop selective inhibitors of the neuronal isoform to protect the brain from injury. In fact, experimental studies using selective nNOS inhibitors, 7nitroindazole[111] or ARL 17477,[112] have reported neuroprotection.

CASPASE-MEDIATED CELL DEATH

Apoptotic cell death can be mediated through several pathways. Death signals can be transduced from the extracellular medium into the cell via death receptors located on the cell surface. Death signaling cascades may also be initiated intracellularly from mitochondria, DNA, or endoplasmic reticulum. Activation of all these pathways has been demonstrated by detecting biochemical alterations taking place in these pathways during focal as well as global ischemia (see Endres et al.[32] for review).

Detection of the active form of caspase-8 in neurons suggests that the death receptors are activated upon ischemic injury.[113] Upregulation of Bax and down-regulation of Bcl-2/Bcl-xL levels and formation of Bax/Bcl-xL dimers have also been demonstrated at the onset of ischemia, which may account for the activation of the mitochondrial pathway.[22,114] Downstream events to translocation of Bax to the mitochondria, such as release of cytochrome *c* and activation of caspases-9 and -3, have been detected as well.[22,30,115,115a] That the Bid knockout mice are resistant to ischemia suggests that there is a cross-talk between these two pathways during ischemic cell death.[116] Bid, following its cleavage by caspase-8, translocates to mitochondria and initiates caspase-3-mediated apoptosis. Several markers of DNA damage-induced apoptosis (upregulation of p53, GADD45, MdM2) have also been detected in ischemic brains.[32] In all apoptotic pathways, a group of caspases called 'executioner caspases' appear to be dismantling several cellular structures by their proteolytic activity following their activation. Caspases have a wide range of targets, cleavage of some of which is thought to contribute to the development of morphological features characteristic of apoptosis. Several cleavage products of caspase activity (gelsolin, actin, PARP) have also been detected in brains after ischemia.[31,74,117]

Overexpressing anti-apoptotic proteins (e.g., Bcl-2) or knocking out genes encoding pro-apoptotic proteins (e.g., Bid, Bax, p53, caspases3, -11) in transgenic animals confers resistance to ischemia,[4,32,118,119] emphasizing the role of apoptotic mechanisms in ischemic cell death. Similarly, pharmacological inhibition of caspase activity leads to a reduction in cell death in focal as well as global ischemia[28,29] and appears to be a promising therapeutic target. Loddick et al.[120] and Hara et al.[121] reported that peptide inhibitors of caspases z-VAD and z-DEVD protected brain from ischemic injury and improved neurologic deficits in rats and mice. Caspase inhibitors were effective if administered up to 1 hour after reperfusion following 2-hour MCA occlusion. After milder ischemia (30 min), z-DEVD-fmk protected the brain when injected up to 9 hours after restoration of blood flow.[122] The 9-hour treatment window corresponded to the onset of both DEVDase activation and caspase-3 cleavage, suggesting that activation of events downstream to caspase-3 may represent irreversible injury. Although longer than for NMDA receptor antagonists, this time window is still shorter than desirable for clinical practice. Recently, a synergy was reported between an NMDA receptor antagonist and caspase inhibitors.[123] Not only did combination of subthreshold doses of two agents protect against ischemia but also the therapeutic window for caspase administration was extended. A similar synergy was also observed between a growth factor (bFGF) and caspase inhibitors.[124]

CELL SURVIVAL PATHWAYS

As described above, overexpression of the anti-apoptotic protein Bcl-2 inhibits cell death in response to a wide variety of insults. The *bcl-2* gene encodes an approximately 26 kDa protein that is found mainly on the membranes of mitochondria, the endoplasmic reticulum, and the nucleus.

When *bcl-2* is overexpressed in transgenic mice, these mice are resistant to cell death and brain injury caused by focal and global cerebral ischemia.[125,126] The mechanism of action of Bcl-2 (and other closely related family members, e.g., Bcl-x) is linked with their ability to protect mitochondria against several forms of injury. This occurs by potentiating maximal Ca^{2+} uptake of the mitochondria, presumably by preventing the opening of the mitochondrial transition pore (MTP).[127] Bcl-2 also strongly protects against freeradical-mediated cell death. These effects are likely to protect against necrotic cell death. Bcl-2 also enhances survival via an anti-apoptotic mechanism by preventing cytochrome *c* release from the mitochondria, and thereby inhibiting the mitochondrial pathway of caspase activation.[128]

A potent survival-promoting molecule for neurons and other cell types is bFGF, which is able to protect neurons *in vitro* and *in vivo* from a variety of toxic effects (e.g., NO, anoxia, Ca^{2+} ionophores[129]) and, moreover, protects neurons against apoptotic cell death. Recently, it has been shown that administered bFGF upregulates the expression of Bcl-2 in the ischemic penumbra after focal cerebral ischemia in rats, which may be one way in which bFGF can reduce neuronal cell death.[130] bFGF protects synergistically with caspase inhibitors against cerebral injury after transient focal cerebral ischemia, by reducing caspase-3 activation.[124] Endogenous neurotrophic factors, neurotrophin 4 (NT 4) and brainderived neurotrophic factor (BDNF), also exert a protective influence in cerebral ischemia: mice lacking one allele of BDNF or both alleles of NT 4 are more vulnerable to ischemic injury.[131] Exogenous administration of NT 4 or BDNF, which both bind to the TrkB receptor (tyrosine kinase coupled receptor B) are protective in several animal models of cerebral ischemia.[132–135]

The serine-threonine protein kinase, Akt, is a well-established survival factor that exerts antiapoptotic effects by preventing the release of cytochrome *c* from mitochondria (for review, see Testa and Bellacosa[136]): it also inactivates forkhead transcription factors that are known activators of pro-apoptotic genes such as the Fas ligand. Akt directly phosphorylates the proapoptotic factors BAD and pro-caspase-9, resulting in their inactivation. It further activates IγB kinase, a positive regulator of NF-γB, causing transcription of the anti-apoptotic genes regulated by nuclear factor kappa B (NF-γB) (see below). Excitingly, Akt is activated after focal cerebral ischemia in the rat.[137,138] VEGF and the receptor-coupled signal transduction pathways involving phosphatidylinositol 3'-kinase and Akt are induced, suggesting they could participate in neuroprotective responses in ischemia, but so far mechanisms are unknown.

NUCLEAR FACTOR-KAPPA B AND INFLAMMATION

Nuclear factor-kappa B is a ubiquitously expressed transcription factor involved in apoptosis, the cell cycle, inflammation, and the immune response.[139] It is an inducible transcription factor important for glial and neuronal function in the central nervous system. NF-γB consists of five known subunits—p50, p52, RelA (p65), RelB, and cRel—that associate to form homo- or heterodimers. In nonstimulated neural cells, the dimer of NF-γB (typically, p50 and p65) is bound by the inhibitory factor IγB, which masks a nuclear localization signal, thereby maintaining the complex in the cytoplasm. Upon stimulation, IγB is degraded in the proteasome unmasking the nuclear translocation domain and NF-γB is translocated to the nucleus, where it activates a wide variety of genes by binding to response elements in their promoters.[139] NF-γB is a crucial transcription factor in focal cerebral ischemia, being induced dramatically in the brains of animals after

experimental ischemia.[140,141] It is activated 6–96 hours after ischemia in neurons and in certain studies in astrocytes, depending on the model and the species.[142–144]

Many of the genes induced in cerebral ischemia are regulated by NF-κB *in vitro,* including cell adhesion molecules, chemokines, *iNOS, COX-2, p53, bcl-2, bcl-x,* and *Fas-L.*[145] Recently, it has been shown that NF-κB activates transcription after cerebral ischemia *in vivo*.[143,146]

Many studies have investigated the role of NF-κB in ischemic brain injury. Several lines of evidence indicate that NF-κB plays a role in promoting cell death after ischemia.[142] Injurious cytokines are strong activators of NF-κB, which in turn is an activator of several pro-apoptotic genes (for example the *Fas-L*). Inhibition of NFκB activity by treatment with proteasome inhibitors (for example, CVT-634) reduces infarct volumes in a rat model of transient focal ischemia.[147] Neuroprotection is also observed after aspirin administration, which acts as an inhibitor of NF-κB.[148]

Further evidence that NF-κB has an overall role in promoting cell death comes from null mice lacking p50 subunits which have significantly smaller lesions in focal cerebral ischemia.[143]

Recently, however, it has been shown that NF-κB is also capable of activating anti-apoptotic genes: for example, *MnSOD* and *bcl-2*.[149] In this respect it has been reported that TNFγ receptor null mice are more susceptible to ischemic cell damage. This particular protective effect is thought to be mediated by NF-κB-induced expression of the free radical scavenger SOD enzyme.[150] Experiments *in vitro* have demonstrated that NF-κB expression in neurons makes them more resistant to glucose deprivation and glutamate excitotoxicity.[151] Furthermore, the expression of the neuronal apoptosis-inhibiting protein (NAIP) is responsive to NF-κB, and overexpression of NAIP renders neurons resistant to ischemia *in vivo*.[152,153]

Although different experimental paradigms might be the reason for conflicting roles of NFκB, it is possible that NF-κB has dual actions, either pro-apoptotic or anti-apoptotic, and resulting effects are dependent upon the circumstances in which it is activated.[154] NF-κB therefore promises to be an interesting factor for the design of pharmacological agents that might alter or push pathways toward cell survival.

INFLAMMATION

Cerebral ischemia triggers an inflammatory cascade that is driven by a complex array of genes (see Iadecola and Alexander,[155] for a detailed review). Inflammation was first demonstrated in autopsy material 12–72 hours after acute stroke and later corroborated in animal models of ischemia. There is mounting evidence that leukocyte infiltration contributes to late ischemic injury progression and may negatively impact neurologic outcome. In rats, for example, depletion of neutrophils reduces lesion size significantly,[156] as does inhibiting leukocyte adhesion and infiltration by an anti-ICAM antibody after reperfusion.[157] Moreover, ICAM and P-selectin knockout mice are less susceptible to ischemic damage.[158] However, disappointingly, an anti-adhesion molecule 1 antibody did not improve outcome in patients with ischemic stroke, although the study design was probably flawed (see Iadecola and Alexander[155] for discussion). Cytokines such as interleukin-1γ (IL-1γ) and tumor necrosis factor-γ (TNF-γ) can produce neuronal damage directly (reviewed in Barone and Feuerstein[159]) but, as described above, TNF-γ receptor null mice show increased susceptibility to ischemic damage and TNF-γ is required for protection from sublethal ischemic injury (pre-conditioning).

Inflammatory cells cause direct toxic effects on neurons by generating oxygen free radicals, and activating inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). iNOS is induced in infiltrating neutrophils and in cerebral blood vessels and generates toxic levels of NO. Results using iNOS inhibitors and iNOS null mice suggest that iNOS is an important enzyme in delayed ischemic damage. Like iNOS, COX-2 is up-regulated in a delayed manner, and inhibitors of COX-2 attenuate ischemic injury. It

has been shown that iNOS-derived NO is required for the full extent of COX-2 neurotoxicity.[155] The iNOS and COX-2 transcription factors, NF-γB and IRF-1, play a major role in the later stages of ischemic brain injury. It should be pointed out that iNOS and COX-2 contribute to tissue damage in focal cerebral ischemia, but can be protective in other models of brain damage.[155] To a great extent, outcome depends upon the amount and location of the generated NO.

SUMMARY

This chapter briefly introduces some of the most important susceptibility elements contributing to cell and tissue outcome after ischemic injury. An understanding of these factors together with their role in the regulation of the cerebral circulation may prove useful in generating new treatments for ischemic injury and its repair.

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19.
What is the future of imaging in acute stroke?

Max Wintermark, Pierre Schnyder, Reto Meuli and Julien Bogousslavsky

INTRODUCTION

Strokes are the third leading cause of death, after cardiovascular diseases and cancers. Each year, they are diagnosed in 750 000 patients and contribute to at least 150 000 deaths in the United States.[1] Strokes have a high personal and social impact because of the important disability rate they are responsible for.

Thrombolysis, which is now an approved therapy for acute human stroke,[2–4] intends to rescue the penumbra and to reduce the final infarct size, and thus the final handicap. Present indications for intravenous thrombolytic therapy relate to the time interval since the onset of symptoms (less than 3 hours); the non-contrast cerebral computed tomography (CT) findings (absence of cerebral hemorrhage and a cerebral hypodensity extending to less than one-third of the middle cerebral artery (MCA) territory); and absence of contraindications constituting risk factors for intracranial hemorrhage.[2,3] However, even with such restrictive criteria, thrombolysis is associated with a significant risk of intracranial bleeding (up to 15%),[5,6] and selection of patients to be included in thrombolysis protocols according to the present criteria is not completely satisfactory. This is probably related to there being neither an absolute viability threshold nor an absolute time window of tissue viability but rather an intricate model of cerebral tissue viability that includes four factors: a time factor, a hemodynamic factor, a tissue factor, and an intervention factor.[7] Hence, individual imaging assessment of brain perfusion in stroke patients, affording the delineation of infarct and penumbra and the evaluation of their relative extents, has been suggested as a possible selection criterion for treatment. Indeed, thrombolysis achieved in cases of extended cerebral infarcts with limited penumbra would not only have little benefit but would also increase the risk of intracranial bleeding.[8–11]

CONVENTIONAL CT TECHNIQUE

The CT technique has the major advantage of being readily available and accessible in the emergency setting, which is not the case of magnetic resonance imaging (MRI), at least in the majority of medical centers.

Conventional cerebral CT has been demonstrated to have a low sensitivity to acute cerebral ischemia of about 75% during the first 6 hours when compared with DWI-MR.[12–16] This sensitivity can be significantly improved if the clinical history and results of the neurologic examination are available.

CT hypodensity in the first 6-hour period is highly specific for irreversible ischemic brain damage[17]and its extent is predictive of the risk of hemorrhagic transformation.[18] On the other hand, there is controversy about the prognostic value of early CT signs of cerebral ischemia and the patient's global outcome after stroke. Some authors have attempted to design a systematic analysis method for assessing conventional CT

in acute stroke, leading to a score they have demonstrated as prognostic.[19,20] Others have found that there is no straightforward relationship between early ischemic changes on conventional CT and adverse outcome after recombinant tissue plasminogen activator (rt-PA) treatment.[21,22]

DIFFUSION-WEIGHTED AND PERFUSION-WEIGHTED MRI

Diffusion-weighted imaging (DWI) is one of the MR imaging techniques that has gained popularity in the field of stroke management and that has been implemented in most MR scanners. DWI has assumed the role of a valuable imaging technique because it provides information that is not available on standard T1- and T2-weighted MR images. It has the ability to show hyperacute brain ischemia within minutes after stroke onset, whereas CT or T2-weighted MR images become positive only after several, usually 5 or 6, hours after stroke onset.[23–27] In an animal model, sensitivity of DWI in the detection of acute infarction has amounted to 60% within 50 min and 100% within 2 hours after symptomatology onset.[28,29] During the first 48 hours after symptom onset, the addition of DWI to conventional MRI in acute stroke patients improves the accuracy of identifying acute ischemic brain lesions from 71% to 94%.[30] There are, however, emerging reports on the absence of early DWI abnormalities in later-on infarcted tissue.[31–35] Another major concern is the question of the true reversibility of restricted diffusion seen on admission diffusion-weighted images,[31,36–39] especially when therapeutical strategy selection relies on the distinction between irretrievable infarct and salvageable penumbra.

Perfusion-weighted magnetic resonance imaging (PWI) by bolus tracking demonstrates hemodynamic abnormalities and may provide additional information to DWI for the early characterization of hyperacute cerebral ischemia. The initial PWI abnormality is usually larger than the initial DWI abnormality. It has been postulated that the DWI/PWI mismatch may identify cerebral regions in which the perfusion deficit is not below the level critical for maintenance of the energy-dependent Na^+,K^+-ATPase pumps. These regions might reflect salvageable penumbra and represent a potential target for thrombolytic therapy. DWI and PWI have been shown to correlate with the final infarct volume. By following the progression of the lesion and determining the factors that influence its development, DWI and PWI have thus the potential to be prognostic tools and to predict neurologic outcome.[40–50]

PERFUSION CT

The advent of functional CT or perfusion CT affords a renewal of CT techniques, again able to advantageously compete with DWI-/PWI-MR and to predict acute stroke patients' outcome, and this all the more since such techniques are easier to perform. They are indeed more widely available and accessible in the emergency setting, and less time consuming.

Perfusion CT relies upon the extraction of functional rather than morphological information from the CT data. Actually, there is not one single perfusion CT technique, but several; schematically, they can be divided into two categories.

The first perfusion CT technique, referred to as whole brain perfusion CT, is able to evaluate the whole brain perfusion but can only provide information related to cerebral blood volume. Thus, the whole brain perfusion CT technique can assess cerebral infarct but not penumbra, which is the target of thrombolytic drugs.[51–53]

The second perfusion CT technique, referred to as dynamic perfusion CT, involves dynamic acquisition of sequential CT slices in a cine mode during intravenous administration of an iodinated contrast material. Using multislice CT technology, its anatomical coverage can be increased up to a 4-cm thickness of brain

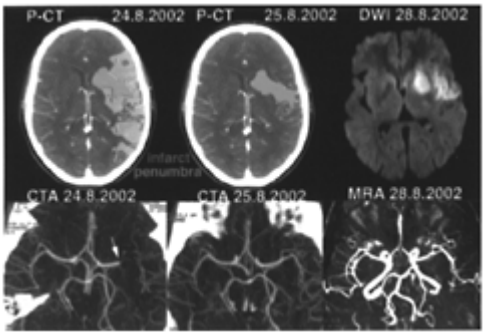

Figure 19.1 (a) Admission perfusion CT demonstrates mixed infarct and penumbra in the left sylvian territory in a patient with a right hemisyndrome, whereas (b) CT angiography (CTA) relates it to an occlusion at the left M1-M2 junction (arrow).

The patient underwent intravenous thrombolysis and his clinical condition evolved favorably. Twenty-four hours after admission, (d) follow-up CTA features a recanalization of the left sylvian artery, later confirmed (f) on the MR angiography (MRA). (c) Follow-up perfusion CT shows an almost complete resolution of the penumbra, afforded by the early arterial recanalization. The final perfusion CT infarct has progressed in only a very limited fashion when compared to the admission perfusion CT infarct; its extent closely correlates with that of the abnormality on the delayed DWI trace image (e).

parenchyma,[54,55] or even more if subtle technological arrangements are used.[56] Dynamic perfusion CT has the major advantage of being able to assess both cerebral blood flow and cerebral blood volume, in a robust quantitative way.[57–59] It thus allows a direct insight into cerebral vascular autoregulation and can describe the salvageable penumbra. In both penumbra and infarct, regional cerebral blood flow (rCBF) is lowered below 15–20 ml per 100 g and per min. However, in penumbra, rCBV is increased as a result of a local vasodilatation, in an attempt by the autoregulation processes to compensate for rCBF lowering. In infarct, autoregulation reflexes are compromised and rCBV is lowered. The penumbra, as featured by dynamic perfu sion CT, has been demonstrated as accurate by comparison with acute[54]and delayed DWI-PWI-MR[55] (Fig. 19.1).

Perfusion CT studies can thus be easily and quickly performed in the emergency setting, as part of the admission cerebral imaging survey, and they are well tolerated even in acute patients. Data acquisition is achieved in less than 5 min.[60]

Perfusion CT can be performed in all hospital institutions equipped with CT units, as they are usually available round the clock and 7 days a week. It necessitates neither specialized technologists nor extra material, but only a dedicated post-processing software.

It should finally be emphasized that the dynamic perfusion CT data, which consists of time-enhancement curves registered in each pixel, can be analyzed according to the maximal slope model[61–63] or the central volume principle [54,55,57,64] The latter model is the only one leading to quantitative results.[64]

CT ANGIOGRAPHY

The other element of the modern admission CT survey of acute stroke patients (Fig. 19.2) is CT angiography.[65] CT angiography, with the advent of multislice technology, has achieved major progress and now affords accurate assessment of carotid arteries in the setting of acute cerebrovascular diseases.[66,67] It also facilitates the accurate assessment of vessel patency in acute stroke, which may be of value in selecting

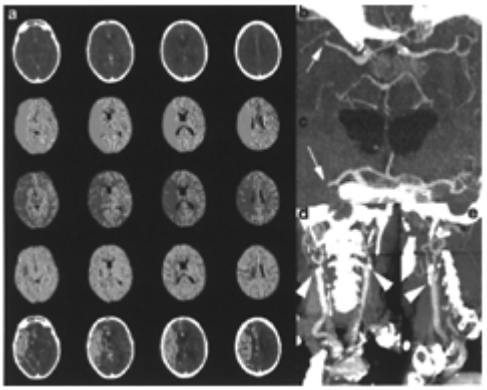

Figure 19.2a-e Modern CT survey in a 62-year-old male patient admitted in our emergency room with a left hemisyndrome, including (a) perfusion CT and (b-e) CT angiography (CTA).

(a) From the perfusion CT raw data (first line), three parametric maps can be extracted, relating to mean transit time (MTT, second line), regional cerebral blood flow (rCBF, third line), and regional cerebral blood volume (rCBV, fourth line), respectively. Application of the concept of cerebral vascular autoregulation leads to a prognostic map (fifth line), describing the infarct in red and the penumbra in green, the latter being the target of thrombolytic drugs. (b), (c) CTA affords identification of the origin of the hemodynamic disturbance demonstrated by perfusion CT. In the present patient, it relates to an occlusion at the right M1-M2 junction (arrows). (d), (e) Finally, CTA features bilateral calcified atheromatous plaques at both carotid bifurcations (arrow heads).

patients for aggressive treatment,[68] and it can add important information about potential collateral blood flow.[69]

Because of its diagnostic potential, CTA carries major logistic advantages in an emergency setting when rapid treatment decisions are necessary. It can be performed immediately after conventional CT, which avoids transfer to other diagnostic procedures such as Doppler sonography, MR angiography, or digital subtraction angiography, with subsequent treatment delay. Furthermore, owing to the tremendous reduction in examination time, it is even possible in critically ill or uncooperative patients without sedation or intubation.

In the near future, multislice CT, combined with cardiac gating, might also substitute for transesophageal echography and allow for the evaluation of the heart and aortic arch, as part of the admission CT survey.[70]

CONCLUSIONS

Currently, thrombolytic therapy is still underutilized because of problems with clinical and time criteria and also the lack of public and professional education in regarding stroke as a treatable emergency. If applied more widely, thrombolytic therapy may result in profound cost savings in health care and reduction of long-term disability of stroke patients.

Individual imaging assessment of brain perfusion in stroke patients, affording the delineation of infarct and penumbra and the evaluation of their relative extents, is likely to be used as a possible selection criterion for treatment. In such a scenario, perfusion CT combined with CT angiography represents an efficient solution[71]that can be easily performed in the acute setting and affords a comprehensive survey of stroke patients on emergency admission. Such a survey can help physicians to diagnose the extent and mechanism of stroke more rapidly. Instead of the current practice of treating all stroke patients uniformly

until subsequent diagnostic tests, patients with large-artery strokes could be treated in a more aggressive acute way to prevent long-term neurologic disability, whereas patients with lacunar strokes could benefit from safer, less-invasive and lessexpensive treatment.

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20.
Trends in protecting ischemic brain

Kennedy R Lees

INTRODUCTION

The last decade has seen a profusion of clinical trials of various neuroprotective strategies. Initially, these grew from isolated ideas born in hope rather than from firm scientific evidence. For example, the use of steroids to limit cerebral edema following ischemic stroke may have been fatally flawed, since steroids act primarily on vasogenic edema seen around tumors rather than cytotoxic edema seen with infarction. Nevertheless, with each trial that was undertaken, there was greater understanding of the possibility of undertaking acute stroke research as well as of the difficulties. This chapter will consider some of the issues that arise, the drug approaches that have been tested, and the hopes for the future.

MECHANISMS OF BRAIN INJURY

A thorough understanding of the mechanism of brain injury is central to any neuroprotective strategy. Our level of understanding has greatly improved since the first observations of Astrup and colleagues, who demonstrated that reductions in cerebral blood flow led first to loss of electrical activity and then to failure of intracellular energy mechanisms leading to membrane disruption and ultimately cell death.[1] The important interaction between the extent of ischemia and its duration has provided the premise for much of the neuroprotective clinical work that has been undertaken.[2] The idea that there is penumbral tissue which is destined for infarction without any intervention and yet which may be salvageable during the early hours of the process supported a wealth of laboratory research. The processes were mostly studied in small animal species.

EXCITOTOXICITY

We learned that reduction in perfusion led to depolarization of presynaptic cells and to excessive release of excitatory neurotransmitters, particularly glutamate.[3,4] The loss of energy compromised reuptake and removal from the synaptic cleft of glutamate, allowing the excitatory process to be excessive in both extent and duration. This overstimulation of postsynaptic cells mediated by *N*-methyl-D-aspartate (NMDA), AMPA, and kainate receptors promotes calcium influx and sodium influx (with potassium efflux). The calcium influx, which is largely NMDA-mediated, leads directly to activation of intracellular proteases, lipases, etc., which can be lethal to the cell. The sodium influx, which is accompanied by chloride, encourages intracellular swelling: cytotoxic edema. The process of glutamate release and NMDA-mediated excitotoxic damage occurs early and lasts for a short period—60–90 min—in animals.

Numerous pharmacologic attempts to abort the process have been considered. Thus, competitive or non-competitive antagonists of glutamate at the NMDA receptor have been tried, polyamine site or glycine site antagonists at the NMDA receptor have been tested, and antagonists at the AMPA receptor have been explored. Because there is more than one type of postsynaptic receptor, glutamate release inhibitors were thought perhaps to be more attractive; since calcium was closely involved, calcium antagonists have been tested. The history of some of these compounds is reviewed below. Unfortunately, results have been generally discouraging. Reappraisal of the evidence, perhaps with a more objective eye, highlights the substantial discrepancy between the time window within which many of these drugs operate successfully in animals and the realistic time at which they can be given in man. There is, however, also considerable encouragement, since glutamate-mediated excitotoxic injury is not the only process which is initiated after cerebral ischemia.

Zinc may be implicated in some of the pathophysiology, since it can cross the cell membrane via calcium channels. Increased zinc concentrations in subpopulations of neuronal cells appear to precede and localize with delayed cell death.[5]

New channels are still being discovered. The so-called maxi-K channel appears to be a natural homeostatic mechanism to correct depolarization: it consists of a large conductance channel for potassium, capable of hyperpolarizing even ischemic cells. More important, this maxi-K channel can be opened by drugs such as BMS204352, creating a new strategy for neuroprotection that is effective in experimental focal ischemia.[6]

FREE RADICAL INJURY

Once the ischemic process has been set in action, some of the damage is due to formation of highly reactive oxygen free radicals.[7] The formation of these free radicals is enhanced when reperfusion occurs; indeed, there is good evidence that late reperfusion can be worse than sustained ischemia. Several pharmacologic agents have been developed to limit reperfusion damage: some have so far been unsuccessful,[8] but others remain attractive candidates for neuroprotection.[9–11]

APOPTOSIS

The problems with time window have also prompted exploration of other processes involved in ischemic injury. While cell necrosis has been the primary concern after an ischemic insult, the initiation of apoptosis, programmed cell death, has also attracted enthusiastic study, though so far no strategy for limiting this process has reached large clinical trials. Either ischaemia per se or free radical injury seems capable of prompting cells to enter a self-destructive process which causes penumbral cells to succumb unnecessarily to an ischemic insult. These cells can be recognized by histologic features that are distinct from necrosis.[5] Apoptosis may be reduced by caffeine and calcium channel blockers; conversely, theophylline and nitric oxide both seem capable of increasing apoptosis.[12]

Although infarct damage appears to reach a peak within 1–3 days of the ischemic insult in rats, there is evidence that some continuing damage may occur for several weeks. Partly, this may be due to apoptosis but delayed neuronal degeneration may be seen in selected cell types, perhaps due to loss of growth factors or neuronal activity.[13]

INFLAMMATORY RESPONSE

The other process which occurs relatively later in the timescale of injury is the inflammatory response. Leukocytes begin to accumulate in the infarct zone within 30 min of ischemia, peaking between 24 and 48 hours later.[13] While some of the inflammatory response is undoubtedly a mopping-up exercise to remove dead tissue, the invasion of inflammatory cells at least in the early stages may further restrict perfusion through the capillary bed and contribute to free radical induced injury. There is laboratory evidence to suggest that anti-inflammatory approaches may reduce infarct volume and improve outcome. There is some evidence that broadly acting anti-inflammatory drugs such as the calcineurin inhibitor, tacrolimus, may be neuroprotective.[14] Conversely, clinical trials with both general (corticosteroids) and with specific (enlimomab) anti-inflammatory agents have been unsuccessful.[15–17] These trials have their flaws, however, and it has been argued that clinical use of anti-inflammatory strategies remains inadequately tested.[18] On the one hand, redundancy and overlap of the effects of individual inflammatory mediators cast doubt around the chances of successful intervention using agents acting at single sites; on the other hand, without optimal timing of the intervention, carefully judged duration of action, and suitable formulations, broad suppression of the inflammatory response could clearly be deleterious.

APPROACHES TO TREATMENT

Trends in the use of neuroprotective drugs have run in cycles. Antihypertensive drugs were initially used, particularly calcium antagonists such as nimodipine and isradipine. Some of the excitement about nimodipine came from its success in subarachnoid haemorrhage;[19] some came from an initial small and possibly misleading trial published by Gelmers.[20] With hindsight, the importance of trial monitoring and confirmation of positive findings is clear.[21] There has been accumulating evidence to suggest that early blood pressure lowering may have deleterious effects.[22] This may be a matter of degree, however. Laboratory data certainly show that reductions in blood pressure increase the volume of infarction but the effects on blood pressure in acute stroke patients have not been systematically studied: even the Cochrane overview contains limited data.[23–27] The place of early blood pressure lowering remains unclear.

Interest turned away from drugs with obvious cardiovascular side effects, to excitatory amino acid antagonists. These drugs appeared much more potent in experimental circumstances but possessed obvious psychological or CNS side effects. The competitive and noncompetitive NMDA antagonists had profound psychotomimetic, sedative, hallucinogenic, or catatonic reactions associated with their use.[28] These effects were transient and it was considered that they were a tolerable price to pay if neuroprotection could be achieved. Selfotel, a drug which penetrated and exited the brain extremely slowly, was examined in two phase III trials but these were abandoned early. There was significant evidence of early mortality due to possible brain toxicity, outweighing any trends towards efficacy, and making it impossible to justify continuing.[29,30] Similarly, the noncompetitive antagonist aptiganel made it to a phase IIb/III trial that was also abandoned after interim analysis. None of these trials studied patients early after stroke: for both drugs, the time window to treatment was 6 hours.

There was then a move towards better-tolerated glutamate antagonists, with drugs such as the glycine antagonist gavestinel. Gavestinel was certainly very well tolerated but it has been suggested that this was because it did not penetrate the brain. Certainly, evidence available after the major clinical trials had nearly completed offered little reassurance on this topic and the result of the trials was unequivocally neutral.[31,32] Again, the time window employed was 6 hours.

The potassium channel opener BMS204352 was tested in two large phase III trials, neither of which showed any hint of efficacy.[33,34] The excellent tolerability and wide dose range studied together suggest that this drug may not have been administered in optimal dosage, however.

INTERPRETATION OF CLINICAL EXPERIENCE

Reviewing the history of clinical trials in this area, it is readily apparent that the science remains in its infancy. Several issues have come to the fore after these trials.[35–38] These include speed of treatment, selectivity of protection, sufficient drug, selection of patients, safety issues, selection of suitable endpoints, and statistical considerations.

TIME TO TREATMENT

We have too little understanding of the relationship between the timescale and relative importance of events in animals compared to those in humans. Nevertheless, whereas the optimistic assumption used to be widely held that, with a slower metabolic rate, the time window for intervention in man may be substantially longer than in small animals, the evidence from reperfusion approaches with thrombolysis and from the unsuccessful trials of glutamate antagonists, etc., has strengthened the more pessimistic view that results in animals can be directly extrapolated to humans.[13,39]

The misplaced optimism of the early 1990s is giving way to realism, that infarction is well established when 6 or 12 hours have elapsed, in most patients.[40–42] It certainly is possible that there is some continuing ischemic damage after the first few hours in a handful of patients but in order to demonstrate that a drug is effective, it has to have an effect in a majority rather than a small minority of patients. Thus, patients must be treated early after stroke onset. While this was once thought impractical, the NINDS trial with tissue plasminogen activator (t-PA) has demonstrated that patients can be successfully recruited to trials and can be treated in practice with a drug even if specialist assessment and investigation is needed before that treatment.[43] Trials with time windows of 12 or 6 hours are now giving way to trials with 3- or 4-hour windows and strategies to treat patients even earlier are being developed. For example, the FAST-MAG offshoot from the IMAGES Trial with magnesium is aiming to recruit patients within 2 hours of stroke onset, using paramedics to assess the patient and deliver initial care. This is possible because of trends toward better-tolerated drugs where the safety issues are less likely to be a problem.

SELECTIVITY OF PROTECTION

Efforts over the last 10 years have concentrated on protecting neurons from cell death. There is no question that neurons are required for brain function, but there is now increasing recognition that they cannot survive and function on their own. Brain protection rather than neuroprotection is gaining recognition: protection of the oligodendrocytes and glial cells now assumes greater importance.[44–46] Whereas oligodendrocytes can be protected by reperfusion and possibly by AMPA antagonists, NMDA antagonists appear incapable of protecting them.[46] Histologic evidence of neuronal survival may also be a sine qua non, but there has to be sustained survival and this has to be accompanied by functional improvement or recovery. Thus, criteria for judging the strength of a preclinical package have been formulated.[47] These include the need:

- to confirm experimental data in several laboratories and species, including some independent work
- to define a target dose and/or plasma concentration associated with neuroprotective efficacy

- to assess outcome on both histologic and functional measures
- to assess late outcome in case neuroprotective effects are merely transient
- to ensure that confounding variables are controlled—including blood pressure, temperature, and blood glucose—and that mortality is reported
- to incorporate concurrent, randomized controls
- to conduct intention-to-treat analysis.

Few drugs have yet been subjected to such rigorous assessment and survived to reach the clinic.[11]

SUFFICIENT DOSE

One of the major criticisms of trials with gluta-mate antagonists was that tolerability was relatively poor and dosing was compromised as a result. Plasma concentrations with selfotel or aptiganel that could be achieved in stroke patients were not clearly above the threshold required for neuroprotection based on extrapolations from animals.[48] Dosing was based on the maximum tolerated dose. This is no longer seen as an acceptable approach if target plasma concentrations cannot also be achieved. The difficulties of choosing the correct dose where tolerability is not the limiting factor have led to development of new trial designs. Adaptive dose allocation may offer a solution to this problem and is being piloted by Pfizer in their neuroprotective trial at present. For review, see *http://Hb.stat.cmu.edu/bayesworkshop/Bayes99.html*.

SELECTION OF PATIENTS

Even if patients are given sufficient drug early after stroke, many of the patients who may be treated have a low chance of contributing to the trial outcome. This may be because they are too severely affected, too mildly affected, or because for other reasons the infarct is already established, i.e. there is no penumbra to be salvaged.[42] There is increasing interest in identifying patients in whom salvageable tissue is still present. The most popular method at present for this purpose is to use magnetic resonance imaging (MRI) scanning and in particular evidence of a mismatch between large perfusion deficit and limited diffusion deficit.[34–36,49,50] This is discussed in Chapter 5. Other methods of selecting patients for clinical trials may be equally valid. For example, it is well established that stroke severity interacts with age and other factors to determine final outcome. Until now, insufficient attention has been paid to this interaction and either all comers have been accepted—i.e., including young patients with very mild stroke and old patients with very severe stroke—or excessive restrictions have been placed on each of these selection criteria; more recently, there is interest in assessing individual patients for their expected prognosis,[51] aiming to select a middle group. This can be done not just on the basis of a single baseline prognostic factor but on the sum or interaction of these prognostic factors. Thus, a very elderly patient with mild stroke may have equal value to the trial as a young patient with a severe stroke. Access to large databases of trial baseline and outcome data is required in order to develop the necessary models.

SAFETY ISSUES

The early neuroprotection trials involved drugs with inherent safety problems,[28] that were seen as acceptable because they were to be balanced against a powerful neuroprotective effect. We now realize that the neuroprotective effect of any drug is likely to be much more limited. If the greatest benefit that can be seen is a 10% absolute improvement in outcome when reperfusion is instituted within 3 hours of stroke

onset,[43] neuroprotection is unlikely to achieve more than a few percent improvement in outcome.[52] Even a low incidence of a serious safety problem could quickly offset that small benefit and, thus, the drugs that are now going into trials must have a wider safety margin. Clinically important issues to be avoided include hypotensive effects,[22] induction of hyperglycemia,[53] induction of vomiting[54] and disruption of the swallowing reflexes or esophageal sphincters,[55] thus predisposing to aspiration.

ENDPOINTS

The outcome measures that are presently used are recognized to be crude.[56–61] Without doubt, a successful stroke treatment will need to improve the functional outcome of patients and not just some subtle neurologic sign. Nevertheless, the use of insensitive measures means that potentially valuable treatments cannot be tested in acceptable sizes of trials. With these present measures, 1500–3000 patients are required to seek an effect size of 5–10%: with a useful effect being only 1–2%, each drug that may be considered would need to be tested in tens of thousands of patients. We must find ways of assessing outcome for phase II trials at least, more sensitively: approaches to this include the use of imaging, particularly growth of a diffusion lesion over the first few weeks from stroke onset, and of patient-specific endpoints. For the latter, a patient with a severe stroke would be judged to have made an acceptable recovery if severe disability is avoided; in contrast, a patient with a mild stroke should be measured on whether he has made a full recovery. Once again, greater utilization of existing trial databases is required to facilitate development of these endpoints.

STATISTICAL ISSUES

Finally, several statistical issues come into play. Some of the earlier small trials were confounded by imbalance in prognostic variables at baseline, by the possibility of center- or country-specific effects, or even by selection of weak analysis plans for outcome measures. The availability of interactive voice response systems to permit telephone randomization of patients and stratification or adaptive randomization[62,63] on numerous baseline variables has permitted us to run large trials with almost guaranteed balance between groups on all factors apart from the treatment intervention.[31,32] This must lead to greater reliability of the trials that we undertake.

PROPHYLACTIC TREATMENT

The difficulty with administering treatment early after stroke onset raises the question of prophylactic neuroprotection. Stroke is common in the elderly and particularly in patients with evidence of previous stroke. There is no doubt that secondary prevention is a very effective means of improving outcome in large numbers of patients. Trials such as PROGRESS have recently confirmed this.[64] The use of antihypertensive drugs may be a form of prophylactic neuroprotection. Blood pressure lowering may prevent stroke but by adjusting cerebral autoregulation and improving the level of resistance to cerebral ischemia, antihypertensive treatment may also have a neuroprotective effect. With the sort of drugs that have been tested as neuroprotectants in stroke so far, there was little hope of these being well enough tolerated to administer them daily over many years, but with increasing improvements in tolerability, this may be a possibility for the future. It will be difficult to demonstrate benefit, however. Secondary prevention trials are usually designed to reduce numbers of events rather than to measure the severity of the events accurately. The PROGRESS trial demonstrated reduced disability and decline in cognitive function as a result of

recurrent stroke, but it is much more difficult to show that these outcome measures reflect a reduction in stroke severity rather than in its incidence.

The lipid-lowering statin drugs have been proposed as neuroprotectants.[65] Apart from reducing atherosclerotic plaque and having antithrombotic properties, statins also possess potentially neuroprotective effects via nitric oxide regulation —enhancing endothelial versus inducible nitric oxide synthase—and perhaps preserving blood flow. They may also have anti-inflammatory and antioxidant properties. Long-term use of statins is under trial in the British Heart Protection Study which uses simvastatin, with results due to be presented in late 2001, in the SPARCL trial with atorvastatin (which is specifically targetting stroke patients), and in the PROSPER trial with pravastatin.

The possibility of prophylactic neuroprotection has been explored within selected circumstances. Patients undergoing carotid endarterectomy or coronary bypass grafting are at high risk of perioperative cerebral ischemia. Short-term prophylactic treatment with a neuroprotectant could limit excitotoxic damage in case embolization or watershed ischemia occurs. This has been attempted with the low-affinity noncompetitive NMDA antagonist remacemide.[66] The results were encouraging but not spectacular; fortunately, perioperative stroke is relatively uncommon and surrogate measures of outcome based on psychological tests are necessary. These tests remain difficult to interpret.

SUMMARY AND CONCLUSIONS

Neuroprotection for stroke is a young field treating a disease of the elderly. There have been scientific, practical, and ethical issues that have limited advances. Even the most widely tested group of drugs, the NMDA antagonists, have not yet received a fair trial. Nevertheless, considerable advances in selection of compounds for clinical development and in clinical trial methodol ogy are pointing the way forward. Prophylactic or therapeutic neuroprotection remains an attainable goal.

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21.
Gene and cell therapy in stroke

Antoine M Hakim, Mukul Sharma and Charlie Thompson

THE CHALLENGE OF STROKE

Stroke is a growing health care burden internationally. Gains in life expectancy worldwide were greater in the last century than at any other time. Since stroke tends to be an older person's disease, the rise in the number of stroke patients is projected to be much larger than the expected rise in the population. Using the disability-adjusted lifeyear measure to estimate the burden of major diseases, injuries, and risk factors in regions of the world, it was concluded that the rank order for cerebrovascular disease will rise from sixth in 1990 to fourth by 2020.[1] Considering that a stroke occurs every 53 seconds in the United States currently,[2] all jurisdictions are increasingly cognizant of the burden that stroke will present to the individual affected, the caregiver, and to our health care delivery services.

The research and clinical care communities have not been sitting idle in the face of this challenge, but it is fair to say that despite enormous effort to treat stroke in the acute phase, success in this domain has been limited. According to Kidwell et al.,[3] the 20th century saw the publication of 178 controlled clinical trials of acute stroke therapies in the English language literature, yet only three studies yielded positive results, with only one drug, tissue plasminogen activator (t-PA), finding any practical use. This very limited success, and the increasing realization that any therapy for the acute phase of stroke will likely be hampered by the short therapeutic window, have changed the emphasis in stroke therapy from the interruption of the metabolic and ionic events that accompany the acute phase to the promotion of mechanisms and methods aimed at recovery from the injury and restitution of the functions.

In this chapter we summarize aspects of brain plasticity relevant to the stroke condition and then review current knowledge in gene and cell therapy, particularly as it relates to stroke. We explore the potential for applying this knowledge to promote recovery from stroke and point out where additional knowledge may be needed.

CURRENT CONCEPTS ON BRAIN PLASTICITY

Spontaneous recovery, which includes recovery due to rehabilitation and adaptation, occurs early after stroke.[4,5] The Copenhagen Stroke Study[4] demonstrated that maximum neurologic recovery occurs on average 13 weeks after stroke, while resumption of activities of daily living is maximal within 20 weeks. It is now accepted that this return of function is partially due to remodeling of neuronal cortical connections in the adult. Many studies have demonstrated chemical and anatomic plasticity in the cerebral cortex of adult animals.[6] Animals reared or housed as adults in complex and stimulating environments develop more dendritic branching and more synapses per neuron and have higher gene expression for trophic factors than

animals housed individually or in small groups in standard cages.[6,7] Similar changes can be induced during learning.[8,9] Another aspect of brain plasticity is that cortical representation areas, cortical maps, can be modified by sensory input, experience, and learning, as well as in response to brain lesions.[10,11] The potential relevance of such data for stroke rehabilitation was proposed more than a decade ago.[12] If we regularly have to perform a very skilled motor task, the cortical representation for the muscles involved will remain enlarged, as seen for the fingers of the left but not the right hand in string players.[13] Similarly, the sensorimotor cortical representation of the reading finger is expanded in blind Braille readers[14] and, furthermore, fluctuates with the reading activity pattern.[15]

Several mechanisms are likely to be involved in brain plasticity.[16] Activity-dependent modification of synaptic connections and reorganization of adult cortical areas are thought to involve long-term potentiation (LTP) and long-term depression (LTD), mechanisms by which information is stored in the mammalian central nervous system. [17,18] Synaptic plasticity in cortical horizontal connections has been proposed to underlie cortical map reorganization.[19,20] Glutamate, the main excitatory neurotransmitter, plays a crucial role. Cortical map reorganization in the primary somatosensory cortex can be prevented by blockade of *N*-methyl-D-aspartate (NMDA) receptors.[21] γ-Aminobutyric acid (GABA)-A receptor antagonists can facilitate LTP induction in neocortical synaptic systems, and the induction can be blocked by GABA-A receptor agonists.[20] Nitric oxide is another candidate for dynamic modulation of cerebral cortex synaptic function.[22] Local neurotrophin actions, transmitter release, and synaptic protein synthesis are thought to promote synaptic remodeling and changes in receptor expression or activation.[7] Thus, a complex array of biochemical influences is brought to bear on the brain, resulting in its remodeling.

SPONTANEOUS EVENTS AND TRAINING EFFECTS

After a brain lesion, changes in other brain regions have been documented at different post-lesion times, from minutes to months.[23,24] Post-lesion events may be due to deafferentation, removal of inhibition, activity-dependent synaptic changes, changes in membrane excitability, growth of new connections, or unmasking of preexisting connections.[25] Unmasking has generally been proposed to be responsible for rapid changes in cortical maps,[15] and there is evidence that synaptic plasticity can be very rapid.[26] Cortical mapping by intracellular recording in primates has demonstrated that the tissue surrounding a small lesion in the hand-representation area of the primary motor cortex undergoes a further territorial loss in the functional representation of the affected body part, perhaps through nonuse or disruption of local intrinsic cortical circuitry.[27] This further tissue loss could be prevented by retraining of hand use, starting 5 days after induction of the lesion.[28] Similarly, reorganization of primary somatosensory cortex occurs in parallel with the recovery of sensorimotor skill in monkeys after restricted lesions. Morphologic studies in the rat indicate that cortical lesions can induce an increase of dendritic branching in the contralateral hemisphere, with a maximum 2–3 weeks after the lesion.[29] If the rats were prevented from using the intact forelimb, both the morphologic changes and functional recovery were inhibited,[30] although some studies could not verify these findings.[31] Using immunohistochemistry, an increased density and distribution of GAP 43 immunoreactivity has been observed in the ipsilateral cortex 3–14 days after a focal brain infarct, and of synaptophysin immunoreactivity in the same areas at postoperative days 14–60.[32] A larger distribution of synaptophysin immunoreactivity was also noted in the contralateral hemisphere.[32] An increased neuronal labeling of MAP-2, GAP43, and cyclin D1 immunoreactivity from day 2 and up to 28 days has been found in the penumbra zone.[33]

ENRICHED ENVIRONMENT AND NEUROTROPHIC FACTORS

There is substantial evidence that the poststroke environment can influence the outcome. After experimental brain infarction, rats housed in an enriched environment with the opportunity for various activities and interaction with other rats perform significantly better than rats housed in a standard laboratory environment,[34] even if transfer to an enriched environment was delayed for 15 days.[35] A comparison between enriched environment, social interaction, and physical activity showed that social interaction was superior to wheel-running and that an enriched environ ment, free physical activity combined with social interaction, yielded the best performance.[36]

The beneficial effect of enriched environment might be caused by increased synthesis of neurotrophic factors. Local neurotrophin action may promote synaptic remodeling and changes in receptor expression.[7] Ischemia is a strong inducer of gene expression in the brain.[37,38] Ischemiainduced changes in several immediate-early genes[39] have been reported. In fact, hundreds of genes have been shown to be acutely induced or suppressed, generally with an early peak or trough within minutes or hours of onset of ischemia and a rapid return to normal or subnormal levels. Whether the early transient increase in gene expression during the initial postischemic hours is related to outcome is not known.

There is some evidence that trophic factors can rescue neurons in the acute stage. In addition to reducing infarct size even when given hours after the ischemic insult, basic fibroblast growth factor may attenuate the thalamic degeneration following cortical infarction.[40,41] Nerve growth factor has been reported to improve memory and motor functions and reduce dendritic atrophy in the remaining pyramidal neurons.[42] As reviewed elsewhere,[43] several other growth factors, including brain-derived growth factor (BDNF), insulin growth factor-1, transforming growth factor (31, and glial cell line-derived neurotrophic factor, have been reported to be beneficial in the early ischemic period. Clearly, the potential for benefit from induction of trophic factor genes in the rehabilitation phase needs to be evaluated.

CLINICAL EVIDENCE FOR REORGANIZATION OF CORTICAL CENTERS

Studies using positron emission tomography (PET), functional MRI (fMRI), transcranial stimulation, and magnetoencephalography (MEG) support the concept of functional reorganization after stroke.[44,45] PET studies on blood flow distribution during finger movements in a previously paretic hand have demonstrated complex patterns of activation, with increased activity with large individual variations.[44,46] Individuals may use different compensatory strategies before and after training, and the activation pattern can change with time.[45,47] It has been reported that changes in activation pattern can be induced by forced training of the paretic hand even 4–15 years poststroke.[48]

In conclusion, the adult brain retains the ability to repair itself after injury, and the cellular, molecular, and electrophysiological contributors to the repair process are becoming better known. Environmental stimulation would appear to improve recovery. The possibility of actually replacing cells lost to injury through mobilization of endogenous or supply of exogenous stem cells adds an entirely new and exciting dimension to the field of brain repair poststroke. In addition, the tools to change the genetic status of the cells themselves, or the environment they acquire, or both, are becoming more available. It is now possible to imagine that physicians will not only give therapies to help patients live better with their genetic constitutions but also will use novel therapies to alter the genetic make-up of the patient. Somatic gene therapy and stem cell transplantation are two of the most promising novel treatment modalities.

THE POTENTIAL FOR REPAIRING BRAIN AFTER STROKE

GENE THERAPY

Gene therapy can be defined as the modification of the genetic make-up of cells to produce a therapeutic effect.[49] Such genetic modifications can be by ex-vivo approaches if carried out in cultured cells that are subsequently administered to the patient, or involve modifications of cells *in vivo*. Most approaches to gene therapy involve three interacting components:

a therapeutic gene or other nucleic acid
a vector that allows delivery of the therapeutic nucleic acid to the appropriate cell
a method of delivering the gene/vector combination to the appropriate tissue *in vivo*.

There have been numerous reports of gene modification in animals to attenuate the consequences of stroke, targeting both the vascular space and the brain itself. The technology for transfer of genes into blood vessels and brain is at hand.[50] In the blood vessels, the emphasis has been on reducing stroke damage by modifying vascular hemodynamics, and gene therapy has largely been used for control of hypertension,[51,52] particularly through the transfer of the endothelial nitric oxide synthase gene to the blood vessel. Nitric oxide not only leads to the relaxation of vessels,[53–55] including the carotid artery,[56] but also inhibits smooth muscle cell proliferation, thus decreasing neointimal hyperplasia.[57] The utility of this approach in studying the role of nitric oxide in atherosclerosis and its potential relevance for human gene therapy was recently reviewed.[58]

A number of attempts have been made to modify the response to ischemic injury in the brain. Steinberg and his group pioneered the use of herpes simplex viral vectors expressing Bcl-2 in the brain, and showed that the vector is protective when administered after the injury.[59] Others have shown the same benefit when the vector is given prior to the ischemic episode.[60] Steinberg's group also confirmed the effectiveness of gene therapy in increasing the expression of HSP72 and reducing neuronal death in focal cerebral ischemia and kainic acid administration.[61]

Recombinant adenovirus vector expressing glial cell line-derived neurotrophic factor has also been used to reduce ischemia-induced damage.[62] Others have reported the attenuation of focal injury in the mouse following transfection with the receptor antagonist gene for the inflammatory cytokine interleukin-1beta.[63] The same group had performed a similar experiment in the rat.[64] Increasing the expression of neuronal apoptosis inhibitory protein (NAIP) using an adenoviral vector resulted in reduced ischemic damage in the hippocampus.[65] These experiments have led Gunnett and Heistad[66] to conclude in their recent review article that gene therapy in stroke is feasible because of the ability it offers to increase the concentrations of therapeutic agents in a relatively localized environment.

Some gene therapy clinical trials have had tragic complications.[67] Despite this, successful gene therapies have now been reported in humans,[68] although none so far in the setting of ischemia or in an attempt at modifying its risk factors. Much work remains to be done before human gene therapy is safe and effective. In particular, vectors are needed that can be easily produced at high titers and in large quantities, that can be safely targeted to specific cell types, and that can produce regulated transgene expression. Devices also are needed for efficient and targeted delivery of these vectors to the appropriate tissues *in vivo*. Finally, a better understanding of the biochemical and genetic changes occurring in stroke are needed. For all these reasons, the application of gene therapy to human stroke, while promising, appears to still be a rather remote

possibility, particularly with the advent of stem cell therapy, which offers the potential for tissue replacement and repair.

STEM CELL THERAPY

The discovery of stem cells in adult tissues, the unexpected plasticity of both adult stem cells and differentiated cells, and the isolation of human embryonic stem cells have expanded the potential therapeutic utility of cell-based therapies. Stem cell therapy, like gene therapy, is in its infancy. Nevertheless, cell-based therapies hold tremendous promise for the treatment of both acquired and inherited diseases involving tissue degeneration and cellular dysfunction.[69]

Neural stem cells, multipotential cells that are precursors to neurons and glia, have been identified in the adult vertebrate central nervous system.[70] Although first reported to be present in brains from rodents in the 1960s,[71] stem cells have been extensively studied only recently.[72,73] They are predominantly found in the periventricular ependymal or subependymal zone and in the dentate gyrus, but may also be present in small numbers in other regions.[74] Stem cells from the adult brain proliferate and differentiate into neurons and glia in tissue culture with the same efficiency for neuronal differentiation as found in fetal stem cells. Recent studies have also shown that they can differentiate to neurons in the adult human dentate gyrus *in vivo*.[75] With the observation that such cells in experimental studies can be manipulated *in vivo* by growth factors and by environmental enrichment,[76,77] the clinical potential of stem cell in humans is currently being studied intensively.[72,74]

Neurogenesis increases in response to brain injury (Table 21.1). It has been shown to occur in excitotoxic and mechanical lesions in the dentate gyrus (hippocampus) in the adult rat[78] and after transient global ischemia in gerbils.[79] In models of apoptotic neurodegeneration, neural precursors that are transplanted migrate selectively to degenerating layers of cortex.[80] The stem cells then differentiate into projection neurons and reform appropriate long-distance connections to the original targets. Recently, it has been demonstrated that stem cells from the subventricular zone can migrate to degenerating regions induced by synchronous apoptosis.[81]

These findings make it less likely that human embryonic stem cells,[82,83] which can be isolated from early fetuses and made to differentiate *in vitro* into a wide variety of cell types, will be a common source of stem cells for human brain repair. Embryonic stem cells are totipotent cells derived from the inner cell mass of an early-stage fertilized embryo. Under appropriate tissue culture conditions, embryonic stem cells have the capacity for unlimited replication while maintaining totipotency and, when reimplanted into a blastocyst, such cultured embryonic stem cells can contribute to all of the organs of the resulting adult animal. The promise this holds for a variety of human diseases is obvious, but the ethical issues it raises will undoubtedly lead to other avenues being explored for stem cell therapy.

Successful implantation of fetal neocortical cells after cortical lesions was shown almost a decade ago in several laboratories.[84] Transplanted cells are thought to interact with the host tissue by forming connections, but also by being a source of trophic factors that can influence the surrounding tissue. Both anatomic and functional integration with the host animal brain have been observed,[84] but improvement in behavioral tests has been found only when transplantation was combined with post-transplantation housing in an enriched environment.[85,86] When implanted into the neocortex of adult mice undergoing targeted apoptosis of neocortical pyramidal neurons, neural progenitors migrate long distances into the regions of cell death, where they differentiate and make appropriate long-distance projections.[87,88] The results indicate the presence of environmental signals that promote differentiation of the implanted cells. Furthermore, adult

mature astrocytes in the host brain have been shown to retain the capacity to transform into developmental radial glia that may help the active migration of transplanted neural precursors.[89]

Recent discoveries have indicated that organspecific adult stem cells display much more plasticity than originally thought. Stem cells isolated from one tissue can differentiate into a variety of unrelated cell types and tissues. For example,

Table 21.1 Stem cell behavior depends on the host environment

- In the normal adult brain, stem cells migrate to where turnover of neurons is higher, i.e., to regions that are 'active'
- Transplanted stem cells survive longer in a lesion environment
- Stem cells develop into dopaminergic neurons more strongly in dopamine-depleted striatum
- Neural precursors migrate toward neurons undergoing targeted apoptosis
- Rapid proliferation, migration, and differentiation of stem cells occur better where there is a lesion, and the microenvironment is
- manipulated with growth factors

recent animal experiments have demonstrated that neural stem cells can differentiate into hematopoietic lineages.[90] Similarly, bonemarrow-derived stem cells can differentiate into several nonhematopoietic cell types, including microglia and astroglia in the brain.[91,92] More recently, the skin has been reported as the source of pluripotent stem cells[93] and amniotic epithelial cells have been shown to transform into neuronlike cells in the ischemic brain.[94] These findings raise the exciting possibility of using bonemarrow-derived cells, skin explants, and cells from other sources to treat a wide variety of disorders, including stroke. Also, experiments demonstrating that nuclei from terminally differentiated cells can be reprogrammed to totipotency raise the possibility of generating specific types of therapeutic stem cells *in vitro,* starting with small numbers of differentiated cells from the patient to be treated (e.g., a skin or muscle biopsy specimen) and thereby avoiding immune responses to the transplanted cells.

There is much evidence from animal studies that neuronal replacement and at least partial reconstruction of damaged neuronal circuitry is possible. Clearly, what is needed is a precise assessment of the role neurogenesis plays in determining outcome from stroke, and whether that role can be exploited for the benefit of the patient. The molecular mechanisms regulating neurogenesis and death of neural precursor cells[95,96] as well as the factors that control their proliferation[97,98] have been examined. Clinical trials have started in a number of neurologic conditions, such as Parkinson's disease, where there is evidence of circumscribed cell loss and clear evidence for efficacy obtained in animal experiments." Trials with cell replacement have started in stroke patients,[100] but some believe that this may be premature in view of the lack of supporting animal studies.[101]

DEVELOPING A STRATEGY FOR STROKE REPAIR

The desire to proceed with clinical trials in stroke with stem cells, in their 'natural' state or in an engineered form, is understandable, considering there are no known alternative therapies that can promote brain repair after a stroke. Nonetheless, there are serious gaps in our knowledge that must be closed if we are to design clinical trials in stroke that have a higher chance of successful outcomes. These deficits in our knowledge are in the basic science surrounding both gene and stem cell therapies, in methods of getting stem cells to their targets, in the selection criteria for the patients and their evaluation, and finally in understanding the interrelationship between the therapies administered and the patient's external environment. Some of these issues are reviewed below.

BASIC KNOWLEDGE NEEDED

It is essential to understand the molecular mechanisms regulating neurogenesis and to optimize conditions to support the survival of stem cells. Three areas where our basic scientific knowledge is still deficient and must be more complete before we can proceed safely with clinical trials are:

1. understanding the molecular mechanisms that regulate stem cell death and survival
2. developing a more complete understanding of the mechanisms regulating stem cell migration and axon guidance
3. identifying the novel genes that regulate neurogenesis and differentiation.

Previous studies have demonstrated a high turnover rate of neural stem cells in both developing and adult brains.[102] Animals with targeted disruption of apoptotic regulators such as caspase-3 and caspase-9 exhibit a dramatic expansion in neural stem cell populations.[103,104] Other studies have demonstrated that the mechanisms regulating apoptosis in the progenitor population are distinct from those mediating cell death in postmitotic neurons.[105] Little is known regarding the molecules that regulate apoptosis in neural stem cells. The high turnover rate as well as stress-induced apoptosis represent a major obstacle in the use of stem cells in regeneration studies. Indeed, most of the stem cells delivered to injury sites by heterologous implantation succumb to apoptosis rather than differentiating and establishing functional connections. These findings suggest that we must identify the key molecular regulators of naturally occurring cell death in neural stem cells, and use this knowledge to promote regeneration after injury. These studies will likely involve studying stem cells derived from transgenic mice deficient in key apoptotic genes, and genetically manipulating stem cells to promote their survival.

It is also possible to imagine a means of mobilizing the stem cells resident within the brain. This would avoid having to develop an implantation route, which would be necessary if the stem cells are from an extracranial source. However, studies must be conducted on the migratory signal transduction pathways that would allow the therapist, if needed, to direct stem cells toward specific brain areas. Activation, migration, and differentiation of neural stem cell pools may involve the induction of novel ‘regeneration’-specific genes during brain injury and repair. The ability to determine if stem cells develop viable and functional connections is also desirable. Are they electrically active? Do they integrate brain circuitry? Do they grow neurites and axons? Are there enough of them to make a difference? Answers to these questions would improve the chances of success in the performance of clinical trials for therapy poststroke.

HOW SHOULD STEM CELLS BE ADMINISTERED?

It is possible that the whole issue of stem cell administration may be avoided, by learning how to mobilize the stem cells that are endogenous to brain.[106,107] Otherwise, once we have established that stem cells differentiate and survive following injury, a method of administration must be established. Some data[108] suggest that administering stem cells into the carotid bloodstream is sufficient, and that cells given this way can cross the blood-brain barrier. If this proves accurate, controlling the migration of the cells to the locations where they are needed would be necessary. In the current trial of stem cells given to parkinsonian patients, the migratory pathways of the cells and their contribution to potential side effects of the therapy have aroused debate,[109] suggesting that an imaging method that allows tracking the trajectory of stem cells introduced into the brain would be necessary. Such methods are now being suggested.[110]

ASSESSING FUNCTIONAL OUTCOME FOLLOWING STEM CELL THERAPY

The role of stem cells in functional recovery has not been measured. This is partly due to the difficulty in determining behavioral outcome from stroke in rodents, although recent publications have compared a number of behavioral tests and identified those which are more efficient.[111] Brain imaging techniques are also being developed to allow the evaluation of the functional response of the recipient brain to the administration of stem cells or their mobilization from internal stores.

The benefit from the administration of stem cells will be synergistic with other behavioral or environmental influences. The influence of training and environmental stimulation on recovery poststroke, particularly in animals that have been genetically altered or in which stem cells have been activated or have been supplied, must be better understood. One important specific goal would be improving our understanding of the appropriate time course for training intervention after stem cell mobilization or administration. Clinical data are strongly in favor of early mobilization and training,[112,113] but the literature suggests that early forced use of the affected limb may increase tissue damage.[114] Even if the increased tissue loss did not correspond to unfavorable outcome, it is clearly an unwanted effect, one which might make the brain more vulnerable and neutralize any benefits from the stem cells. Thus, while therapy combined with training is likely to be more effective than either alone, the ideal combination is still unknown and must be determined.

DESIGN OF CLINICAL TRIALS WITH STEM CELLS AND GENE THERAPY IN STROKE

In human stroke, the hypothesis that a cellular graft of neuronal cells placed in a cortical region of ischemic injury integrates with local cortical networks and enhances recovery is testable. Clinical trials of new technologies or treatments are performed when the preclinical data demonstrate that the intervention is feasible and safe. The study population is chosen from a group in which the least biological variability is expected. Each subject should have the potential to gain from the intervention and show minimal potential for loss. Endpoints should be convincing and free from bias.

Novel interventions are often evaluated in two stages, with the first establishing safety and providing input for sample size calculations, and the second using a larger sample with a control arm to demonstrate effectiveness. Outlined below is a proposal for a trial of transplantation of autologous stem cells.

The effects of interventions, whose aim is improved function by neural regeneration/ replacement with a possible impact on functional cortical mapping, will be easiest to demonstrate in a population with a stable baseline neurologic and functional state. Interventions carried out at an earlier stage of recovery, although intellectually appealing, may risk compromising spontaneous recovery.

An attempt at neuronal transplantation in this setting has been made by Kondziolka and colleagues in an open-label trial of implantation of human neuronal cells derived from a teratocarcinoma cell line.[100] In this study 12 patients with basal ganglionic infarcts with or without associated cortical infarcts had cultured cells instilled by means of stereotactic surgery. All were immunosuppressed with cyclosporin and steroids around the time of surgery. An outcome evaluation blinded to the number of neuronal transplants was carried out 6 months after surgery. In this pilot study no deaths or cellulargraft-related side effects were observed clinically or by MRI, which is significant given the neoplastic origin of the transplanted cells. Not surprisingly, the European Stroke Scale, NIHSS, and Barthel index did not demonstrate statistically significant changes over baseline, as this pilot study was neither designed nor powered to give this information, but the study demonstrated the feasibility and safety of cellular transplantation in a human stroke population.

Based on this demonstration, it would be reasonable to carry out a trial of stem cells in stroke patients in two phases—a pilot study to demonstrate safety and feasibility, followed by a randomized trial to demonstrate effectiveness. The target population would be adult stroke survivors with measurable, significant, and relatively stable deficits. Stability of the deficit would be ensured by neurologic examination along with stroke scale and functional scales 1 month prior to the intervention and at the time of intervention. Discrete cortical infarcts in eloquent areas would be the best choices for benefit from this form of therapy. Several possible hemispheric regions could be selected on the basis of their functional significance —motor strip, visual cortex, primary language cortex and, possibly, frontal cortex involved in executive function.

The most likely intervention will probably consist of transplantation of autologous stem cells. This would obviate the need for immunosuppression and its potential confounding influences. If preclinical data support the possibility of delivery to the brain via carotid injection, then this would remove the need for stereotactic surgery. Otherwise, stereotactic surgery may be used to deliver the cells into viable regions surrounding the infarcted cortex. This delivery system has a significant advantage of being well proven, reliable, and easily accessed. Delivery of cellular grafts to regions in which blood flow is too low to support additional neurons should be avoided, as it raises the potential of worsening function. Thus, measurement of cerebral blood flow by PET scanning or computed tomography (CT) perfusion methods may be advisable prior to grafting. It would also be very desirable to be able to monitor the stem cells after they are mobilized or administered. Initial thoughts in this regard are to tag them magnetically or metabolically to monitor their progress in the brain by MRI or PET, respectively. Primary outcome measures would be functional scales (Modified Rankin, Barthel, neuropsychological scales). Functional MRI would provide the main secondary outcome measure.

Clinical and radiological follow-up for a period of 1 year would be ideal since the primary purpose of the pilot study would be to demonstrate safety and feasibility. Experience gained during the pilot trial could be used to target a more homogenous group of patients with regard to region of injury in the full trial. The effectiveness trial would randomize patients with similar cortical injuries at baseline. As the primary outcome measures are potentially subject to bias, this trial is best conducted as a double-blind study with sham surgery. Since the control group would be subjected to an invasive procedure from which there is no reasonable hope of benefit, careful ethical review and consent process would be required. A trial in which the control group is not subjected to sham surgery would require more objective outcome measures to be convincing. Control and experimental groups would be matched with respect to social setting, access to medical care, and rehabilitation services. Standardized clinical evaluations would be performed through the first year, with the primary outcome measure at 1 year. Clinical and safety follow-up would continue for several years.

Stroke survivors face severe functional limitations, with no effective therapy available to them. Stem cell therapy has the potential for effecting improvement: it is time to subject this potential to rigorous evaluation.

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22.
Combination therapies, restorative therapies and future directions

Majaz Moonis and Marc Fisher

COMBINATION THERAPIES

Several factors make the treatment of acute stroke both challenging and disappointing. The concept of an ischemic penumbra (area of low perfusion that is viable and potentially reversible) is now well established.[1] Factors that determine the duration of viability of the penumbra include the acuteness of the ischemic insult, size and duration of the occlusion, collateral circulation, the speed of recanalization, as well as reflow-related reperfusion injury. Ischemia results in the activation of the ischemic cascade via release and reduced uptake of glutamate, which leads to the activation of postsynaptic receptors. This, in turn, results in calcium influx and a cascade of cell injury, release of cytokines, free radical generation, compounded by reperfusion injury, that eventually may reduce blood flow again.[2] Part of the reperfusion injury phenomenon is dependent on intercellular adhesion molecules (ICAM) and their secondary effects.[2]

Studies of acute thrombolysis within the first 3 hours intravenously and first 6 hours intra-arterially have been shown to reduce the infarct size and improve the chance of a good outcome.[3–5] However, only a limited percentage of acute strokes can be treated because of the short time window. Large hemispheral infarcts —greater than one-third of the middle cerebral artery (MCA) territory—are a relative contraindication to thrombolytic therapy since there is a significantly higher risk of secondary hemorrhagic conversion. Furthermore, once reflow is established, reperfusion injury may limit the usefulness of intervention.[2] All of these observations suggest that if there are ways of reducing tissue damage by other mechanisms (neuroprotection), there may be a potential to enhance recovery.

Neuroprotective drugs have been shown to be useful in animal models. These drugs act at several different levels of the ischemic cascade. Drugs may reduce glutamate release, prevent glu-tamate-linked activation of receptor-mediated calcium influx—*N*-methyl-D-aspartate (NMDA) receptors and AMPA receptor antagonists, glycine antagonists. Selfotel, an NMDA receptor antagonist was highly effective in reducing infarct size in animals. However, a large multicenter phase III trial was stopped prematurely secondary to excessive mortality in the treated group. Patients experienced significant cognitive side effects (phencyclidine (PCP)-like effects). Drugs acting at receptor mediated calciumconducting channels (AMPA and glycine antagonists) while demonstrating lesser side effects did not show clinically beneficial outcome. The recently completed phase III study of a glycine antagonist gavestinel (GV 150526) in ischemic stroke treated within the first 6 hours was found to be negative. Moreover, in this trial, patients who received recombinant tissue plasminogen activator (rt-PA) also did not show any benefit.[6]

Drugs that are calcium antagonists prevent excess calcium influx into cells and thereby prevent activation of the calcium-induced ischemic cascade. Nimodipine, a voltage-mediated calcium channel antagonist reduced the volume of infarction in the permanent occlusion models but did not prove to be clinically

useful.[7] Gamma-aminobutyric acid (GABA) agonists have been effective in reducing infarct size in animal models. Clomethiazole, a GABA agonist, was tested in a phase III trial and was found to be ineffective.[8] Patients with acute ischemic stroke were treated within 12 hours of stroke onset. The study failed to show any significance with clomethiazole compared with placebo.

Drugs acting further downstream in the ischemic cascade, including free radical scavengers, nitric oxide inhibitors, and inhibitors of lipid peroxidation, were all effective in reducing infarct size in animals but failed to demonstrate efficacy in clinical trials. Lubeluzole, a nitric oxide inhibitor that was initially promising, had a higher death rate in the treated group in the high-dose category. Two other larger trials revealed no difference between the treated and placebo groups. Several clinical trials of membrane stabilizers, including GM1 gangliosides and CDP-citicoline were again found to be ineffective.[9] Fibroblast-derived growth factor in conjunction with a vehicle bypassed the blood-brain barrier and revealed a highly significant reduction of 70% in the infarct volume in an MCA occlusion model but failed in clinical trials.[10] In a multicenter randomized controlled trial, tirilazad, a lipid peroxidase inhibitor, was found to be ineffective.[11]

Overall, many neuroprotective drugs acting at different levels of the ischemic cascade have all been effective in reducing infarct volume in various animal studies but have failed to demonstrate efficacy in clinical trials. There could be several explanations for this discrepancy: patient groups were not homogenous; enrollment periods were long ranging, from 6 to 12 hours; and serious side effects limited the use of doses that may have been effective.

RATIONALE BEHIND COMBINATION THERAPY

Combination therapies have the potential to counteract some of the limitations imposed on previously acute therapy and potentially to improve neurologic outcome. Thrombolytics could be combined with neuroprotective drugs, and neuroprotective drugs acting at different sites of the ischemic cascade could be used in combination. Such combinations may be potentially useful in extending the time window for thrombolysis, reducing infarct size, and ameliorating the adverse effects that limit therapy.[12,13]

COMBINATION THERAPY OF RT-PA AND NEUROPROTECTIVE DRUGS

Combining rt-PA with neuroprotective drugs may be helpful in several ways. First, initial treatment with neuroprotective medications may extend the window for administering thrombolytic therapy. This may allow for the large number of patients seen outside the current time window of 3 hours to receive thrombolytic therapy. Secondly, pretreatment with a neuroprotective agent followed by effective reperfusion may minimize tissue loss and allow for a better functional outcome. Thirdly, neuroprotective agents, by reducing the potential size of the infarct, may reduce the incidence of intracerebral hemorrhage. Post-hoc analysis of the ECASS-II data revealed intracerebral hemorrhage to correlate with infarct size.[14] The combination of appropriate classes of neuroprotective drugs, e.g. free radical scavengers with thrombolytics, could potentially reduce the extent of reperfusion injury.

Although no phase III clinical trials of combination therapy exist at present, animal data show promise. In a rat embolic stroke model, citicoline (250 mg, 500 mg) was injected into the middle cerebral artery at 75 min and rt-PA was administered 45 min later. The combination of citicoline and rt-PA resulted in a greater reduction of the infarct volume than either drug used alone.[15] In a rabbit thrombolysis model, rt-PA was given successfully with antibodies to ICAM (enlimomab). The rationale was to reduce reperfusion injury and reocclusion. Thrombolysis with rt-PA alone given within 2 hours was not sufficient but combined with

anti-ICAM-1 resulted in a significant treatment effect. In another study with an embolic stroke model in rabbits, pretreatment with a CD18 anti-ICAM antibody before rt-PA reduced the infarct size by 21%, improved perfusion, and reduced free radical formation.[16] Although results with ICAM antibodies in human trials have been negative, nevertheless, they do suggest that the idea itself is sound and that another such drug may be better tolerated.[17–19]

Lyden et al.[20] conducted a study of clomethiazole in combination with rt-PA. Clomethiazole was administered within 12 hours of onset of stroke and continued as a 24-hour infusion. Thrombolysis with rt-PA was administered according to the NINDS protocol. Serious adverse affects were similar in the treated and placebo group. A Barthel score of greater than 60 was achieved in 53% and 45% of the treated group and placebo group, respectively. The study demonstrated that this combination therapy appeared safe with respect to mortality and serious adverse effects and highlighted the need for an efficacy study. Another combination therapy trial of rt-PA and lubeluzole was terminated prematurely when a concurrent phase III study of lubeluzole was found to be negative. At the time of termination, no serious adverse effects were reported and overall mortality of 26% was comparable in the lubeluzole and placebo groups.[21]

COMBINATION THERAPY OF NEUROPROTECTIVE DRUGS

Another possible combination could be two neuroprotective drugs that have synergetic effects. Furthermore, if the combination allows for the use of reduced doses of the individual drugs, the dose-related adverse effects of the individual drugs may be reduced.

Muscimol, a GABA agonist, combined with MK-801, resulted in marked improvement over the individual neuroprotective effects of the two drugs alone. The risk of white matter vacuolation was reduced as well, and reperfusion injury was reduced.[22,23] Another example is the combination of citicoline with MK-801. Both drugs were given in small doses. Citicoline was given at half the dose (250 mg) previously shown to be effective alone. The two drugs were given at 60 and 75 min, respectively, after MCA occlusion. After 7 days, neither citicoline or MK-801 had any significant individual effect, but the combination resulted in greater than 50% reduction in infarct size.[15] Similarly, using a suture occlusion rat model of middle cerebral artery stroke, Schaebitz et al.[24] demonstrated a synergistic effect of basic fibroblast growth factor with citicoline.

How do we translate the results of these animal studies into effective combination therapy clinically? First, it is evident that neuroprotection in conjunction with rt-PA would be most effective if given early after the ischemic event. Secondly, the choice of drugs should be based on results of animal studies, as well as the site of action. Drugs targeting the initial and subsequent parts of the ischemic cascade should be considered in combination. Drugs with favorable adverse-effect profiles, such as maxi-K channel openers combined with free radical scavenger or nitric oxide inhibitors such as lubeluzole, would provide a rational combination. Similarly, certain drugs such as lubeluzole, citicoline, and channel channel antagonists that came close to significance in individual phase III trials could be used in combination or with thrombolytic therapy.

ENHANCING STROKE RECOVERY

The primary focus of acute stroke therapy is to improve outcome by salvaging ischemic brain tissue destined for infarction and then reducing disability. This approach has proven to be a daunting challenge, with few successes and many unsuccessful trials. There are many potential reasons to explain why acute stroke interventions have not proven to be beneficial, but one important likely explanation is that the time

window during which ischemic tissue might be rescued appears to be quite short.[25] If this is the case, then even very potent thrombolytic or neuroprotective therapies may only demonstrate benefit when initiated very rapidly after stroke onset.

Another therapeutic approach to improving outcome after stroke is to enhance the natural tendency toward improvement. Recovery can take place by the unmasking of function in non-damaged brain regions or by new learning.[26,27] There is considerable evidence from brain activa tion studies that undamaged brain regions can subsume functions lost secondary to ischemic injury elsewhere in the brain.[27] Neuronal sprouting and new synapse formation may both contribute to the process of adaptation.[28] Pharmacological enhancement of these processes is possible and is one approach to enhancing recovery after stroke. Neurotrophic growth factors such as basic fibroblast growth factor (bFGF), nerve growth factor (NGF), and osteogenic protein-1 (OP-1) have been shown to improve functional outcome after stroke without affecting infarct size.

The most extensively studied growth factor is bFGF, an enhancer of axonal sprouting. When given acutely after stroke onset in rats, bFGF reduces infarct size.[29] Delayed, intracisternal administration of bFGF 24 hours after stroke onset and then twice weekly for 4 weeks improved functional outcome without reducing infarct size.[30] In two clinical trials employing bFGF, no overall beneficial effect was observed, although in one trial patients who were treated for 24 hours intravenously and had a delayed onset of treatment demonstrated a trend toward better outcome.[31,32] OP-1, a member of the bone morphogenic protein family, is expressed widely in the brain: it promotes dendritic growth in tissue culture.[33] The administration of OP-1 at 1 and 4 days after stroke onset into the cisterna magna of rats subjected to permanent MCA occlusion significantly improved functional outcome 1 month after stroke onset without affecting infarct size.[34] Even initiating OP-1 therapy 3 days after stroke onset improved delayed outcome. Clinical trials of OP-1 have not been initiated yet.

Amphetamines are another potential pharmacological approach that might enhance stroke recovery. Amphetamines induce release of monoamine neurotransmitters. In rats, D-amphetamine initiated 3 days after stroke onset and then given as a daily intraperitoneal dose until day 30 improved functional outcome.[35] This behavioral benefit was associated with increased levels of the growth cone protein, GAP-43 and synaptophysin expression. Several very small clinical trials with D-amphetamine have been performed. The results of two trials suggest that D-amphetamine might improve motor function, but a third study did not support these observations.[36] A much larger clinical trial of amphetamine as an enhancer of recovery after stroke is underway and will likely provide more conclusive information as to the presence or absence of treatment effects.

CDP-choline (citicoline) is a substance that enhances membrane repair and also has anti-free radical effects. When given acutely after stroke onset, CDP-choline reduces infarct size.[37] However, the membrane repair effect suggests that it might also improve recovery by other mechanisms.[38] Several clinical and magnetic resonance imaging (MRI) studies with CDP-choline were performed with initiation of therapy up to 24 hours after stroke onset.[39,40] The overall results of these studies have not achieved a statistically significant benefit on the primary outcome. However, a meta-analysis of the trials does support an overall treatment effect in moderate and more severely affected patients. With the late initiation of treatment in most patients, the majority of the benefit potentially associated with CDP-choline is likely to be related to enhancement of recovery and not acute neuroprotection. An additional CDP-choline clinical study is contemplated and will presumably resolve whether this drug is an effective stroke treatment or not.

A novel and potentially very exciting approach to enhancing recovery after stroke is the application of cell-based therapies. Cell-based therapies are related to the transplantation of neural stem cells, post-mitotic neuronal cells, or xenogenic cells into the central nervous system (CNS). These transplanted cells have the

potential to directly replace injured CNS tissue and replicate lost function or to indirectly improve functional outcome. After transplantation, neural stem cells can migrate over substantial distances and then differentiate into neuronal and glial elements at sites of prior injury. In rats subjected to experimental stroke, neural stem cells have been shown to migrate to the site of ischemic injury and to improve function in a water maze task.[41] It may also be possible to activate endogenous neural stem cells in the adult brain after ischemic injury to produce effects similar to those observed after transplantation.[42] Non-neuronal stem cells have also been transplanted into the brain and have demonstrated improved functional outcome after experimental stroke. In a very interesting recently reported experiment, bone marrow stromal cells were injected intravenously into rats 24 hours after the induction of experimental stroke.[43] At 14 days, functional improvement was observed in animals that received the cell injections and histological assessment demonstrated the presence of these injected cells within the region of ischemic injury. Preliminary reports about the safety and feasibility of stem cell transplants into stroke patients have begun to appear. Much further information is needed about the safety of such a treatment approach before large efficacy trials can begin. However, cell transplantation appears to offer a novel and potentially exciting modality for improving function after stroke that can likely be initiated days, weeks, or even longer after stroke onset.

FUTURE DIRECTIONS

Currently, the only approved therapy for acute stroke is intravenous (IV) rt-PA within the first 3 hours after stroke onset based upon the results of the NINDS trial.[44] The results of PROACT-2 suggest that intra-arterial (IA) thrombolysis may be effective in selected patients up to 6 hours after stroke onset and subset analyses of ECASS-1 and ECASS-2 are also suggestive that IV thrombolysis may be useful in some patients beyond 3 hours.[45–47] These suggestions will need to be confirmed in larger trials that clearly demonstrate which patients are likely to benefit. Despite the lack of precise evidence, IV and IA thrombolysis is being used beyond the 3-hour window in some centers. The use of diffusion and perfusion MRI to identify patients who still appear to have salvageable ischemic tissue may enhance the selection of patients who are more likely to benefit from delayed thrombolysis. These MRI techniques are being used in a few centers to select patients for delayed thrombolysis with encouraging preliminary results.[48] Despite the lack of clear-cut, incontrovertible evidence that delayed IA thrombolysis improves outcome, this treatment is being used. The most commonly employed approach is IA rt-PA, although no controlled studies are available and the most appropriate dose remains uncertain. The status of neuroprotective therapy for acute ischemic stroke is murky. So far, none of the neuroprotective trials in acute ischemic stroke have demonstrated positive results.[49] In fact, the three most recent large, phase III trials with GV150529, clomethiazole, and Maxi-Post have been dramatically negative, with either no difference in the active treatment versus placebo group or a trend toward better outcome in the placebo group.

Considering the current status of acute stroke therapy, it is clear that newer drugs must be developed that can be shown to be effective when initiated over a longer time period after stroke onset and in a greater percentage of patients. Currently, with the narrow 3-hour window for the use of IV rt-PA, only a very small percentage of stroke patients (2–5%) are estimated to be receiving this therapy.[50] It is unknown how many patients receive IA therapy. It appears that the most viable strategy to extend the therapeutic window for thrombolytic or neuroprotective therapy will be better case selection. Diffusion-perfusion MRI can be used to identify potentially salvageable ischemic tissue. The simplest way to do this is to identify a mismatch between the perfusion lesion volume and the diffusion lesion volume, a so-called diffusion-perfusion mismatch.[48] It must be recognized that the diffusion-perfusion mismatch is only a rough approximation of the ischemic penumbra. Quantitative evaluation of diffusion and perfusion values will provide more precise

estimates of ischemic tissue status and likely extend our ability to determine which stroke patients have the capability of responding to effective therapies irrespective of the time from onset. The basic concept of imaging-based patient selection for clinical trials and ultimately clinical decision making is that the pathophysiological status of the patient, not fixed time windows, will govern treatment decisions. Other imaging technologies may also be useful for identifying stroke patients with the likely presence of salvageable ischemic tissue.[51] Perfusion or xenon computed tomography (CT) combined with CT angiography appears to be a promising approach for identifying patients with an intracranial vascular occlusion and regions of moderate cerebral blood flow decline. Such moderately perfused ischemic tissue is still potentially amenable to therapy within a few hours after stroke onset. The disadvantage of CT is the lack of precise characterization of the extent and severity of parenchymal injury.

The other likely strategy for extending the therapeutic time window for acute ischemic stroke will be to use combination therapy. The concept of combination therapy has been widely developed in other disorders such as AIDS, cancer, and ischemic coronary artery disease. For acute ischemic stroke, combination therapy can be envisioned in a variety of ways.[49] One approach would be to employ a neuroprotective drug early after stroke onset to delay the evolution of the ischemic penumbra toward irreversible injury. After the neuroprotectant is given, an MRI battery can then be used to document the presence of a penumbral pattern, followed by IV thrombolysis beyond the 3-hour window. In clinical trials, placebo groups will have to be employed to document the benefits of the active treatments with this approach.

Another approach to combination therapy would be the addition of a therapy against reperfusion injury after the use of thrombolytic therapy. It is now clear from both animal and human studies that reperfusion injury does occur, although the mechanisms inducing it and the clinical significance and prevalence remain to be precisely elucidated.[52,53]

A third approach to combination therapy would be to combine two similar therapeutic modalities. For example, a pilot study of combined IV and IA thrombolysis is currently underway. Appropriate patients are treated with IV rt-PA within 3 hours of stroke onset. Patients who show no obvious clinical benefit are then studied to document the presence of a vascular occlusion and, if present, they then receive IA thrombolysis. This is an elegant and intensive treatment approach that is likely to show benefit. Unfortunately, it will be difficult to implement in most hospitals and does not extend the time window for treatment beyond 3 hours because patients must still be initially treated with IV rt-PA before 3 hours. Combinations of neuroprotective therapeutic modalities can also be envisioned. An interesting approach would be to combine a therapy directed at the initial steps in the cascade of ischemic injury with one directed at a more downstream portion of the cascade. In thinking about combination therapy, one important point to consider is that combination therapy trials should begin without proof that both agents are definitely effective by themselves. A key element in combination therapy is that synergy between the two treatment modalities should enhance the chances for overall success and that one or both elements of the combination may not be effective on its own.

The field of acute stroke therapy has been predominantly one filled with disappointments balanced by a few successes. Many lessons have been painfully learned. It remains an area of great need for advancement, with a very large gap in effective treatment. New strategies must be considered to move us forward toward the goal of having therapies that work and can be used in a large percentage of the ischemic stroke population. The novel approaches proposed by others and ourselves will hopefully help to meet these challenges.

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Index

Numbers in italics indicate *tables* and *figures*.