Foreword

The foreword to volumes 11 and 12 of the first series of the *Handbook of Clinical Neurology* dedicated to vascular diseases (1972) started with a famous maxim ("On a l' âge de ses artères"), emphasizing the importance of vascular diseases and their relation to the aging process. Nowadays, other pathological processes are considered as even greater threats to normal aging. Cerebrovascular diseases, however, continue to be the most common life-threatening and disabling neurological disease in the USA and in many other countries. It is therefore with great pride that we present this volume of the *Handbook of Clinical Neurology* which is one of three volumes dedicated to stroke.

These three volumes are part of the third series of the *Handbook of Clinical Neurology*, for which we have editorial responsibility. In order to provide insight into physiological and pathogenetic mechanism and a basis for new therapeutic strategies for neurological disorders, we have specifically ensured that the neurobiological aspects of the nervous system in health and disease are covered, as well as the more clinical aspects of neurological disease. During the last quarter-century, dramatic advances in the clinical and basic neurosciences have occurred, and these are emphasized in each volume of the handbook. In addition to the print form, the series is now available electronically on Elsevier's Science Direct site. This makes the handbook more accessible to readers and will also facilitate search for specific information.

The present three volumes deal with various aspects of strokes. This group of disorders is bound to acquire even greater importance with the aging of the population throughout the world. The chapters gathered in these volumes were written at the original instigation of Julien Bogousslavsky and Marc Fisher, and were under their editorial supervision. For personal reasons unrelated to this series, however, Dr. Bogousslavsky has felt compelled to withdraw his name as volume editor, but we wish to record our gratitude to both editors and to all the authors for the time and effort that they dedicated to this project. As series editors, we reviewed all the chapters and made suggestions for improvement, but we were delighted to read such scholarly and comprehensive accounts of different aspects of stroke.

We hope that these volumes will appeal to clinicians and neuroscientists alike. Until a few years ago, strokes were considered "experiments of nature" which provided enormous help in understanding the functional anatomy of the brain, but for which little could be done in terms of therapeutic intervention and prevention. Advances in our understanding of the biochemical background of strokes coupled with advances in fields as diverse as epidemiology, genetics, neuroimaging, interventional radiology, surgery, and even clinical psychology have profoundly altered our approach to stroke. In the previous series dedicated to vascular diseases, only two or three chapters dealt with therapy. In the present series, no less than 11 chapters cover therapy, including prevention and management. Significant new advances continue to occur in all aspects of stroke research, leading to new insights that demand a critical appraisal. Our goal is to provide basic researchers with the foundations for new investigations. We also intend to give clinicians a source reference to enable them to gain a thorough knowledge and understanding of the clinical features and management of the many neurological manifestations of stroke.

We are grateful to all those who contributed their time and expertise to summarize developments in their field and helped put together this outstanding volume. As always, we are especially grateful to the team at Elsevier for their unfailing and expert assistance in the development and production of this volume.

Michael J. Aminoff
François Boller
Dick F. Swaab

Preface

The *Handbook of Clinical Neurology* has been a vital and comprehensive source of information for decades, encompassing the entire gamut of knowledge related to clinical neurology and its basic science underpinning. The current revamping and expansion of this historically important resource represents a major endeavor for the series editors, volume editors, and contributors. It has been my privilege to participate in this task as the volume editor for the cerebrovascular portion of the updated series.

The field of cerebrovascular disorders has experienced a rapid expansion of many aspects of knowledge from basic mechanisms of disease to enhanced diagnostic and therapeutic capabilities. These volumes dedicated to cerebrovascular diseases were conceived with the intent of comprehensively covering all of the major aspects of neurovascular disorders managed by physicians around the world. This comprehensive effort required contributions from a large number of authors from many disciplines, leading to three volumes and several thousand pages of material. I thank the contributors for their comprehensive, insightful and illuminating chapters. Their efforts and time made the completion of these volumes related to cerebrovascular disorders possible. I also thank the staff at Elsevier for their considerable efforts related to the completion of these volumes. I thank Julien Bogousslavsky for his contributions in the design and implementation of these volumes.

The knowledge base related to the field of cerebrovascular disorders continues to expand at a rapid pace. It is my hope that the material contained within these volumes will educate those who are interested in this area and inspire some to contribute to this ongoing effort so that understanding of the pathophysiological basis of these disorders and patient care will continue to improve over the coming decades.

Marc Fisher

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Chapter 48

Assessment of a patient with stroke: neurological examination and clinical rating scales

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48.1. Neurological examination

The neurological examination is a time-honored physician skill that is honed by neurologists and a key component of the clinical assessment of a patient with suspected stroke. The emphasis of the neurological examination may vary among patients and differences in evaluation are influenced by the patient's history or other findings detected prior to the physical examination. Unfortunately, none of the abnormalities found on neurological examination are specific for stroke; other acute brain illnesses can produce the same neurological findings. Besides defining the neurological deficits, clinical issues that are addressed by the examination are also influenced by the time since the stroke. The initial examination helps localize the lesion and provides clinical–anatomical correlations to help answer the question: "Where is the stroke?" This question is answered by the pattern of neurological impairments and because specific combinations of signs point to a defined brain location (Bogousslavsky et al., 1988; Bogousslavsky, 1991; Donnan et al., 1993; Vuilleumier et al., 1995; Tatu et al., 1996, 1998). In addition, the baseline neurological examination provides information that addresses the question: "How severe is the stroke?" In general, the types and severity of neurological deficits correlate with the size of the brain injury and thus the seriousness of the vascular event. This information affects decisions about acute treatment and may provide prognostic guidance.

Subsequent examinations may be performed to detect neurological worsening or improvement. In particular, detection of increased neurological impairments affects management, including treatment of medical or neurological complications. Persisting neurological impairments found on examination have a direct correlation with subsequent disability or societal handicap and the severity of findings found on a convalescent examination are used to rate outcomes from stroke. Enduring neurological deficits also affect decisions about the types of and locations for rehabilitation. All these features of the neurological examination are of direct relevance to the patient, family, physician, and society. Because of its many attributes and clinical utility, the neurological examination remains the clinical standard to which other components of the evaluation of the patient are compared. Specific sections of the neurological examination are used to construct the various clinical rating instruments to assess patients with stroke.

The components of the neurological examination are outlined in Table 48.1. The sequence of performance of the parts of the examination varies greatly but it is important to do as complete an assessment as possible. In addition, the emphasis of parts of the examination diverges among patients. Depending upon the patient's status and other neurological findings, some components of the examination may be omitted. For example, station and gait may not be tested in a critically ill patient because the patient's status or the severity of other neurological impairments may preclude testing. A comatose patient cannot do this part of the examination or many other aspects of the neurological examination that requires communication with and cooperation of the patient. A patient with a volatile blood pressure may be too unstable medically for

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Table 48.1

Components of the neurological examination

Level of consciousness
Cognition and behavior
Station and gait
Motor system
Sensory system
Coordination
Reflexes
Vision
Eye movements
Other cranial nerves

the patient to be asked to stand. Conversely, station and gait may be the key aspect of the neurological examination of a patient with a suspected infarction of the cerebellum or during assessment of recovery from stroke. Thus, parts of the examination that were omitted at baseline might be tested as the patient's condition improves.

Detailed assessment of focal cognitive impairments might not be possible in a patient with impaired consciousness. An acute delirium, aphasia, or disturbance in consciousness affects the patient's ability to cooperate with the examination and alternative strategies to test parts of the examination may be needed. For example, visual field defects might be detected by responses to direct threat if the patient cannot comply with instructions to count fingers. Because the bedside neurological examination often provides limited information about subtle cognitive impairments, a more formal neuropsychological assessment may additionally be used to define important but restricted behavioral or higher brain disturbances. Other limitations of the neurological examination include the expertise of the physician in performing the assessment, the physician's inability to recognize the presence of any subtle deficits, and the failure to integrate the findings.

Some basic principles may be applied when interpreting the findings detected on neurological examination. In the acute stroke setting, impairment in consciousness or a delirium is more likely to be found among patients with hemorrhages than among patients with infarctions (Harrison, 1980). The exception to this rule is a major infarction in the brainstem, which causes coma. Severe headache, nausea, and vomiting are also more common with hemorrhages than with infarction (Arboix et al., 1994; Ferro et al., 1995). In general, the presence of nausea and vomiting in a patient whose other signs point to an acute vascular event of the cerebral hemisphere suggests a hemorrhage. The combination of prominent headache, nausea, and vomiting with the absence of other neurological signs is most commonly associated with subarachnoid hemorrhage. Approximately 20% of patients with infarction having the complaint of headache, severe nausea and vomiting can be found with infarctions in the brainstem or cerebellum (Gorelick et al., 1986; Ferro et al., 1995).

Because most infarctions are secondary to occlusion of one artery, the resulting neurological signs should reflect injury to a discrete area of the brain. The patterns of deficits are relatively stereotyped. Findings can be used reliably to predict the location of infarction. On the other hand, hemorrhages often do not respect a specific vascular anatomic territory and the types of secondary neurological impairments do not follow the patterns that are often seen with infarctions. Infarctions more commonly affect the cerebral cortex than hemorrhages do. Thus, the presence of discrete cognitive or behavioral impairments points to ischemia as the underlying vascular event.

Much of this chapter focuses on the importance of the types of neurological impairments in predicting the location of an infarction (Table 48.2). This localization is important for management, including decisions about evaluation, acute care, and long-term treatment. In general, infarctions are differentiated into lesions that primarily involve (1) the cerebral cortex and adjacent lobar white matter, (2) the deep nuclear and white matter structures of the hemisphere, (3) both deep and more superficial cerebral brain, or (4) the brainstem and cerebellum. The patterns and combinations of neurological impairments differ among these four groups. In many cases, the neurological signs are stereotypical for specific locations for infarctions.

The most likely cause of stroke can be predicted by the location of the infarction. Lesions restricted to cortical vascular territories are usually secondary to embolic occlusions of branch pial (cortical) arteries (Bogousslavsky et al., 1989; Bogousslavsky, 1991). The emboli may arise from an extracranial or intracranial arterial lesions or from the heart. Most small infarctions restricted to the deep hemispheric areas are due to local small-artery disease, often in the setting of chronic hypertension or diabetes mellitus (Fisher, 1982, 1991; Boiten and Lodder, 1991). Infarctions affecting both deep and cortical structures are usually secondary to occlusion of a major intracranial or extracranial artery such as the internal carotid artery or the proximal segment of the middle cerebral artery (Lhermitte et al., 1970; Caplan et al., 1985).

Both the acute and long-term prognosis for an infarction is influenced by the pattern of the neurological impairments. The 30-day mortality among patients with large hemispheric infarctions producing multiple

Table 48.2

General patterns of neurological abnormalities pointing to the location of infarction

	Local cortical infarction	Hemisphere lacunar infarction	Multilobar cerebral infarction	Brainstem infarction
Consciousness	Normal	Normal	Normal or drowsy	Normal to coma
Cognitive impairments	Prominent	Subtle	Prominent	Absent
Motor impairments	Contralateral, arm, face, or leg not equal	Contralateral, arm, face, and leg equal	Contralateral, arm, face, and leg equal	Contralateral, bilateral, ipsilateral face
Articulation	Usually normal	Mild/moderate dysarthria	Mild/moderate dysarthria	Moderate/severe dysarthria
Cutaneous sensory impairments	Contralateral, arm, face, or leg not equal	Contralateral, arm, face, and leg equal	Contralateral, arm, face, and leg, equal	Contralateral, ipsilateral face dissociated
Comparison of motor and cutaneous impairments	Often concordant	Usually discordant	Usually concordant	Usually discordant
Abnormal coordination secondary to motor or sensory loss	Contralateral	Contralateral	Contralateral	Contralateral
Abnormal coordination secondary to cerebellar impairments	Absent	Absent	Absent	Ipsilateral
Visual loss (homonymous)	Prominent contralateral	Subtle contralateral	Prominent contralateral	Absent
Abnormal eye movements	Ipsilateral, conjugate gaze palsy	Absent	Ipsilateral, conjugate gaze palsy	INO+ contralateral gaze palsy
Cranial nerve palsies	Absent	Absent	Absent	Present, ipsilateral

Patterns vary if infarction is in the dominant or non-dominant hemisphere. Can be bilateral hemisphere in exceptional cases. + internuclear ophthalmoplegia.

deficits is considerably higher than among patients with cortical or isolated deep hemisphere strokes (Heinsius et al., 1998). Patients with mild or restricted impairments generally have a favorable outcome. Patients with more severe impairments, including those with cognitive defects, are more likely to have serious residuals that lead to disability or loss of independence.

No approach to the neurological examination is foolproof. Predicting the localization of the infarction is based on probabilities and patients may violate the "rules." The severity of the neurological impairments may change spontaneously or as a consequence of other factors such as fatigue, concomitant illnesses, or complications of the stroke or its treatment. Worsening in neurological signs also reflects progression or recurrent stroke, while improvements generally reflect recovery. Thus, physicians should interpret the neurological signs in light of the patient's history, including interval developments.

48.1.1. Level of consciousness

Both the public and medical personnel recognize the importance of impairment in consciousness. In reality, it is a vital sign. Consciousness should be evaluated first. Consciousness is included in any scoring system that determines the severity of a stroke. The level of consciousness is usually described as alert, drowsiness, stupor, or coma. These are the descriptions of level of consciousness that are included in the National Institutes of Health Stroke Scale (NIHSS) (Brott et al., 1989a). In addition, a delirium may be detected among patients with a hemorrhage. Regardless of the type of illness, depression in consciousness is an important negative prognostic finding (Szczudlik et al., 2000).

A decline in consciousness usually means that the vascular event is severe and the prognosis is poor. For example, among patients with aneurysmal subarachnoid hemorrhage, survival was approximately 85% among patients who were initially alert and 15% among patients who arrived in a coma (Torner et al., 1981). Detection of stupor or coma affects emergency management. Protection of the airway, probably including intubation, is needed to avoid obstruction, aspiration, or pneumonia. Other measures of life support are also critical.

Most patients are alert during the first hours following an infarction (Table 48.2). Almost all patients with a lacunar infarction within the cerebral hemisphere or a branch pial occlusion (cortical infarction) have normal consciousness. While patients with major hemispheric infarction may act stunned, their level of consciousness is not impaired. Most patients with stroke respond quickly to stimuli and are aware of their environment. They interact with the physician and will follow commands or often mimic gestures. For example, an aphasic patient maintains good eye contact and attempts to communicate in non-verbal ways. Drowsy patients are sluggish in response to verbal stimulation but their responses are correct. They may have waxing and waning of alertness. With severe drowsiness bordering on stupor, responsiveness wanes quickly. Painful stimuli are usually applied to assess consciousness in patients with stupor. Still, the response is appropriate; the patient will protect himself from the stimulus. Comatose patients have no response to painful stimuli or responses that are not protective and that often includes posturing. A delirious patient is usually agitated and irritable. He will not respond correctly to stimuli and usually will not make eye contact with the physician. While a delirium is generally uncommon among persons with infarction, it may be prominent with subarachnoid hemorrhage, strokes secondary to infections, or metabolic derangements such as hypoglycemia (Wallis et al., 1985).

Patients with non-dominant hemisphere infarctions may exhibit neglect severe enough to mimic stupor. The patient is typically encountered at the bedside with closed eyes (cerebral ptosis) and no spontaneous speech or interaction. They do not answer when asked an open-ended question such as "How are you today?" They respond immediately to specific commands or concrete questions, however, such as "Hold up two fingers." Such patients should not be considered to be in a stupor, and non-neurologically aware personnel must be counseled to avoid treating them as such.

Consciousness is a function of the reticular activating system, which is located in the brainstem. Based on a review of comatose patients with brainstem stroke, Parvizi and Damasio (2003) found that lesions causing coma are located bilaterally in the rostral pontine and caudal mesencephalic tegmentum. Thus, early coma following infarction is most likely to occur among patients with an occlusion of the basilar artery (Table 48.3). Patients with unilateral infarctions of the brainstem usually do not have coma. Waxing and waning alertness or disturbances of the sleep–wake cycle may also develop with bilateral medial thalamic infarctions secondary to embolic occlusion of the distal basilar artery or the interpeduncular-thalamic artery (artery of Percheron), known as top-of-the-basilar syndrome (Caplan, 1980; Bassetti et al., 1996). Bilateral hemispheric ischemic events may also cause coma including bilateral watershed infarctions following a major hypotensive event, or a stroke complicating major cardiovascular procedures.

Among patients with hemorrhage, early declines in consciousness are usually attributed to mass effect of the hematoma, acute hydrocephalus, or increased intracranial pressure (Harrison, 1980) (Table 48.3). A large (>2 cm in diameter) cerebellar infarction or hematoma may induce acute hydrocephalus secondary to distortion of the brainstem or compression of the fourth ventricle or aqueduct of Sylvius. In this situation, consciousness may deteriorate within hours of onset of the vascular event. Other potential causes of a decline in consciousness are seizures or metabolic disturbances such as hypoglycemia or hyponatremia.

Any decline in consciousness may be a manifestation of worsening of the stroke or development of

Table 48.3

Causes of depressed consciousness patients with stroke

Hemorrhage	
	Mass effect of hematoma
	Acute hydrocephalus
	Increased intracranial pressure
	Brainstem destruction
Infarction	
	Secondary brain edema
	Hemorrhagic transformation
	Hydrocephalus
	Basilar artery occlusion
	Bilateral thalamic infarctions (top-of-the-basilar)
	Bilateral infarctions
Other causes	
	Seizures
	Hypoxia
	Glucose disturbances
	Electrolyte disturbances
	Medications

medical or neurological complications (Table 48.3). An increase in intracranial pressure with secondary cerebral hypoperfusion or brainstem dysfunction is the most serious cause. In such a case, the deterioration in consciousness usually does not occur within the first hours following stroke. Subacute hydrocephalus (noncommunicating secondary to compression of cerebrospinal fluid pathways by the mass of the stroke or communicating resulting from decreased absorption of cerebrospinal fluid in patients with subarachnoid hemorrhage) or secondary seizures are other causes of delayed declines in consciousness. A sudden decline in consciousness may represent recurrent stroke or a symptomatic hemorrhagic transformation of an infarction. Other causes include hyponatremia, hypoxia, hypoglycemia, hyperglycemia, systemic infection such as pneumonia or urinary tract infections, or side-effects from medications. Management of the comatose patient includes supportive care to protect the patient and specific measures to treat the presumed cause of the coma.

A prolonged impairment in consciousness has a very negative effect on the prognosis. Affected patients need extensive and expensive care to prevent complications and to protect the patient. Issues such as maintenance of hydration and nutrition need to be addressed. Decisions about placing feeding tubes will need to be made. Rehabilitation is hampered because the patient is not sufficiently alert to cooperate. Plans for therapies to prevent recurrent stroke are affected. Patients with prolonged impairments in consciousness are usually admitted to a long-term care facility. Prolonged unconsciousness is a cause of considerable pain and stress to family members. Decisions about palliative care or withdrawal of life-sustaining measures often need to be addressed.

48.1.2. Cognition and behavior

Focal behavioral or cognitive impairments primarily reflect injury to the cerebral cortex. These signs are detected by the bedside examination that includes assessment of orientation, attention, memory, language, knowledge, and executive function. Talking to the patient during the time of obtaining the history usually detects problems in memory, language, attention, or orientation. Impairments in cognition can also affect the entire neurological examination; the patient may not understand the requests or questions of the physician. As a result, many of the components of the examination need to be modified to meet the patient's ability to cooperate. Some parts of the examination may need to be omitted. For example, it might be impossible to adequately test fund of knowledge in a patient with global aphasia.

The pattern of cognitive impairments may lead to the diagnosis of unilateral or bilateral disease of the cerebral cortex. The pattern of cognitive abnormalities also provides important clues about the affected area of cerebral cortex. The patterns of cognitive or behavioral abnormalities have stereotypical clinical–anatomical correlations. The presence of a restricted cognitive impairment such as aphasia without other major signs is also an important clue as to the type of cerebral infarction; it often suggests an embolic occlusion of a branch (pial) cortical artery. The pattern of cognitive impairments can also provide more detailed localization with the cerebral hemisphere. The severity of deficits also reflects the extent of the vascular injury. Disorders of cognition affect the prognosis of the patient and influence decisions about rehabilitation. For example, a patient with profound neglect, anosognosia, or Wernick's aphasia will not appreciate the nature of other impairments or the need for rehabilitation. Cognitive and behavioral disorders complicating stroke also affect both the patient's and family's perceptions on quality of life. These deficits also limit the person's ability to return to work or perform many of the activities of daily living. Thus, higher brain dysfunction affects the patient in all stages of stroke.

Because most infarctions are unilateral, it is important to differentiate the signs reflecting injury to either the right or left hemisphere (Table 48.4). Almost all

Table 48.4

Localizing value of the types of cognitive or behavioral deficits in patients with stroke

Left (dominant) hemisphere	
	Aphasia
	Alexia
	Acalculia
	Apraxia
	Gerstmann syndrome
	Abulia
Right (non-dominant) hemisphere	
	Dysprosody
	Geographical disorientation
	Neglect
	Anosognosia
	Asomatognosia
Bilateral	
	Abulia
	Impaired executive function
	Prosopagnosia
	Balint syndrome
	Anton syndrome

right-handed patients and a majority of left-handed patients have a dominant left hemisphere. The signs of dominant hemisphere stroke differ from those found with lesions in the non-dominant hemisphere. Many are readily detectable on the neurological examination. Language abnormalities are pre-eminent with infarctions in the left (dominant) hemisphere. Non-fluent aphasia associated with preserved comprehension is generally found with anterior hemisphere lesions, while fluent aphasia with associated impaired comprehension is detected with lesions in the parietal lobe or superior portion of the temporal lobe. Aphasias marked by prominent impairments in the ability to repeat are usually due to strokes near the Sylvian fissure. Watershed infarctions may also produce language impairments denoted by the retention of the ability to repeat sentences (transcortical motor or transcortical sensory aphasia). Occasionally, an atypical aphasia is detected in a patient with a striatocapsular infarction or hemorrhage in the thalamus or basal ganglia (Donnan et al., 1991). Other behavioral abnormalities with strokes in the dominant hemisphere include alexia, acalculia, apraxia, or Gerstmann's syndrome. Occasionally, abulia is detected with an infarction affecting the medial aspect of the frontal lobe.

Strokes in the non-dominant (right) hemisphere may produce dysprosody, neglect, geographical orientation impairments, anosognosia, or asomatognosia. Bilateral paramedian hemisphere infarctions, including those that complicate rupture of anterior communicating artery, may have abulia or prominent changes in executive function. Bilateral infarctions may also produce behavioral abnormalities. Those affecting the posterior aspects of the cerebral hemispheres may lead to profound behavioral disorders of vision including prosopagnosia, Anton's syndrome, or Balint's syndrome.

Behavioral or cognitive impairments are included directly or indirectly in most clinical scales that rate the severity of stroke. Among the most commonly tested items are orientation, language, and neglect. Impairments also affect the ratings found on outcome rating instruments and they influence both the patient's and family's perceptions that can be detected by scales that assess the quality of life after stroke.

Although a stroke may cause major impairments in a specific component of cognition, a single vascular event usually does cause dementia. Multiple infarctions may lead to global cognitive disturbances including impairments in memory and recurrent stroke is second to Alzheimer's disease as a cause of dementia. Stroke also may potentiate the mental impairments of degenerative dementia. Several patterns of vascular dementing syndromes including Binswanger's disease and multi-infarction dementia have been reported.

48.1.3. Station and gait

Evaluation of the patient's posture (station) and the ability to walk (gait) is a part of the examination of most patients with neurological disease. First, the patient is usually asked to stand. Then, the ability to maintain the station with eyes closed (Romberg test) is also evaluated. Thereafter, the patient is asked to walk and potential impairments are stressed by maneuvers such as tandem walking or turning. While most patients are able to walk without the use of assistive devices (braces, canes, or walkers), some may need this equipment. The need for the use of these devices in order to maintain mobility should be noted. The use of such devices is an important feature of scales that rate physical limitations following stroke (Mahoney and Barthel, 1965).

This assessment provides a screening function because walking is a sophisticated neurological activity that tests motor and sensory systems, coordination, vestibular function, vision, and higher brain function. The pattern of a gait disturbance points to the localization of the brain injury. For example, a stroke in the brainstem or cerebellum can cause truncal and gait ataxia. The patient may lurch to the affected side of the cerebellum. More commonly, many patients with a stroke in a cerebral hemisphere have a hemiparetic gait with decreased function of both the upper and lower extremities, contralateral to the lesion. Bilateral or multiple strokes can lead to other disturbances including gait apraxia or a spastic gait.

The severity of any impairment in standing or walking may affect rehabilitation; improvements in both activities are major goals for physical therapy. However, some patients may be at very high risk for falls and potential for injury greatly affects decisions about mobilization and medical management. For example, the physician may not prescribe oral anticoagulants as part of a regimen to prevent recurrent stroke because of the potential for traumatic intracranial hemorrhage or other bleeding secondary to falls.

In general, neither station nor gait is tested in the setting of acute stroke and as a result, these are not included in most acute stroke scales. The exception is the Scandinavian Stroke Scale (Lindenstrom et al., 1991). However, once the patient's neurological and medical status is stabilized, both station and gait should be tested, but with caution. The ability to stand or walk is included in most instruments that rate the outcomes following stroke. Some scales, such as the Barthel index, specifically test the ability of the patient to walk (Mahoney and Barthel, 1965). Other instruments test these activities indirectly. Major impairments in the ability to stand or walk are strongly correlated with unfavorable outcomes.

48.1.4. Motor system

Examination of the motor system is a leading component of the neurological assessment; it is evaluated during both the acute setting and convalescence. Motor responses are a key component of all clinical rating instruments including both acute stroke and outcome scales, and are the most reproducible (inter-rater agreement) items in the examination. Abnormalities are found with vascular events happening throughout the central nervous system. The pattern and severity of motor impairments provide information about the site of the stroke (Kunesch et al., 1995). Motor deficits in the upper and lower extremities are generally due to dysfunction of the corticospinal tract and are contralateral to the lesion. Motor impairments in the face and bulbar musculature may be secondary to a lesion in the corticospinal tract or to injury to one or more cranial nerves. The facial and bulbar motor abnormalities may be either ipsilateral or contralateral to the lesion. The most common motor impairment is a hemiparesis. Less commonly, a monoparesis, paraparesis, or quadriparesis is found. In addition, chorea or athetosis can be an acute motor manifestation of a stroke located deep in a cerebral hemisphere.

The degree of involvement of the contralateral arm, leg, and side of the face provides clues for localization (Table 48.2). A monoparesis may occur with a cortical lesion (Mohr et al., 1993; Boiten and Kappelle, 1995). Greater weakness of the face and arm than the leg points to a stroke affecting the lateral aspect of the cerebral cortex (middle cerebral artery) while weakness of the leg suggests that the vascular lesion has affected the medial aspect of the cerebral hemisphere (anterior cerebral artery). Relatively selective motor impairments affecting the shoulders and arms with less weakness in the hand, face, or legs can develop with a watershed infarction (Bogousslavsky and Regli, 1986a,b). If the lesions are bilateral, then "man-in-the-barrel" syndrome may result (Sage and Van Uitert, 1986). The same degree of involvement of the face, arm, and leg usually implies that the stroke has affected an area where the corticospinal fibers are concentrated; the most common locations are the internal capsule or the rostral brainstem. The finding of ipsilateral facial weakness and contralateral arm and leg weakness (crossed motor signs) points to a stroke in the brainstem. Isolated motor impairments (paralysis without other deficits) are most commonly found with small vascular lesions affecting the internal capsule or the basis pontis.

In the acute setting, the first step in assessing the motor system is to note the position of the patient's limbs in relationship to the body. This can be done while the patient is lying on a cart or an examination table. The finding of an externally rotated lower extremity (foot everted), which mimics the posture that is found with a fractured hip, usually points to a hemiparesis. The physician can also observe the spontaneous movements of the limbs to denote normal or paretic limb function. Absence of any voluntary movement points to profound paralysis (hemiplegia). Abnormal motor responses (decerebrate [extensor] or decorticate [flexor] posturing) may also be observed. These motor phenomena, which are found among patients with devastating vascular events, usually happen in response to stimulation such as endotracheal suctioning or pinching.

Alert patients are asked to move limbs. The spectrum of responses may be: (1) normal movement, (2) mild weakness manifested by a drift of the limb, (3) some difficulty moving against gravity, (4) inability to move the limb from the surface of the examination table, (5) a flicker of movement, or (6) absence of any movement. The right and left sides of the body are compared, as are the upper and lower extremities. This testing, which corresponds to the motor assessments in the NIHSS, emphasizes motor function of the proximal muscles (Brott et al., 1989a). Testing of the strength of individual muscles or muscle groups, including distal muscles, is also performed. Testing coordination is another measure of motor function. While coordination may not be assessed in a paralyzed limb, such testing might accentuate mild-to-moderate weakness or a paretic extremity. For example, difficulty with fine finger or rapid alternating movements is often a manifestation of motor impairments. In some patients with mild strokes, these impairments may be the most prominent motor deficits.

Motor function of face usually is evaluated by asking the patient to smile or make other facial gestures. The function of the orbicularis oculi and other facial muscles may also be assessed by asking the patient to resist opening the eyes or making other facial movements such as smiling. The aim is to determine the pattern of facial muscle weakness, which is important in differentiating an upper motor neuron pattern (sparing the muscles of the eye and forehead) secondary to a lesion of the corticospinal tract from a lower motor neuron pattern (involving the whole half of the face) secondary to an injury of the pons affecting the facial nucleus or facial nerve.

Muscle tone is generally normal or slightly reduced in the setting of acute stroke. However, increased tone (spasticity) in the affected muscles is often found within the first few days and increases during convalescence. Movement disorders, most commonly hemichorea or hemiathetosis, may occur acutely with

stroke or appear in the subsequent days afterwards. The abnormal movements may be of sufficient severity to necessitate early treatment. Atrophy of the affected muscles is a late consequence of stroke.

Seizure activity, which is either localized or generalized, may be detected. Seizures are more likely to occur with embolic events that affect the cerebral cortex or hemorrhages. A history of seizure complicating stroke needs to be differentiated from a focal seizure with secondary post-ictal paralysis (Todd palsy).

Problems in articulation (dysarthria) are also found among patients with strokes in either hemisphere or the brainstem. Speech disturbance therefore does not have great localizing value (Table 48.2). Dysarthria is rare with cortical lesions, present but not severe among patients with stroke affecting the deep structures of the cerebral hemisphere, and more severe with lesions affecting the brainstem. Speech that is unintelligible from articulatory problems is usually secondary to a brainstem lesion. The presence of a nasal sound in the speech points to weakness of the palate secondary to a brainstem stroke. Speech that is arrhythmic and that has a "scanning" component is found with lesions of the cerebellum.

48.1.5. Sensory system

Neurological examination includes an evaluation of the patient's ability to perceive cutaneous stimuli. Testing involves the patient's report of feeling the stimulus and whether there is any diminution in sensation or hypersensitivity. In most cases, the patient is asked to describe the quality and to quantify the severity of the sensory loss. Some patients may describe a sensation that is painful or hyperesthetic. Because the ascending tracts carrying the modalities of temperature and pain are anatomically distinct from those transporting vibration and position sense, testing includes assessments of modalities from both systems. Generally, the face, trunk, and both upper and lower extremities are tested with comparisons made between the right and left sides. Areas of sensory abnormalities may be plotted and the pattern of the sensory loss may be used to help localize the lesion. Accurate sensory testing may be limited in a patient with impaired consciousness or the ability to communicate, therefore adjustments in the testing paradigm are needed. For example, the patient's facial or emotional motor reactions to stimuli such as pain may be noted. Among comatose patients, a movement of the affected limb in response to a painful maneuver provides a clue that the stimulus was felt.

Disturbances in cutaneous sensation are found with strokes throughout the central nervous system (Table 48.2). The goal of the examination is to help localize the lesion and to provide an estimate of the severity of the stroke. In general, the sensory loss is contralateral to the lesion, whether the stroke is in the cerebral hemisphere or brainstem. Typically, sensory loss following a stroke in the cerebral hemisphere affects all cutaneous modalities. Similar to the pattern of motor impairments with cortical lesions, differences in the severity of sensory loss can vary among the contralateral side of the face and the arm and leg. The usual pattern is more involvement of the hand and face with lateral lesions and leg involvement with parasagittal lesions. Characteristically, sensory loss secondary to an infarction involving deep hemisphere (thalamus) structures affects the face, arm, and leg equally (Paciaroni and Bogousslavsky, 1998). Crossed sensory loss with impaired sensation on the ipsilateral side of the face due to dysfunction of the trigeminal system and impaired feeling on the contralateral side of the body can be detected with a lesion in the caudal brainstem, most commonly with a stroke producing the dorsolateral medullary syndrome of Wallenberg (Fisher and Tapia, 1987; Sacco et al., 1993). Because of the anatomic location of the ascending sensory pathways, bilateral sensory loss is uncommon following a vascular event in a single site. Dissociated sensory loss (selective loss of pain and temperature or vibration and position sense) is found with brainstem lesions. In some patients, the sensory loss may be accompanied by pain or hyperesthesia; this situation is relatively uncommon in the acute setting and most often develops during the period of recovery from stroke.

The abnormalities detected during the sensory examination should be compared to those found on motor testing. Differences in the location and severity of motor or sensory loss should be sought because such findings provide important clues as to the location of stroke. While some accentuation of the motor deficits is found with anterior hemispheric strokes and more severe sensory loss is found with posterior hemispheric lesions, vascular effects primarily affecting the cerebral cortex generally affect both systems. Because the primary motor and sensory cortices abut each other, strokes in the area of the central sulcus usually cause similar degrees of motor and sensory loss. The absence of any sensory findings in a patient with marked motor impairments, or vice versa, strongly points to a primary subcortical location for the vascular event. Sensory loss without paralysis can be found with restricted vascular events affecting the thalamus or brainstem. The syndrome of pure sensory stroke is most commonly found with a lesion of the thalamus. Because the spinothalamic tract, the

trigeminal complex, and the ascending trigeminal connections are located in the dorsolateral brainstem, isolated loss of pain and temperature sensation without paralysis is found with strokes in this location.

48.1.6. Coordination

Coordination of the limbs may be tested in cooperative patients. Activities include examination of fine finger movement, finger-to-nose or finger-to-finger testing, heel-to-shin testing, and rapid alternating movements. The goal is to look at the speed and smoothness of the movements, the actions between agonist and antagonist muscles, and the ability to accurately place the limb in space. While these tests are often described as measures to evaluate the function of the cerebellum, evaluation of coordination also tests the integrity of the motor and sensory systems. Incoordination secondary to motor or sensory loss is usually contralateral to the location of the stroke and the resultant clumsiness usually affects the arm more than the leg. A patient with profound motor impairments will not be able to do the tests. A patient with mild-to-moderate weakness will have problems in accurately performing the tests. The loss of sensation of position means that the patient may not know where the limb is located in space and as a result tests of coordination will be impaired. Thus, the physician should be cautious about ascribing abnormalities in coordination to cerebellar disease unless the motor or sensory impairments are mild or absent.

Disturbances in motor function are prominent with cerebellar disease (Amarenco, 1991; Barth et al., 1993) however. Because they have an important role in localizing the cerebellar areas affected by a stroke, testing coordination is important (Table 48.5). Although vascular lesions affecting the cerebellar vermis and peri-vermian portions of the hemispheres are uncommon, such strokes may produce truncal and gait ataxia, which could be detected by testing station and gait. Severely affected patients may not be able to maintain a sitting position without support. Patients with midline lesions also may have prominent scanning speech. Vascular events affecting the inferior portion of the cerebellum (flocculo-nodular lobe) may produce vertigo and nystagmus. Most vascular lesions affect the cerebellar hemispheres and the resultant impairments usually involve the upper extremity more than the lower, with the abnormalities found ipsilateral to the stroke. The abnormalities include dysmetria, dyssynergia, dysdiadochokinesia, an action and terminal tremor, and hypotonia. Rebound or overshoot can also be found. Most of these findings are elicited by asking the patient to move the affected upper extremity. Because vascular events affecting the cerebellum often involve the brainstem, affected patients often have the combination of the above neurological impairments in conjunction with cranial nerve abnormalities, paralysis, or sensory loss.

Table 48.5

Abnormalities found with strokes affecting the cerebellum

Lesions affecting the vermis and other midline structures	
	Prominent truncal and gait ataxia
	Dysarthria
Lesions affecting the flocculonodular lobe	
	Nystagmus
Lesions affecting the cerebellar hemisphere—ipsilateral	
	Dysmetria
	Dyssynergia
	Dysdiadochokinesia
	Action tremor
	Hypotonia
	Rebound or overshoot

48.1.7. Reflexes

Examination of reflexes is a traditional component of the neurological assessment but it does not add much to the determination of either the location or severity of stroke. Any changes detected by their evaluation are usually associated with other impairments. Thus, abnormalities on reflex testing buttress other signs including motor or sensory loss. Changes in muscle stretch reflexes, most commonly hyper-reflexia, help confirm that the stroke has affected the corticospinal system. Initially, muscle stretch reflexes may not be affected or hypoactive following stroke. Subsequent testing could demonstrate an increase in reflex responses. Pathological reflexes, such as the Babiński sign, also help confirm the presence of dysfunction of the corticospinal system.

Because reflexes may usually be tested in an uncooperative patient, its utility increases during the evaluation of a patient with impaired consciousness. Asymmetry of muscle stretch reflexes or the presence of pathological reflexes help distinguish the location of a major vascular event that leads to coma. Testing of cranial nerve reflexes also provides information about the functional integrity of brainstem circuits; the gag reflex tests the vagal and glossopharyngeal

nerves, the jaw jerk evaluates the trigeminal nerves, and the corneal reflexes assess the trigeminal and facial nerves. The finding of asymmetrical cranial nerve reflexes facilitates the localization of strokes. Responses are impaired ipsilateral to the brainstem lesion.

While testing the reflexes is useful in examination of a patient with suspected stroke, the results do not have important prognostic implications. As such, the results of reflex testing are usually not included in scales that test the severity of impairments or disability following stroke.

48.1.8. Visual system

Testing of the visual system provides important information about the type and severity of intracranial vascular events. In particular, abnormalities found by visual testing give data about the localization of strokes affecting the cerebral hemisphere. The components of the assessment include testing visual acuity, visual fields, pupillary responses, and funduscopic examination. Communicative patients may be asked to count fingers, to identify objects, or to read; the results provide knowledge about the visual acuity and the integrity of the visual fields. Eye opening to look at the examiner is included as a key component of the Glasgow Coma Scale. Non-communicative patients may have their vision tested by watching their responses to visual threats. They may blink when a threat is perceived in the preserved visual field while they do not react when the threat is in the impaired visual field.

Among patients with cerebrovascular disease, monocular visual loss is usually secondary to occlusion of the ophthalmic, central retinal, or cilioretinal artery. A branch retinal artery occlusion can cause a restricted monocular visual loss. Binocular visual field defects are most commonly found with intracranial vascular events. Bitemporal visual field defects may be found with pituitary apoplexy. Complete blindness of both eyes can also occur with cavernous sinus thrombosis or other acute anterior cranial fossa lesions.

Detection of a visual field defect has important localizing value; it provides strong evidence that the stroke involves the posterior portion of the contralateral cerebral hemisphere (Table 48.2). Visual field defects are relatively uncommon with small infarctions or hemorrhages involving the deep structures of the hemisphere. A lesion of the lateral geniculate nucleus may produce a homonymous sectoropia. Besides being rare, finding this defect on bedside examination is difficult. Generally, the presence of a homonymous visual field defect points toward damage in the cortex or lobar white matter. Bilateral occipital lesions can also cause complete loss of vision in both eyes (cortical blindness). Complex neurobehavioral syndromes such as Balint's or Anton's syndrome may occur (Aldrich et al., 1987). A contralateral homonymous visual field defect can occur with vascular lesions of the cerebral hemisphere. Occlusion of the posterior cerebral artery, which is accompanied with preserved blood flow to the occipital tip, may produce a contralateral homonymous hemianopia with macular sparing. Alexia may complicate an infarction in the dominant occipital lobe if the lesion extends into the genu of the corpus callosum. Lesions in the parietal lobe or supra-calcarine portion of the occipital lobe may cause a contralateral homonymous inferior quadrantopia while vascular events of the temporal lobe or infra-calcarine areas of the occipital lobe produce visual loss in the superior quadrant. Abnormalities in vision are included in most scales assessing the baseline severity of cerebral infarction and residual visual field impairments are included in some disability and outcome scales.

The pupillary responses to light test both afferent (vision) and efferent (oculomotor parasympathetic nerve) functions. An abnormality in light reaction (afferent pupillary defect) may occur with a retinal or optic nerve lesion. Blindness secondary to ischemic disease in both eyes may produce an absence of pupillary responses. Assessment of the pupils and their responses is a key component of the evaluation of the patient with impaired consciousness. Bilateral unreactive pupils may be secondary to severe brain disease. Differences in pupil size (anisocoria) also provide important information. An abnormally small pupil that does not react quickly to light is a sign of Horner's syndrome, which may be found with an ipsilateral brainstem infarction (dorsolateral medullary syndrome of Wallenberg) or damage to the ipsilateral internal carotid artery. An abnormally large pupil that does not react to light is a finding with parasympathetic dysfunction secondary to an oculomotor nerve injury. The abnormality may be secondary to an intrinsic lesion of the mesencephalon, an ipsilateral aneurysm of the posterior communicating or basilar artery, or herniation secondary to a major hematoma or infarction of the ipsilateral cerebral hemisphere. While the pupillary responses are important parts of the clinical examination of patients with stroke, they do not provide information that affect either prognosis or outcomes. Thus, pupillary responses customarily are not included in stroke scales.

Ophthalmoscopic examination also provides insights about stroke. Retinal hemorrhages can be found among patients with severe intracranial hemorrhage. Other

findings include papilledema, optic pallor, or emboli. Funduscopic examination may also reveal retinal changes secondary to diabetes mellitus or chronic hypertension.

48.1.9. Eye movements

The position of the eyes should be assessed and any spontaneous eye movements may be noted. Abnormalities in eye movements are important for localization of strokes that affect either the hemisphere or brainstem. Impairments may reflect dysfunction of specific cranial nerves or circuits within the midbrain, pons, and medulla. Impairments in ocular motility do provide important prognostic information. Thus, changes in eye movement are assessed in acute stroke scales.

Normally, the eyes are conjugate and close to the midline. A dysconjugate position of the eyes or a deviation of both eyes can be found with acute brain disease. Alert patients are asked to volitionally move the eyes and those patients with impaired consciousness have reflexive eye movement responses evaluated. In comatose patients, either Doll's eyes responses or caloric testing are performed. Motor dysfunction of the oculomotor nerve is often found in conjunction with pupillary changes.

Conjugate deviation of the eyes may be found with acute lesions of either hemisphere or the brainstem. With acute destructive lesions of the cerebral hemisphere, most commonly in the frontal lobe, the patient has a tendency to look toward the lesion. The conjugate deviation from a loss of volitional eye movements should be differentiated from a gaze preference secondary to a visual field defect or neglect. The eyes also look away from the hemiparesis. Alert patients may briefly look toward the paralyzed side and among comatose patients, the eyes can move to midline or to the other side with Doll's eyes or caloric testing. A conjugate gaze preference, often associated with adversive eye movements, could be found with an irritative lesion of the hemisphere. In this situation, the eyes are deviated towards the side of motor dysfunction. With a pontine stroke affecting the center for conjugate horizontal eye movement, the eyes are deviated away from the lesion and towards the side of the paralyzed arm and leg. An affected patient will often have ipsilateral facial nerve palsy. Alert patients with pontine infarction will not be able to look to the side of the lesion and among comatose patients, neither Doll's eye nor caloric testing will elicit a response. Severe bilateral destruction of the pontine tegmentum may cause bilateral lateral gaze paralysis; this abnormality can be found among comatose patients or among those with locked-in syndrome.

Dysconjugate gaze is generally found among patients with stroke of the brainstem (Table 48.2). Either horizontal or vertical abnormalities may be found. A skew deviation is marked by a dysconjugate vertical position of the eyes (Kobari et al., 1987). Usually, the lower of the two eyes is ipsilateral to the lesion. When the dysconjugate eye positions are horizontal, the eye closest to the midline is usually normal. If the abnormal eye is deviated laterally, the finding suggests medial rectus palsy (oculomotor nerve dysfunction). A medial deviation of the eye points to a lateral rectus palsy (abducens nerve dysfunction). The abnormality can be accentuated by asking the patient to volitionally look to the left and right or up and down. A small infarction of the rostral pons or caudal midbrain may produce an internuclear ophthalmoplegia. Besides impairment in movement in the adducting eye, nystagmus is found in the abducting eye. The stroke is ipsilateral to the adducting eye. Other disorders of ocular motility include nystagmus secondary to vestibular or cerebellar dysfunction or jerking movements consistent with seizures (Brazis, 1992; Dieterich and Brandt, 1992). Abnormal recurrent involuntary vertical eye movements (ocular bobbing) are most commonly due to pontine hemorrhage.

48.1.10. Cranial nerve palsies

In addition to affecting the facial, trigeminal, and oculomotor nerves, strokes also alter the function of the other cranial nerves (Table 48.2). Dysfunction of the acoustic, glossopharyngeal, vagus, or hypoglossal nerves may occur with lesions of the caudal pons or medulla (Vuilleumier et al., 1995). Hypoglossal nerve palsy usually is unilateral and secondary to a paramedian medullary lesion (medial medullary syndrome) (Kim et al., 1995). It causes paralysis of the ipsilateral half of the tongue. Rarely, bilateral hypoglossal nerve palsies can occur with caudal medullary infarction and produce a clinical state that appears similar to the locked-in syndrome that is found with bilateral pontine infarction.

The other cranial nerve palsies are found with dorsolateral lesions. Unilateral hearing loss most commonly is secondary to an occlusion of the anterior inferior cerebellar artery with secondary ischemia of the ear (Hankey and Dunne, 1987; Huang et al., 1993). Less commonly, hearing loss can be secondary to brainstem injury. Nystagmus, most prominent on the affected side, may also be secondary to dysfunction of the labyrinth, acoustic nerve, or brainstem (Kim, 2003). Unilateral vocal cord paralysis secondary to a vagal nerve dysfunction usually produces

hoarseness, one of the cardinal symptoms and signs of infarction of the dorsolateral medulla. Vagal and glossopharyngeal nerve dysfunction also leads to dysphagia and a nasal component to the speech. Ipsilateral impairment of the gag reflex is also found.

48.1.11. Conclusions about the neurological examination

Because of the diversity of impairments following stroke, the neurological examination remains a key clinical tool. Detected findings help the physician localize the area of brain injury. The types and severity of the neurological impairments reflect the seriousness of the stroke and are associated with outcomes. The pattern and severity of neurological impairments affect acute treatment decisions and plans for rehabilitation. Because the results of the neurological examination are of direct relevance to the physician, the patient, and society, its importance will not decline in the future.

48.2. Stroke scales

Several stroke scales are used to help quantify the types and severity of neurological defects found among patients (Table 48.6). Stroke scales are used in clinical care and in clinical trials. Quantitative scales use numerical scorings of clinical findings to give some sense about stroke severity and the scores are used to categorize groups of patients with a wide diversity of signs. The clinimetric features of a variety of scales have been reviewed (Lyden and Lau, 1991; Boysen, 1992; Hantson and De Keyser, 1994; D'Olhaberriague, 1996). The astute neurologist should be aware of the deficiencies of all currently available rating instruments; a stroke scale score is an imperfect description of an individual patient that is useful for quick communication among healthcare workers about the severity of the stroke symptoms in their patients. For the most part, the currently used stroke scales were designed to reliably describe cohorts of patients enrolled in clinical trials. To improve reproducibility among examiners of varying backgrounds, the scales use arbitrary scoring rules that are occasionally counterintuitive. Recently, stroke scales have been used to monitor individual patients treated in a clinical setting. While the score does provide information about the patient's status, the examiner should understand that the score on a stroke scale does not necessarily provide a complete description of an individual patient's deficits. Rather, the score should be considered as complementary to the other neurological and medical findings.

Some scales are used to differentiate hemorrhagic from ischemic stroke or to distinguish subtypes of ischemic stroke, either by location and clinical syndrome or by presumed etiology. The scores obtained on the scales provide prognostic information and also help select patients for treatment. Repeated performance of the stroke scale can be used to monitor the patient's course with either neurological improvement or worsening quantified by the changes in score. Finally, scales are used to help determine outcomes following stroke. Stroke scales cannot describe all the nuances of stroke and thus the rating instruments include some element of lumping of patients into groups.

The items assessed vary among the scales. Some of the rating instruments include variables other than findings detected on neurological examination. For example, some of the commonly used stroke scales can include history or epidemiological data, findings on general medical examination, the results of brain imaging, or the abnormalities detected on other diagnostic studies. These scales may be most suitable for prognostic purposes.

Clinical rating scales themselves should be tested before they are implemented in either clinical research or patient care (Feinstein et al., 1986; Asplund, 1987). Clinical scales should be easy to administer and the components should be germane to the question that is being addressed by the scale. For most stroke scales, this is the type and severity of neurological impairments found on examination. These attributes are especially important for any scale that is used in the acute setting. The findings tested by the scale should be clinically relevant; that is, the resulting scores should be of importance for physicians, patients, and society (face validity). The score should provide an image or impression of the patient's status. The scale should be tested for reliability, inter-rater agreement, and intra-rater reproducibility. These attributes are aimed to provide assurance that the scale actually rates the clinical items that are important, that more than one examiner should achieve a similar score when

Table 48.6

Stroke scales

Differentiate hemorrhagic from ischemic stroke
Categorize stroke by clinical syndrome and vascular territory
Categorize stroke by etiology (ischemic stroke subtypes)
Pre-hospital rating of the severity of impairments
Rating the severity of impairments—ischemic stroke
Rating functional outcomes
Rating outcomes by quality of life

evaluating the same clinical situation, and that one examiner will score impairments in a consistent manner. In order to assure that clinical researchers do achieve similar scores, most trials now require a process of certification in the performance and assessment of the clinical rating instruments (Albanese et al., 1994; Lyden et al., 1994).

48.2.1. Differentiating hemorrhagic from ischemic stroke

Clinical rating instruments have been developed to help differentiate hemorrhagic from ischemic stroke. The most commonly used scale is the Guy's Hospital Score (Sandercock et al., 1985) (Table 48.7). The instrument combines information about past medical history, concomitant heart disease, risk factors for atherosclerosis, history of the neurological event, and physical findings. The score adds and subtracts points; if the patient has a score of −30 to 0, the probability of an infarction is 95%; if the score is 25 to 50, the probability of a hemorrhage is 95%. The intermediate scores (0–25) are not specific for either type of stroke. Unfortunately, in validity testing done to date, these scales show a relatively low specificity and sensitivity in differentiating hemorrhagic and ischemic cerebrovascular events (Weir et al., 1994; Besson et al., 1995; Hui and Tang, 2002; Badam et al., 2003; Soman et al., 2004). Therefore, these scales should not substitute for brain imaging when evaluating a patient with suspected stroke.

Table 48.7

Guy's Hospital Score

Apoplectic onset			
	None of the following		0 points
	Two or more of the following		21.9 points
		Loss of consciousness	
		Headache within 2 hours	
		Vomiting	
		Stiff neck	
Level of consciousness			
	Alert		0 points
	Drowsy		7.3 points
	Unconscious		14.6 points
Plantar responses			
	Both flexor or one extensor		0 points
	Both extensor		7.1 points
Diastolic blood pressure (within 24 hours)			0.17 point × value
Atheroma markers			
	None		0 points
	Angina, claudication or diabetes		−3.7 points
History of hypertension			
	None		0 points
	Present		−4.1 points
Previous TIA or stroke (any number)			
	No		0 points
	Yes		−6.7 points
Heart disease			
	None		0 points
	Aortic or mitral murmur		−4.4 points
	Cardiac failure		−4.3 points
	Cardiomyopathy		−4.3 points
	Atrial fibrillation		−4.3 points
	Cardiomegaly on chest x ray		−4.3 points
	Myocardial infarction last 6 months		−4.3 points
Constant			−12.6 points

48.2.2. Categorization of stroke by clinical syndrome and vascular territory

Bamford et al. (1991) developed a system to categorize ischemic stroke based on the pattern of neurological impairments (Table 48.8). The Oxfordshire system categorizes the strokes as being consistent with a large hemispheric infarction (total anterior circulation syndrome, or TACI), less severe infarctions affecting primarily the cerebral cortex (partial anterior circulation syndrome, PACI), lacunar infarctions (lacunar infarction syndrome, or LACI) affecting primarily the deep structures of the hemisphere and strokes affecting the brainstem (posterior circulation syndrome, POCI). The rating system is relatively straightforward and is based on the types and severity of neurological impairments that would be apparent on admission and before extensive laboratory or radiological investigation. Although the system has not been extensively tested for validity, reliability, inter-rater agreement, or intra-rater reproducibility, it likely would meet all these criteria because of the nature of the scale (Bamford et al., 1989; Mead et al., 2000; Lyden et al., 2002). Clinical researchers have used the system to help describe the cohort of patients enrolled in studies (Lyden et al., 2002). In this regard, the classification system has utility. In addition, the type of stroke in the classification is strongly associated with prognosis, with the patients with TACI having the poorest prognosis (Dennis et al., 1993). Such a finding is not surprising given the nature of the severity of the vascular event. The Oxfordshire classification is used in clinical trials to help define the type of stroke but its utility in comparison to systems that quantify the severity of neurological impairments directly is untested. While the Oxfordshire

Table 48.8

Oxfordshire classification of stroke

Total anterior circulation syndrome		
	Contralateral weakness of face, arm, and leg	
	Contralateral homonymous hemianopia	
	Behavioral or cognitive deficit	
Partial anterior circulation syndrome		
	Two of the following	
	Contralateral restricted motor or sensory impairment	
	Contralateral homonymous hemianopia	
	Behavior or cognitive deficit	
Posterior circulation syndrome		
	One or more of the following	
	Bilateral motor or sensory signs	
	Ipsilateral incoordination (cerebellar) not explained by weakness	
	Diplopia with or without extraocular muscle palsy	
	Crossed motor or sensory signs	
	Isolated homonymous hemianopia	
Lacunar syndromes		
	Pure motor stroke	
		Contralateral hemiparesis involving face, arm, or leg
		No other impairments
	Pure sensory stroke	
		Contralateral sensory loss involving face, arm, or leg
		No other impairments
	Ataxic hemiparesis	
		Coexistent cerebellar and motor signs
		May have dysarthria
		No visual or cognitive impairment
	Sensory-motor stroke	
		Contralateral sensory and motor signs involving face, arm, or leg
		No visual or cognitive impairment

classification has also been used to define the pattern of clinical findings among patients with intracerebral hemorrhage (Barber et al., 2004b), the utility of this strategy has not been established. While clinical researchers will likely continue to use this system to provide a global description of patients enrolled in trials, it will probably be of less assistance to a clinician when examining an individual patient.

48.2.3. Categorization of stroke by etiology (ischemic stroke subtypes)

Ischemic stroke may be caused by a large number of diseases that affect blood vessels, the heart, or the coagulation system. Because acute prognosis and risk for recurrence are affected by the presumed cause, the most likely etiology of stroke should be established whenever possible. The most common causes of stroke are large extracranial or intracranial arterial atherosclerosis, disease of smaller intracranial arteries, and cardiac sources of embolism. Non-atherosclerotic vasculopathies and diseases of coagulation are less common. Because the clinical findings, including the neurological examination, are often not specific for a particular cause of stroke, diagnostic studies are often required. The location and size of the brain lesion as detected by imaging affects both prognosis and acute treatment decisions. The presence of a small lesion deep in the cerebral hemisphere or brainstem points to small-artery disease. A multilobar hemispheric infarction suggests an occlusion of a major artery, often due to atherosclerosis or cardio-embolism. Smaller infarctions restricted to the cortex are usually associated with emboli that arise from an arterial or cardiac source. The vascular and cardiac abnormalities are confirmed by the use of imaging such as duplex ultrasonography, arteriography, or echocardiography.

In order to facilitate classification of subtypes of stroke by most likely etiology, the investigators in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) developed a system to categorize strokes into five categories (Adams et al., 1993; Gordon et al., 1993) (Table 48.9). The system used clinical findings supplemented by the results of brain, vascular, and cardiac imaging. The diagnoses were categorized as probable or possible based on the strength of the supporting information. If the patient had had an incomplete evaluation, negative evaluation, or findings that pointed to two or more causes of stroke, the category of stroke of undetermined etiology was used. The TOAST classification system allows investigators to lump together patients with a variety of stroke causes into a few broad categories that make sense phenomenologically. In practice, the diagnostic category of large-artery atherosclerosis is the most difficult to establish because it requires the demonstration of an occlusion or stenosis greater than 50% in the relevant artery; the necessary vascular imaging may not always

Table 48.9

Trial of ORG 10172 in acute stroke treatment (TOAST) classification of subtype of ischemic stroke

Large artery atherosclerosis	
	Clinical evidence of cerebral, cortical, or cerebellar dysfunction
	Cortical, cerebellar, brainstem, or subcortical infarct >1.5 cm
	Stenosis or occlusion of relevant major intracranial or extracranial artery
	No high-risk cardiac lesion (for probable diagnosis)
Cardiac embolism	
	Clinical evidence of cerebral, cortical, or cerebellar dysfunction
	Cortical, cerebellar, brainstem, or subcortical infarct >1.5 cm
	Cardiac source of embolism (high vs medium risk)
	No large artery atherosclerosis lesion (for probable diagnosis)
Small artery occlusion	
	Clinical evidence of a lacunar syndrome
	Subcortical or brainstem infarction <1.5 cm
	No cardiac source of embolism (for probable diagnosis)
	No large artery atherosclerosis lesion (for probable diagnosis)
Other cause	
	Evaluation demonstrates another cause of stroke
Undetermined cause	
	Two or more causes identified, not sure which is most likely
	No abnormality found on evaluation
	Evaluation was incomplete

be available. Also, the classification does not permit classification of stroke secondary to large-artery atherosclerosis if a complex plaque does not produce either stenosis greater than 50% or an occlusion. While the TOAST classification was developed before the widespread use of computed tomographic angiography or magnetic resonance angiography, the results of these tests could easily be used in the rating system. Already, there is evidence that the patterns of acute stroke as demonstrated on emergency MRI studies can influence the subtype diagnoses as outlined in the TOAST classification (Ay et al., 2005; Rovira et al., 2007). The TOAST classification exhibits reasonable inter-rater agreement and intra-rater reproducibility after suitable training (Gordon et al., 1993). Still, physicians do disagree and many physicians are reluctant to make the diagnosis of stroke of undetermined cause, which typically is the most common "cause" of stroke in stroke data banks (Foulkes et al., 1988). In addition, the TOAST classification is not easily used in the first hours following stroke, when the results of ancillary studies are not available and hence the initial presumptive stroke subtype diagnosis often changes as more data become available throughout the hospitalization (Madden et al., 1995). This means that careful training of physicians is required to use this system in a reliable way. Fure et al. (2005) used the TOAST system to classify causes of stroke among patients seen shortly after admission to the hospital and found that they were able to successfully differentiate the strokes secondary to small-vessel disease from the other categories. Still, the prudent course for clinical trials is that the study should not use the TOAST classification or similar scoring systems as an entry criterion because the degree of accuracy of subtype diagnosis is not sufficiently high; truly eligible patients will be excluded and ineligible patients will be enrolled. In addition, clinical trials will need to include an adjudication system to address variances in subtype diagnoses.

The TOAST classification has been adapted to hospital-based and epidemiological studies looking at subtypes of stroke, including causes of stroke in young adults (Pinto et al., 2004, 2006; Nedeltchev et al., 2005; Paradowski and Maciejak, 2005; Ghandehari and Moud, 2006; Liu et al., 2006; Tuttolomondo et al., 2007). Ay et al. (2005) used an algorithm based on the TOAST classification to include advances in imaging of the brain and vasculature; with the use of their revised system, they were able to reduce the number of cases of stroke ascribed to undetermined etiology from approximately 40% to 4%. Despite the widespread use of the TOAST classification in clinical trials in stroke, it does have limitations (Landau and Nassief, 2005). There are ways in which the TOAST classification could be improved and, in the future, clinical trials may wish to substitute another more accurate system. Still, until such a rating system becomes available, the TOAST classification remains the most useful adjunctive clinical measure for defining stroke subtypes in stroke studies. It has stood the test of time in a wide variety of stroke treatment and prevention trials.

A variation of the TOAST classification has been developed for strokes occurring in children (Wraige et al., 2005). The subgroups differ considerably from those described for adults. The categories for pediatric ischemic stroke include: (1) sickle cell disease, (2) cardio-embolism, (3) moyamoya, (4) cervical arterial dissection, (5) steno-occlusive cerebral arteriopathy, (6) other determined cause, (7) multiple possible causes, and (8) undetermined etiology. Another subtype classification system has been developed by Han et al. (2007) but this system has not been used outside the original institution that developed the clinical instrument. Hoffman et al. (2007) criticized the TOAST classification for too much "lumping" of subtypes and proposed an expanded classification that included: (1) large-vessel cerebrovascular disease, (2) small-vessel cerebrovascular disease, (3) cardiogenic, (4) dissection, (5) prothrombotic states, (6) migraine-induced, (7) cerebral venous thrombosis, (8) vasculitides, (9) other vasculopathy, (10) miscellaneous, and (11) unknown. While there is some amalgamation of a wide range of causes of stroke in the TOAST category of "other demonstrated cause," it is not clear how this system would improve the classification of subtypes. In addition, such a new rating system would need extensive testing to determine whether it is sufficiently robust for use in clinical research. The large number of categories will weaken the kappa statistics for showing inter-rater agreement.

48.2.4. Pre-hospital rating of stroke and severity of impairments

Several groups have developed instruments that can be used by emergency medical services personnel to determine if the patient's neurological symptoms are secondary to stroke and to provide some insights on the severity of the neurological impairments. (Table 48.10).

The Glasgow Coma Scale (GCS) was first used to assess the severity of brain injury among persons with craniocerebral trauma (Jennett et al., 1979). Its use has been expanded to a wide range of patients including those with stroke (Weir et al., 2003; McNarry and Goldhill, 2004; Mayer et al., 2005; Mendelow et al.,

Table 48.10

Los Angeles Pre-Hospital Stroke Scale

General screening			
Age >45 years	Yes ___	No ___	Unsure ___
No history of seizures	Yes ___	No ___	Unsure ___
Symptoms <24 hours	Yes ___	No ___	Unsure ___
Not in wheelchair/bedridden	Yes ___	No ___	Unsure ___
Blood glucose >60 and <400	Yes ___	No ___	Unsure ___
Examination			
Facial smile	Normal ___	Right droop ___	Left droop ___
Grip	Normal ___	Right weak ___	Left weak ___
	Right absent ___	Left absent ___	
Arm strength	Normal ___	Right drift ___	Left drift ___
	Right falls ___	Left falls ___	
Has only unilateral weakness	Yes ___	No ___	

2005). Emergency medical services personnel, nurses, and physicians are proficient in use of the GCS. It is included in most emergency medical records. Potential scores range from 3 to 14 points and are based on best verbal, eye movement, and motor responses (Table 48.11). In general, patients with a score of less than 8 have a serious brain injury.

Table 48.11

Glasgow Coma Scale

Best eye opening response	
Eyes open spontaneously, not necessarily aware of environment	4 points
Eyes open to speech, not necessarily in response to command	3 points
Eyes open in response to painful stimulus	2 points
No eye opening in response to painful stimulus	1 point
Best motor response	
Follows simple commands, can have paresis or hemiplegia	6 points
Responds to painful stimulus by attempting to remove source of pain	5 points
Withdraws to painful stimulus	4 points
Develops abnormal flexor (decorticate) posturing in response to painful stimulus	3 points
Develops abnormal extensor (decerebrate) posturing in response to painful stimulus	2 points
No motor response to painful stimulus	1 point
Best verbal response	
Patient oriented to time, place, and person	5 points
Patient confused by responds to conversation	4 points
Language is intelligible but no sustained sentence	3 points
Incomprehensible sounds, moans, or groans, no words	2 points
No verbal response	1 point

The GCS is a key component of the World Federation of Neurological Surgeons (WFNS) scale for rating the severity of aneurysmal subarachnoid hemorrhage (Oshiro et al., 1997; Ogungbo, 2002) (Table 48.12). As the name implies, the utility of the GCS is greatest in the assessment of patients with impairments in consciousness; thus its value is greatest in assessing patients with intracranial hemorrhages (Hemphill et al., 2001; Mayer et al., 2005; Mendelow et al., 2005). Because most patients with ischemic stroke have normal consciousness, the GCS probably provides little help in predicting their outcomes. The exception seems to be those patients with major strokes in the posterior circulation; Tsao et al. (2005) found that the score of the GCS was a stronger predictor of outcomes than the NIHSS. Weir et al. (2003) found that the verbal and eye scores of the GCS did provide important prognostic information following ischemic stroke. An alternative scale to assess the severity of subarachnoid hemorrhage is the Hunt–Hess Scale (Hunt and Hess, 1968). This widely used scale has many of the features that are comparable to the WFNS scale.

Table 48.12

World Federation of Neurological Surgeons scale rating severity of subarachnoid hemorrhage

Grade	Glasgow coma score	Focal signs
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Present or absent
V	3–6	Present or absent

Additional scales have been developed to assess patients with possible stroke (Kothari et al., 1997; Kidwell et al., 2000). These have been validated in field-testing and they emphasize a few neurological signs, most commonly facial asymmetry, language, and arm function (Table 48.10). Some of the rating systems also include information about the patient's history and finding on general examination. Emergency medical personnel can use these rating instruments quickly and they achieve a fairly high degree of accuracy in determining that the patient's symptoms are secondary to ischemic stroke. The primary aim of the scale is to help emergency medical personnel confidently report that a patient has had a stroke. This information can be conveyed to the hospital so that appropriate resources to treat the patient can be mobilized. Paramedic use of a field scale to facilitate recruitment into a clinical trial has been validated for the study of magnesium for treatment of acute stroke (Saver et al., 2004).

48.2.5. Rating the severity of impairments in patients with ischemic stroke

Several scales have been developed to rate the severity of neurological impairments following ischemic stroke. Most scales include the same items in the measurement system and include a range of scores for each tested item. Some integrate weighting of certain components; for example, the number of points for each score on language item might be greater than for each increment on a motor or sensory component of the scale. The scales generally have a total score, with some having a maximum total score of 100 or a similar number. In some scales, a high total score is considered to represent a minor stroke while in others a low score denotes a less severe event. Some of the scales have not been widely used. Many have not been tested for validity, reliability, inter-rater agreement, or intra-rater reproducibility.

The Mathew Scale is one of the oldest rating instruments and it includes most of the features of other stroke scales (Mathew et al., 1972) (Table 48.13). The scale does include items that are of limited value; for example, the scoring of the reflexes does not add much to the other neurological assessments. In addition, a large number of points are ascribed to performance or disability. This global rating item is not well defined and it might not be completely applicable to the acute stroke setting. The scale has been shown to rate patients in a similar way to other acute stroke scales (De Haan et al., 1993). The rating instrument was used in a clinical trial of glycerol but it has not been rigorously tested for validity and reliability. While this scale is no longer used, it does provide a historical foundation for the development of other rating systems.

The Orgogozo Scale includes assessments of consciousness, language, and motor function (Orgogozo, 1992) (Table 48.14). An advantage of this scale is that both proximal and distal motor function is assessed. Disadvantages include scoring of tone and the absence of assessment of vision or independent assessment of articulation (included in language). The value of testing tone is not apparent. It is not clear if this item adds greatly to the evaluation of motor function and strength. The scale has been shown to correlate with other acute stroke scales (De Haan et al., 1993). Still, the scale has not undergone the testing of some of the other acute stroke rating instruments and it is not widely used.

The Canadian Stroke Scale (Canadian Neurological Scale or CNS) differs from some of the other acute stroke rating instruments in that it has two ways to calculate the patient's neurological impairments (Cote et al., 1986, 1989). The scale focuses on rating consciousness, language, and motor function but different items are scored for patients with impaired consciousness or for alert patients (Table 48.15). Other variables such as sensory loss, visual loss, and dysarthria are not tested. Cognitive impairments affecting the right hemisphere, such as neglect, are also not included in the scoring. The scale has been used in clinical trials in stroke (Hagen et al., 2003; Leira et al., 2004). The total score of less than 6.5 on the scale also strongly predicts outcomes including mortality at 1 month and 1 year (De Haan et al., 1993; Castillo et al., 1994; Stavem et al., 2003a,b). Castellanos et al. (2005) used the CNS as a measure of severity of stroke among patients with medium-to-large intracerebral hemorrhages. A high score was associated with a favorable prognosis. In general, the CNS correlates well with the NIHSS and other acute stroke scales. However, the CNS does underestimate functional impairments (De Haan et al., 1993). Muir et al. (1996) found that the scale functioned similarly to the NIHSS but also reported that interconversion of scores between the NIHSS and the Canadian scale was problematic. In particular, the two scales show poor concordances among patients with severe strokes or with aphasia. Testing has demonstrated the validity and reliability of the Canadian scale (Cote et al., 1986; D'Olhaberriague, 1996; Stavem et al., 2003). Goldstein and Chilukuri (1997) demonstrated that retrospective scoring of the severity of stroke using an algorithm based on the CNS could be performed reliably. D'Olhaberriague (1996) concluded that the Canadian scale was one of the more effective measures to assess patients with

Table 48.13

Mathew stroke scale

Mentation		
Level of consciousness		
	Fully conscious	8 points
	Lethargic but mentally intact	6 points
	Obtunded	4 points
	Stuporous	2 points
	Comatose	0 points
Orientation		
	Oriented to time, place, and person	6 points
	Oriented to two of the above	4 points
	Oriented to one of the above	2 points
	Disoriented in all three areas	0 points
Language		
	Language—severity of impairments	0–23 points
Visual fields		
	No visual field defect	3 points
	Mild homonymous hemianopia	2 points
	Moderate homonymous hemianopia	1 point
	Severe homonymous hemianopia	0 points
Eye movement		
	Normal eye movements	3 points
	Mild conjugate deviation of eyes	2 points
	Moderate conjugate deviation of eyes	1 point
	Severe conjugate deviation of eyes	0 points
Facial weakness		
	Normal facial motor function	3 points
	Mild facial weakness	2 points
	Moderate facial weakness	1 point
	Severe facial weakness	0 points
Motor function (each limb scored independently)		
	Normal strength	5 points
	Contracts against resistance	4 points
	Elevates against gravity	3 points
	Moves if gravity is eliminated	2 points
	Flicker of movement	1 point
	No movement	0 points
Performance or disability status score		
	Normal	28 points
	Mild impairment	21 points
	Moderate impairment	14 points
	Severe impairment	7 points
	Death	0 points
Reflexes		
	Normal reflexes	3 points
	Asymmetrical or pathological reflexes	2 points
	Clonus	1 point
	No reflexes found	0 points
Sensation		
	Normal sensation	3 points
	Mild sensory abnormality	2 points
	Severe sensory abnormality	1 point
	No response to pain	0 points

Table 48.14

Orgogozo scale

Consciousness	
Normal, awake and responsive to stimuli	15 points
Drowsy, can be awakened to remain awake	10 points
Stupor, localizes and responds to painful stimuli	5 points
Coma, non-purposeful response to painful stimuli	0 points
Verbal communication	
Normal language	10 points
Difficult language, includes dysarthria	5 points
Extremely difficult, impossible to communicate	0 points
Eyes and head shift	
Normal horizontal eye movements	10 points
Gaze failure—neglect, gaze restricted to one side	5 points
Forced deviation, unable to cross midline	0 points
Facial movements	
Normal or slight asymmetry	5 points
Marked facial weakness or paralysis	0 points
Proximal arm movement	
Can raise arm above horizon against resistance	10 points
Can move against gravity but not horizontally	5 points
No arm abduction	0 points
Hand movement	
Normal hand function	15 points
Restriction of fine movements, slow, or clumsy	10 points
Gross movements possible, can hold cane	5 points
Cannot hold or carry objects even if it moves	0 points
Arm tone	
Normal or near normal	5 points
Overt spasticity or flaccidity	0 points
Proximal leg movement	
Can be elevated from bed, similar to other side	15 points
Move against resistance, can elevate but weak	10 points
Possible against gravity but not resistance	5 points
Cannot lift leg from bed	0 points
Foot dorsiflexion	
Possible against resistance even if some weakness	10 points
Can move against gravity, foot off the floor	5 points
Foot drop	0 points
Leg tone	
Normal or near normal	5 points
Overt spasticity or flaccidity	0 points

acute stroke. The CNS remains an important option for both researchers and clinicians.

The Scandinavian Stroke Scale (SSS) is widely used to assess patients with ischemic cerebrovascular disease (Table 48.16). It was developed for a clinical trial of hemodilution and includes two forms of the scale (Scandinavian Stroke Study Group, 1985; Lindenstrom et al., 1991) The acute prognostic scale has a range of 0–22 points, with the higher scores being associated with a good prognosis. The convalescent version has a range of 0–48 points. The two versions of the scale test different components of the neurological assessment. For example, consciousness is rated in the acute scale but not subsequently, while orientation and language are not rated in the acute scale but are important parts of the follow-up score. The utility of the SSS is similar to other acute scales (Lindenstrom et al., 1991; De Haan et al., 1993; Sprigg et al., 2007). Barber et al. (2004a) tested the validity and reliability of components of the SSS when applied in a retrospective manner. They found that most components of the scale, except consciousness and eye movements, could be tested with a high degree of success. A poor (low) score on the SSS is a predictor of early neurological deterioration following acute ischemic stroke (Dávalos et al., 1999). The total SSS score also correlates well with the presence of a lacunar infarction (Sprigg et al., 2007). A low score on the SSS at baseline or 24 hours is a strong predictor of death within 30 days of a hemispheric ischemic stroke (Szczudlik et al., 2000; Willimas and Jiang, 2000). Christensen et al. (2005) found that the SSS score also strongly predicted outcomes among persons with mild stroke. Conversely, improvement (increase in score of 5–10 points) strongly predicted favorable outcomes (Jorgensen et al., 1997). Sprigg et al. (2007) found that a lack of improvement in the SSS score within 4 days of stroke was associated with a favorable functional outcome following stroke. The SSS has been combined with other factors to predict 12-month survival among persons with stroke (Willimas and Jiang, 2000).

The long-term score has not been as extensively evaluated as the early prognostic score. Still, the aphasia component of the SSS was tested in comparison to formal testing by a language therapist in an independent study (Dávalos et al., 1999). While the sensitivity and specificity of the SSS was satisfactory, the positive predictive value was low suggesting that the scale had a high chance for false positive results.

Overall, the SSS is a very useful rating instrument. The definitions for the scoring categories are relatively clear, but information about the scale to assure valid and reproducible results, such as those used for assuring accurate use of the NIHSS, is not available.

Table 48.15

Canadian Neurological Scale

Level of consciousness		
	Alert	3 points
	Drowsy	1.5 points
Orientation		
	Oriented	1 point
	Disoriented, not applicable	0 points
Language		
	Normal	1 point
	Expressive deficit	0.5 point
	Receptive deficit	0 points
Motor function (scoring if normal comprehension)		
Face		
	No facial weakness	0.5 point
	Facial weakness present	0 points
Proximal arm		
	No weakness	1.5 points
	Mild weakness	1 point
	Significant weakness	0.5 point
	Paralysis	0 points
Distal arm		
	No weakness	1.5 points
	Mild weakness	1 point
	Significant weakness	0.5 point
	Paralysis	0 point
Proximal leg		
	No weakness	1.5 points
	Mild weakness	1 point
	Significant weakness	0.5 point
	Paralysis	0 points
Distal leg		
	No weakness	1.5 points
	Mild weakness	1 point
	Significant weakness	0.5 point
	Paralysis	0 point
Motor function (scoring if comprehension is impaired)		
Face		
	Symmetrical	0.5 point
	Asymmetrical	0 points
Arms		
	Equal	1.5 points
	Unequal	0 points
Legs		
	Equal	1.5 points
	Unequal	0 points

Still, the SSS has been used successfully in several clinical trials (Steiner et al., 1998; Lyden et al., 2002; Roden-Jullig et al., 2003; Barber et al., 2004a). The SSS has also been used to rate the severity of neurological impairments among patients with intracerebral hemorrhage (Barber et al., 2004b). The SSS will likely continue to be used in clinical trials in stroke. Data about the widespread use of the scale in general patient care settings are not available.

The NIHSS is the most widely used scale for the assessment of neurological impairments among persons with stroke (Table 48.17). The NIHSS is a 15-item physical deficit-rating instrument that was first described in 1989 to assess level of consciousness; gaze;

Table 48.16

Scandinavian stroke scale

Item	Prognostic score Points 0–22	Long-term score Points 0–48
Consciousness	Calculated	Calculated
Fully conscious	6	
Somnolent, can be awakened	4	
Reacts to verbal command	2	
Orientation	Not calculated	Calculated
Correct for time, place, person	6	
2 of the above correct	4	
1 of the above correct	2	
Completely disoriented	0	
Language	Not calculated	Calculated
No aphasia		10
Limited vocabulary		6
More than yes/no—no sentences		3
Only yes/no or less		0
Eye movements	Calculated	Not calculated
No gaze palsy	4	
Gaze palsy present	2	
Conjugate eye deviation	0	
Arm, motor power, affected side	Calculated	Calculated
Raises arm with normal strength	6	6
Raises arm with reduced strength	5	5
Raises arm with elbow flexion	4	4
Can move, not against gravity	2	2
Paralysis	0	0
Hand, motor power, affected side	Not calculated	Calculated
Normal strength		6
Reduced strength in full range		4
Some movement of fingers		2
Paralysis		0
Leg, motor power, affected side	Calculated	Calculated
Raises leg with normal strength	6	6
Raises leg with reduced strength	5	5
Raises leg with knee flexion	4	4
Can move, not against gravity	2	2
Paralysis	0	0
Facial palsy	Not calculated	Calculated
None or dubious		2
Facial palsy present		0
Gait	Not calculated	Calculated
Walks 5 meters without aids		12
Walks with aids		9
Walks with person helping		6
Sits without support		3
Bedridden or wheelchair		0

visual fields; motor function of the face, upper extremity, and lower extremity; articulation; limb ataxia; sensory function; language; and the presence of neglect (Brott et al., 1989a,b). Some of the scale components were included to allow for measurement of brainstem or cerebellar deficits. The scale includes detailed definitions of the scores for each item that includes advice about scoring when the patient's status

Table 48.17

National Institutes of Health Stroke Scale

Item		Score
Level of consciousness		
	Alert	0 points
	Drowsy	1 point
	Stupor	2 points
	Coma	3 points
Response to two questions (orientation)		
	Know age and current month	0 points
	Answers one question correctly	1 point
	Cannot answer either question correctly	2 points
Response to two commands		
	Follows two commands correctly	0 points
	Follows one command	1 point
	Cannot follow either command	2 points
Best gaze (movement of eyes to left or right)		
	Normal eye movements	0 points
	Partial gaze paresis to one side	1 point
	Forced gaze palsy to one side	2 points
Visual fields		
	No visual loss	0 points
	Partial homonymous hemianopia	1 point
	Complete homonymous hemianopia	2 points
	Bilateral visual loss	3 points
Facial motor function		
	No facial weakness	0 points
	Minor unilateral facial weakness	1 point
	Partial unilateral facial weakness	2 points
	Complete paralysis of one or both sides	3 points
Upper extremity motor function (right and left scored independently 0–8 points)		
	Normal movement	0 points
	Drift of upper extremity	1 point
	Some effort against gravity	2 points
	No effort against gravity but moves	3 points
	No movement	4 points
Lower extremity motor function (right and left scored independently 0–8 points)		
	Normal movement	0 points
	Drift of lower extremity	1 point
	Some effort against gravity	2 points
	No effort against gravity but moves	3 points
	No movement	4 points
Limb ataxia (cannot be tested in presence of paresis)		
	No limb ataxia	0 points
	Ataxia present in one limb	1 point
	Ataxia present in two limbs	2 points

(Continued)

Table 48.17

(Continued)

Sensory function		
	No sensory loss	0 points
	Mild-to-moderate sensory loss	1 point
	Severe-to-total sensory loss	2 points
Language		
	Normal language	0 points
	Mild-to-moderate aphasia	1 point
	Severe aphasia	2 points
	Mutism	3 points
Articulation		
	Normal articulation	0 points
	Mild-to-moderate dysarthria	1 point
	Severe dysarthria	2 points
Extinction or inattention (neglect)		
	No neglect or extinction	0 points
	Visual or sensory inattention or extinction	1 point
	Profound inattention to visual and sensation	2 points

precludes testing some items and although these definitions are frequently—and erroneously—detached from the scale, the validated version uses an answer sheet with the detailed instructions printed on its face. For example, additional points are included for orientation and articulation items when a patient has a severe aphasia and cannot answer questions or speak. Some items of the scale have proven problematic, in particular the scoring of limb ataxia, articulation, and facial weakness has resulted in poor agreement, indicating that some modification of the NIHSS is needed (Goldstein et al., 1989; Goldstein and Samsa, 1997; Dewey et al., 1999; Lyden et al., 2001). Simplified versions have been proposed but most have not been validated. The most frequently used modified version (mNIHSS) eliminates rating levels of consciousness, facial motor assessment, limb ataxia, and articulation and could be used in innovative ways such as telemedicine (Meyer et al., 2002, 2005). The inter-rater agreement was much higher with the elimination of these scale items. It remains to be determined whether the elimination of these components affects the strong prognostic ability of the scale.

The scale was not originally intended to produce an aggregate score but during the initial testing of the NIHSS a strong correlation between the total score and volume of infarction on a day-7 CT was found; the Spearman's correlation was 0.74 (Brott et al., 1989b). The NIHSS has been validated extensively using a variety of clinometric methods. The scale measures two main constructs or factors, each corresponding to one of the cerebral hemispheres (Lyden et al., 1999, 2001, 2004). There is a tendency for left hemisphere strokes to receive a higher rating than those events affecting the right hemisphere (Woo et al., 1999; Lyden et al., 2004). The rating instrument shows excellent reproducibility and inter-rater reliability if the users are properly trained (Goldstein et al., 1989). Non-neurologists and non-physicians can perform the NIHSS successfully (Goldstein and Samsa, 1997). Kasner et al. (2003) found that NIHSS could be estimated by retrospective review of medical records. Initial evaluation of the scale found that the rating instrument could be performed in approximately 6 minutes (Brott et al., 1989b). Still, reliable use of the NIHSS depends on prior training because the rating instrument is designed to maximize reproducibility during a clinical trial. Based on the assessment of scoring of items on the NIHSS obtained during a certification process, Josephson et al. (2006) found that scoring was inconsistent and such results could impact the results of clinical trials. To enhance reproducibility, some of the scoring rules are rather arbitrary and some seem counter-intuitive. In order to provide proper implementation of the NIHSS, video instruction and certification are available (Albanese et al., 1994; Lyden et al., 1994). Digital video disks are available to improve training and certification of the NIHSS (Lyden et al., 2005). These steps enhance the reliability and the reproducibility of the scale when used in clinical trials.

The NIHSS has been used widely in clinical trials testing interventions for treatment of stroke, including the trials testing recombinant tissue plasminogen activator (rtPA) (Brott et al., 1992; Haley et al., 1993a; National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995; Publications Committee for

the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998; Abciximab in Ischemic Stroke Investigators, 2000; Abciximab Emergent Stroke Treatment Trial [AbESTT] Investigators, 2005; Young et al., 2005b). The scale has been adapted for use during evaluating Spanish-speaking patients (Montaner and Alvarez-Sabín, 2007). Because of its widespread use in clinical trials and because the scores obtained on the NIHSS affect decisions about administration of rtPA, the scale is cited in guidelines (Adams et al., 1996, 2003; Adams et al., 2005). The NIHSS has been used to assess patients with intracerebral hemorrhage and it was found to be useful in predicting outcomes including mortality (Cheung and Zou, 2003). Wider experience with the scale in assessing patients with hemorrhagic stroke is limited however. In addition, the scale has been implemented in trials testing therapies for patients with subarachnoid hemorrhage (Todd et al., 2005).

The baseline NIHSS score is an important predictor of outcome following stroke (Adams et al., 1999; Lyden et al., 2004; Kasner, 2006). Schlegel et al. (2003, 2004) found that the NIHSS score was a strong predictor of outcome in a broad range of patients. Glymour et al. (2007) found that the NIHSS is a better predictor of outcomes among patients with subcortical infarctions than among patients with cortical lesions. In general, the NIHSS score on admission is the single most important forecaster of survival or recovery after stroke. Even among patients with basilar artery occlusion treated with intra-arterial rtPA, a low NIHSS score predicts a favorable outcome (Arnold et al., 2004). Patients with a baseline NIHSS score of less than 5 generally have a favorable prognosis while those with scores more than 20 have a low likelihood of favorable outcomes. Improved patient selection for enrollment by the use of the baseline NIHSS score may improve the efficiency of clinical trials (Weimar et al., 2006). As a result clinical trials are using the baseline NIHSS score as a criterion for enrollment; those with very low scores and those with very high scores are often excluded. This practice, however, is not valid and can be criticized for excluding classes of patients that may very well benefit from putative neuroprotection. A more rigorous and statistically justifiable approach uses the baseline NIHSS as a stratification factor for clinical trials enrolling patients with stroke (Abciximab in Ischemic Stroke Investigators, 2000). The baseline NIHSS score is also being used as a baseline forecaster for responses to therapies in clinical trials, the criterion for success is greater for patients with low scores than it is for patients who have major impairments (Adams et al., 2004). The use of an endpoint adjusted by NIHSS score could allow therapeutic effects from medications to be identified easily (Young et al., 2005b). The baseline score also affects responses to treatment, as demonstrated by the trials of thrombolytic therapy (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995; NINDS tPA Stroke Study Group, 1997). The number of patients achieving favorable outcomes with intravenously administered rtPA was much lower among those persons with high NIHSS scores than among those whose scores were less than 10, yet at all levels of severity, the outcome in patients treated with rtPA is better than those treated with placebo. In other words, although more severely affected patients are likely to have a poor outcome, their outcome is improved with thrombolytic therapy, and baseline NIHSS cannot be used to select any particular subgroup for treatment. The baseline score also predicts the risk of hemorrhagic complications following administration of rtPA or other agents aimed at restoring perfusion (NINDS tPA Stroke Study Group, 1997; Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998; Derex et al., 2005). A discrepancy (mismatch) between the baseline neurological impairments (high NIHSS score) and the findings on the initial brain imaging study (CT or MRI) might be used to select patients for emergency treatment (Messe et al., 2007; Tei et al., 2007). However, the utility of the use of this relationship for treating patients has not been established.

Alterations in the NIHSS score have been used to monitor for recanalization following treatment with tPA (Mikulik et al., 2007). Changes in the NIHSS score are used to monitor improvement or neurological worsening (Wityk et al., 1994; Bruno et al., 2006; Kasner, 2006). Early improvements in scores are associated with better long-term outcomes. This effect was found among patients receiving intra-arterial thrombolytic agents (Takada et al., 2004). One of the advantages of using changes in the NIHSS score as an outcome measure is that changes in score are not fully comparable to dichotomized functional outcomes (Bruno et al., 2006).

Despite some obvious limitations, the NIHSS is the most widely used clinical instrument to rate the types and severity of neurological impairments. It strongly predicts outcomes and response to interventions; thus, it has face validity. A wide range of healthcare professionals can use the scale with reasonable assurance of accuracy. Educational programs are available to assure its accurate use (see www.asatrainingcampus.net for example). The scale now is used in almost all acute stroke trials and it also is being used in the community setting. While some modifications of the NIHSS are likely to occur, it will be the standard instrument for rating the severity of acute stroke rating for the foreseeable future.

Because most of the clinical rating scales emphasize assessment of impairments accompanying strokes of the cerebral hemisphere, a new scale that focuses on the scoring of patients with vertebrobasilar infarctions is required. The Israeli Vertebrobasilar Stroke Scale (IVBSS) has been tested in a limited number of patients and its results seem to correlate well with the scores on the NIHSS and modified Rankin Scale (mRS) (Gur et al., 2007).

48.2.6. Functional outcome scales

Stroke-related disability can be assessed by a number of relatively simple functional outcome scales, which can also be used to formulate a functional prognosis. Such assessments have been proposed for guiding rehabilitation, making decisions about placement, and providing continuing services for survivors of stroke; but this function has been difficult to validate (Gresham et al., 1980; Granger et al., 1989). In addition, some of these scales are used to assess the patient's overall outcome from stroke and to measure the success of acute interventions to treat the stroke.

More than 3 million Americans have some degree of limitation of activities (disability) secondary to stroke and more than 60% of all stroke survivors have such limitations. Globally, the impact of stroke may be even greater; being among the leading causes of long-term disability (Wolfe et al., 2004). Thus, simple measures that can be performed reliably and rapidly are needed. Many functional outcome scales measure the patient's ability to perform activities of daily living (ADL) and a plethora of such scales have been developed. The scales differ in their approach to the performance of each patient and the complexity and types of tasks they evaluate. Some scales emphasize observation while others require patient interview or actual performance of specific activities, but the most commonly used scales tend to behave similarly from a clinometric standpoint (Salter et al., 2005). The most commonly used instruments are the Barthel index (BI), Functional Independence Measure (FIM), Katz index of ADL, the Frenchay Activities index, and Pulses Profile (Katz et al., 1963; Mahoney and Barthel, 1965; Granger et al., 1979b; Wade and Collin, 1988; Granger et al., 1989, 1993; Sulter et al., 1999; Kasner, 2006; Appelros, 2007). While the FIM has been implemented widely in rehabilitation settings, it has not been validated for use in clinical trials for stroke (Table 48.18). The most widely used disability (activities dimension) rating instrument in stroke is the BI.

The BI, which measures ADL, was initially developed for use in chronic disease hospitals in Maryland (Mahoney and Barthel, 1965). It was originally used to evaluate patients with neuromuscular or musculoskeletal disorders but the BI became more widespread in intervening years. It is now a frequently used measure of ADL and as an assessment of stroke-related disability in clinical stroke trials (Granger et al., 1979b; Wade and Collin, 1988; Olsen, 1990; Lyden and Lau, 1991; Dods et al., 1993; Hsueh et al., 2002). The BI is used in clinical settings as well, and is also useful for planning strategies for rehabilitation (Kasner, 2006).

The patient or caregiver is asked a series of questions about the patient's activities. Ten items are rated and assessments include feeding, chair/bed transfer, grooming, toileting, bathing, ambulation, stair climbing, dressing, bowel control, and bladder control (Table 48.19). The high priority given to mobility and continence has been considered arbitrary but some authorities consider it to have been a shrewd decision (Gresham et al., 1980). Scores are calculated based on complete dependency, partial dependency, or independence. Full competence in all areas yields a score of 100. Generally, a score greater than 60 indicates functional independence (Granger et al., 1979b). Patients with high scores are likely to be able to live outside an assisted living environment, although a patient with a score of 100 may not necessarily be able to live independently (Granger et al., 1979a; Wade and Collin, 1988; Hsueh et al., 2002). In general, higher scores are associated with shorter hospital stays and less need for intensive rehabilitation after discharge from an acute care setting. The score on the BI also predicts mortality at 12 months after stroke.

The BI does have some limitations. Because of the emphasis on mobility, patients with cognitive impairments, including those with aphasia, may score relatively well. Another limitation of the BI is a ceiling effect and the non-normal distribution of scores (The Ancrod Stroke Study Investigators, 1994; Tilley, 1999; Broderick et al., 2000). Despite these limitations, the BI has been evaluated extensively and concurrent validation has been reported (Granger et al., 1979a; Hsueh et al., 2002). The definitions of the various activities are relatively straightforward. It is easy to administer and to calculate the total score. Not surprisingly, it has substantial inter-rater reliability ($\kappa = 0.80$) and excellent internal consistency ($\alpha = 0.96$). In preparation for a trial of rtPA, NINDS investigators validated the reliability of the BI for studies in stroke, especially when the rating instrument was used during a telephone conversation (Lyden et al., 1995). Agreement with other valid measures of disability is substantial (Gresham et al., 1980). Recently, a study showed that a BI score of 95 correlated with an mRS score of 1, a BI score of 90 matched an mRS score of 2, and a BI score of 75 corresponded to an mRS score of 3 (Uyttenboogaart et al., 2005).

Table 48.18

Function independence measure (FIM)

Personal care		
	Total independence of all aspects of eating and drinking	4 points
	Requires preparation of food or adaptive devices	3 points
	Requires supervision or help during eating and drinking	2 points
	Requires total assistance or enteral feeding	1 point
Grooming		
	Total independence in brushing teeth, washing face, grooming hair, shaving or make-up	4 points
	Requires preparation or assistive devices or is very slow	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, cannot do alone	1 point
Bathing		
	Total independence in bathing and drying body	4 points
	Requires assistive devices, is slow, or unsafe	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, cannot do alone	1 point
Dressing upper body		
	Total independence in dressing and undressing	4 points
	Needs assistive devices, modified clothing	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, cannot do alone	1 point
Toileting		
	Total independence in all aspects	4 points
	Needs adaptive equipment or is slow	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance	1 point
Bladder control		
	Controls bladder, no incontinence	4 points
	Requires catheter, bag, or medication—can use on own	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, incontinent despite use of devices	1 point
Bowel control		
	Controls bowels, no incontinence	4 points
	Requires artificial help including medication, no accidents	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, incontinent most days	1 point
Mobility—transfers to bed, chair, or wheelchair		
	If walking, can sit down and rise without help	
	If wheelchair, can move to and from chair without help	4 points
	Requires special assistive device to transfer	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance	1 point
Mobility—transfer to toilet		
	If walking, can sit down and rise without help	
	If wheelchair, can move to and from toilet without help	4 points
	Requires special assistive device to transfer or is unsafe	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance	1 point
Mobility—transfer to shower or tub		
	If walking, can move into and out of bath/shower	
	If wheelchair, can approach and transfer safely	4 points

(Continued)

Table 48.18

(Continued)

	Requires special assistive device or is unsafe	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance	1 point
Locomotion		
	Walks 50 meters without use of assistive device	
	Walks 50 meters but needs device or orthosis	4 points
	If wheelchair, can maneuver at least 50 meters	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance or cannot achieve	1 point
Stairs		
	Goes up and down one flight of stairs without support	4 points
	Goes up and down one flight of stairs with device	3 points
	Requires supervision or moderate assistance	2 points
	Requires total assistance, cannot go up or down stairs	1 point
Comprehension of language		
	Comprehends spoken or written conversation	4 points
	Has difficulty with spoken or written conversation	3 points
	Does not follow conversation without cues or assistance	2 points
	Does not follow spoken or written conversation	1 point
Expression of language		
	Expresses complex ideas intelligibly and fluently	4 points
	Expresses complex ideas with difficulty but communicates basic wants and needs	3 points
	Expresses thoughts in confused pattern or needs assistance	2 points
	Does not express basic needs or wants	1 point
Social interaction		
	Interacts appropriately with family and other people	4 points
	Participates appropriately in structured situations	3 points
	Unpredictable or uncooperative behavior	2 points
	Does not function in a group or family setting	1 point
Problem solving		
	Able to apply knowledge, to initiate and carry out task	4 points
	Has difficulty in initiating or self-correcting	3 points
	Needs help of another person to complete task	2 points
	Does not solve problems	1 point
Memory		
	Recognizes people and remembers daily routines easily	4 points
	Has some difficulty with memory, has self-initiated cues	3 points
	Requires prompting from another person for memory	2 points
	Does not recognize other people or remember routines	1 point

The BI has been used as a functional outcome measure in several clinical trials, including the NINDS trial of rtPA (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995; Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998). Some trials have been designed with the BI as the primary outcome measure. Because of its ceiling effect and because it may miss important behavioral or cognitive sequelae of stroke, it probably is not the best method for measuring responses to treatment in large clinical trials, but due to its simplicity and the importance of the resulting scores, the BI is widely recognized by physicians treating patients with stroke. The BI will remain an important adjunctive rating instrument for trials testing promising therapies for stroke.

Several global outcome scales rank patient handicap (participation dimension) into one of a limited number of categories. The best of these scales are brief with a few well-demarcated choices. The most frequently used measures are the Glasgow Outcome Scale (GOS) and the Rankin Scale, which is now widely used in a modified version (mRS) (Rankin, 1957; Jennett and Bond, 1975). Other scales also have

Table 48.19

Barthel index

Area assessed	Dependent	Partial	Independent
Feeding/eating	0	5	10
Chair/bed transfers	0	5/10	15
Grooming	0	0	5
Toilet transfers	0	5	10
Bathing	0	0	5
Walking	0	5/10	15
Climbing stairs	0	5	10
Dressing	0	5	10
Bowel control	0	5	10
Bladder control	0	5	10

been proposed (Wahlgren et al., 1995; Essink-Bot et al., 1997). The advantages of these global outcome measures include high reproducibility and widespread familiarity among stroke physicians. On the other hand, the definitions for these scores are rather arbitrary and some difficulty in achieving high inter-rater agreement can be found when physicians deal with those patients who have minimal residuals from their stroke.

The GOS was developed as a companion to the GCS and was oriented to the assessment of outcomes among patients with craniocerebral trauma (Jennett and Bond, 1975; Teasdale et al., 1998) (Table 48.20). Among raters taught the nuances for determining each grade, the GOS has acceptable inter-observer reliability ($\kappa = 0.62$) and intra-observer reproducibility ($\kappa = 0.75$) (Teasdale et al., 1978). Differentiating between a score of 2 (moderate disability) and 3 (severe disability) has been problematic. The GOS has been used in clinical trials testing interventions to treat ischemic stroke (Wahlgren et al., 1995; Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment [TOAST] Investigators, 1998; Yamaguchi et al., 1998; Tirilazad International Steering Committee, 2000). It also has been used as a rating instrument in clinical trials testing interventions for management of subarachnoid hemorrhage (Kassell et al., 1990; Haley et al., 1993b). While the GOS remains an important measure of outcome following acute brain injury, it substantially duplicates the information of the mRS. Because the mRS is more geared towards the assessment of patients with stroke, it has replaced the GOS as an outcome measure in most clinical trials in stroke.

Table 48.20

Glasgow Outcome Scale

5 points	Good recovery (a) Full recovery without symptoms or signs (b) Capable of resuming normal activities, minor complaints
4 points	Moderate disability, independent but disabled (a) Signs present, can resume most former activities (b) Independent in activities of daily living, cannot resume previous activities
3 points	Severe disability, conscious but dependent (a) Partial independence in activities of daily living, cannot return to previous activities (b) Total or almost total dependency for activities of daily living
2 points	Vegetative state
1 point	Death

The mRS was developed in 1957 to assess the extent of handicap (participation dimension) following stroke (Rankin, 1957). Subsequently, it was modified to expand the scale to 6 categories (0–5) (van Swieten et al., 1988) (Table 48.21). In order to receive a score of 0, a patient must have no symptoms from the stroke. This definition presents a problem because even though a patient may enjoy an excellent recovery, a patient with residual but minimal symptoms cannot achieve a score of 0. The definition also means that the score of 1 covers a wide spectrum of patients. On the other hand, the mRS does consider behavioral and cognitive sequelae of stroke as factors in rating outcomes. The mRS has moderate-to-excellent inter-rater agreement (Bonita and Beaglehole, 1988; van Swieten et al., 1988; Broderick et al., 2000). Training enhances the reliability of the instrument (Broderick et al., 2000). The mRS appears to be more powerful than the BI and other scales as a primary measure of success of interventions being tested in stroke trials (Young et al., 2003, 2005a; Weir et al., 2004). As a result, the mRS has been used as a primary outcome measure in clinical trials testing therapies for stroke (Abciximab in Ischemic Stroke Investigators, 2000; Abciximab Emergent Stroke Treatment Trial [AbESTT] Investigators, 2005).

Table 48.21

Modified Rankin Scale

Score	Impairments
0	No symptoms at all
1	No disability despite symptoms
2	Slight disability but does not require assistance
3	Moderate disability but can walk
4	Moderately severe disability
5	Severe disability, often bedridden
6	Dead

Global outcome measures such as the mRS are increasingly popular endpoints for clinical trials testing therapies for stroke, for several reasons (Wilson et al., 2002; Young et al., 2003, 2005a; Weir et al., 2004). Generally, agreement among observers is increased when the scales offer few choices. Close agreement means that the endpoint shows less observer variation and the required sample size for the trial to demonstrate an effect can be reduced (Young et al., 2005a). Because the global outcome scales are relatively simple and do include some lumping of patients with a variety of neurological sequelae together into a group, some skilled clinicians find these rating instruments to be a problem because they do not properly describe an individual patient. This criticism is valid in that the score of mRS for one patient is fairly crude. However, the power of these rating instruments derives from their use in larger groups of patients. The problem with a detailed scoring system is that it assesses a large number of variables and creates large numbers of subgroups. As a result, such scoring may be accurate for an individual patient performed by an individual physician but it will not be appropriate for larger groups, such as those enrolled in a clinical trial. The differences in the scoring among physicians become a problem and inter-observer variations will significantly weaken the results of the trial (Shinar et al., 1985). The nuances and scoring of simple scales may be taught to many raters of varying backgrounds, something that more complex rating instruments cannot achieve. Thus, the simpler the scale, the more accurate the aggregate data become. A simple outcome scale is more sensitive to subtle changes within groups. This phenomenon is true even though a detailed scale might provide a clear description of the status of a single patient.

48.2.7. Assessment of quality of life

Since 1948, when the World Health Organization (WHO) defined health as both the absence of disease and infirmity and the presence of physical, mental, and social well-being there has been increasing academic and clinical interest in the quality of life of patients and the best ways to assess this outcome (Testa and Simonson, 1996). The phrase "quality of life" is part of everyday speech and includes an almost infinite number of concepts. For some healthcare professionals, it translates to the word happiness (McKevitt et al., 2003). However, quality of life probably covers many more areas of functioning. Mayo et al. (2002) found that many stroke survivors complain of a lack of meaningful activity, depression, boredom, and a poor quality of health. The term health-related quality of life (HRQL) refers to the physical, psychological, social, and health domains and are viewed as distinct areas that are influenced by a person's experiences, beliefs, expectations, and perceptions (Ophoff et al., 2001). The HRQL is more easily defined than quality of life. HRQL is influenced heavily by the way patients perceive and react to their health status and to other non-medical aspects of their lives (Testa and Simonson, 1996; Smout et al., 2001).

Despite years of investigation and several attempts to develop rigorous measures of quality of life, such assessments have yet to prove useful in either outcome research or assessment of health technology (Testa and Simonson, 1996; Smout et al., 2001; De Haan, 2002; Buck et al., 2004). Such limitations are particularly true when HRQL measures are used in studies of persons surviving stroke. Despite the lack of rigorous measures, there is ample evidence that the quality of life of stroke survivors is not satisfactory (Lawrence and Christie, 1979; Kappelle et al., 1994; Duncan et al., 1997; Parker et al., 1997; Mayo et al., 2002; Sturm et al., 2004b). Not surprisingly, the severity of stroke is a strong predictor of subsequent quality of life (Tengs and Luistro, 2001; Sturm et al., 2004a). Stroke is a life-changing experience for the patient and the family, so most measures of quality of life will report worsening following a cerebrovascular event and a survey of quality of life will detect these problems (Bluvol and Ford-Gilboe, 2004). The reduction of quality of life is found among persons of all age groups and regardless of the cause of stroke. Both physical and psychosocial aspects of the quality of life are affected by stroke (Kauhanen et al., 2000). Because the perceptions of quality of life for individuals differ considerably, population ratings of quality of life may not be valid for each affected person (McPherson et al., 2004). The real issue is whether any of the current measurements of quality of life can prove to be useful in the setting of an acute stroke trial and whether specific interventions can improve perceived HRQL.

Several assessment scales have been developed in response to the growing appreciation of HRQL and in recognition that no scale properly measures the desire to describe the many factors that are encompassed by the term quality of life (Tables 48.21 and 48.22). Designers of these scales have tried to cover each objective and subjective component (symptom, condition, or social role) that is important for affected persons and that could be affected positively or negatively by interventions (Testa and Simonson, 1996). A scale that meets this criterion is said to have good coverage. To prove useful, the HRQL instruments must have the same vigorous testing as the acute stroke and outcome scales (De Haan et al., 1993;

Table 48.22

Short Form Health Survey (SF—36)

Physical health	
Physical functioning	
	Limited doing vigorous activities
	Limited doing moderate activities
	Limited lifting or carrying groceries
	Limited climbing several flights of stairs
	Limited climbing one flight of stairs
	Limited bending, kneeling, or stooping
	Limited walking more than one mile
	Limited walking one-half mile
	Limited walking 100 yards
	Limited bathing or dressing
Role—physical	
	Cut down amount of time spent on work
	Accomplished less than would like
	Limited in the kind of work
	Difficulty performing the work
Bodily pain	
	Pain—magnitude
	Pain—interference with work
General health	
	Overall rating of general health
	I seem to get sick easier than others
	I am as healthy as anyone I know
	I expect my health to get work
	My health is excellent
Mental health	
Vitality	
	Did you feel full of life?
	Did you have a lot of energy?
	Did you feel worn out?
	Did you feel tired?
Social functioning	
	Extent of limitations
	Time of limitations
Role—emotional	
	Cut down time spent working
	Accomplished less than would like
	Did not work as carefully as usual
Mental health	
	Have you been a nervous person?
	Have you felt down in the dumps?
	Have you felt calm and peaceful?
	Have you felt downhearted and low?
	Have you been a happy person?

De Haan, 2002; Buck et al., 2004). Unfortunately, formal studies testing the validity, reliability, sensitivity, and efficacy of these instruments are few. In addition, many of the measures of quality of life are influenced by family and living situation. Because many patients need the assistance of others, the responses of the family members also affect measures of quality of life (Smout et al., 2001; Bluvol and Ford-Gilboe, 2004; Li et al., 2004).

Many HRQL scales have been developed to assess patients with specific diseases such as heart disease, cancer, or rheumatologic disorders. Some stroke-specific instruments have been developed but have not yet been fully validated (Hamedani et al., 2001; Sturm et al., 2002, 2004b; Buck et al., 2004; Doyle et al., 2004; Fernandez-Concepcion et al., 2004; Muus et al., 2007). Thus, HRQL measurements for patients with stroke are often determined using one of the general instruments (De Haan, 2002; Buck et al., 2004). These scales include the Nottingham Health Profile (NHP) (Essink-Bot et al., 1997; Fjaertoft et al., 2004), the Medical Outcomes Short Form-36 (MOS SF-36) (Hobart et al., 2002), Short Form-12 (SF-12) (Bohannon et al., 2004a,b) and the Sickness Impact Profile (Bergner et al., 1981) (Table 48.22). Hobart et al. (2002) found that five of the eight scales in the SF-36 had limited validity in assessing quality of life among survivors of stroke. They doubted that the SF-36 was a useful rating instrument for clinical trials in stroke. Suenkeler et al. (2002) found that the measures of quality of life as assessed by the SF-36 continued to deteriorate during the first year following stroke. Both global and domain-specific measures worsened.

The Stroke-Specific Quality of Life scale (SS-QOL) includes measures to assess impairments from stroke, including language deficits (Williams et al., 1999; Hilari and Byng, 2001; Hilari et al., 2003; Muus and Ringsberg, 2005). Tests of the SS-QOL demonstrated that good scores were associated with lower NIHSS scores, less depression and higher BI scores (Williams et al., 1999). The Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39) includes testing in physical, psychosocial, communication, and energy domains (Hilari and Byng, 2001). It seems to have reasonable acceptability, internal consistency, test–retest reliability and construct validity. This promising tool needs further testing. Another scale has been developed to assess quality of life among young adults who have had hemorrhagic stroke (Hamedani et al., 2001). This scale has not been implemented widely. The Stroke Impact Scale (SIS) was designed to assess the effects of stroke from the patient's perspective (Kasner, 2006). The SIS was used as a secondary outcome-rating instrument in a trial of a glycine antagonist for treatment of stroke (Duncan et al., 2003a,b). The investigators report that the SIS is valid and that the domain scores differentiated patients into multiple groups. They found that the measures of activities of daily living,

mobility, composite physical and participation domains were the most robust, with the composite physical domain being the most effective in differentiating function among stroke survivors. In a comparison with the SF-36, the SIS seemed to do better in capturing physical functioning and social well-being among survivors of stroke (Lai et al., 2003).

British researchers used two simple questions to determine quality of life following stroke (Dorman et al., 2005). These researchers found this approach to have excellent face validity but other groups have not adopted this minimalist strategy. Although less commonly used, another HQRL scale that is employed in the evaluation of patients with stroke is the Health Utilities Index (Feeny et al., 1995; Grootendorst et al., 2000). Each of the scales has been shown to be feasible in selected patients with stroke. In a meta-analysis of the quality of life estimates for stroke, investigators found that the severity of the stroke and bounds of the individual scale were significant predictors of quality of life (Tengs and Lin, 2003).

However, there is doubt that these scales can provide meaningful data that are useful in clinical trials (Mathias et al., 1997; Tengs and Luistro, 2001). Pickard et al. (2005) concluded that the selection of measures of any HRQL scale depends upon the goals of the study and the specific aim of any intervention being tested. Tengs and Luistro (2001) concluded that quality of life estimates for stroke vary considerably and that they are not determined in good fashion. Additional development of reasonable measures of quality of life after stroke is needed (Golomb et al., 2001). These tools need to meet the same strict criteria that are imposed for other rating instruments. While some flexibility in scoring might be needed to emphasize different domains of life for different patients, some commonality will be needed for the subsequent scores to be useful for researchers or clinicians.

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Chapter 49

Imaging of brain parenchyma in stroke

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49.1. Background: why image an acute stroke patient?

The central premise of acute stroke treatment is to rescue the ischemic penumbra. When a cerebral artery is occluded, a core of brain tissue dies rapidly. Surrounding this infarct core is an area of brain that is hypoperfused but does not die quickly, due to collateral blood flow. This area is called the ischemic penumbra (Astrup et al., 1981; Hossmann, 1983, 1994). The fate of the penumbra depends upon reperfusion of the ischemic brain. In the case of persistent arterial occlusion, the infarct core will grow and progressively replace the penumbra. In the case of early recanalization, either spontaneous or resulting from thrombolysis, the penumbra will be salvaged from infarction (Read et al., 2000).

The presence and extent of the ischemic penumbra is time-dependent, but is also paticularly patient-dependent. Indeed, from patient to patient, survival of the penumbra can vary from less than 3 hours to well beyond 48 hours. Ninety to one-hundred percent of patients with supratentorial arterial occlusion show ischemic penumbra in the first 3 hours of a stroke, but interestingly enough 75–80% of patients still have penumbral tissue 6 hours after stroke onset (Darby et al., 1999; Read et al., 2000; Hacke et al., 2004).

The relatively negative results to date of thrombolysis trials between 3 and 6 hours (Hacke et al., 2004), in spite of the high percentage of patients with penumbra within this time window, relates to the fact that these trials did not use any method of penumbral imaging to select patients for therapy, despite penumbra being the target for treatment. Thus, a tissue clock, where both the extents of infarct and penumbra are determined, would seem an ideal guide to patient selection for thrombolysis, rather than a rigid time window, as in the current thrombolysis guidelines (Donnan and Davis, 2002). Extension of the therapeutic window beyond 3 hours could substantially increase the number of patients able to receive thrombolysis. However, for this to occur with improved outcomes, a rapid and accessible neuroimaging technique able to assess the ischemic penumbra is required (Kaste, 2004).

49.2. Stroke MRI

The advent of new MRI techniques such as diffusion-weighted imaging (DWI) and perfusion-MRI (perfusion "weighted" imaging, PWI) imaging in the early 1990s added a new dimension to diagnostic imaging in stroke (Moseley et al., 1990). In the late 1990s improved gradient hardware that was needed for echo planar imaging was implemented in clinical MRI scanners. Deep brain ischemia leads to a shortage of metabolites, causing a Na^+/K^+ channel failure in each ischemic cell. This membrane channel failure causes a subsequent cytotoxic edema. Without any net water uptake in the affected brain the tissue water content remains unchanged and therefore x-ray attenuation does not change. During this early stage non-contrast CT does not show any changes in tissue contrast. Cytotoxic edema leads to a narrowing of the extracellular matrix and thus to a reduction of Brownian molecular motion in the extracellular space. This phenomenon can be measured with DWI. It was first described in 1965 and it can be measured quantitatively in the form of the apparent diffusion coefficient (ADC) (Stejskal and Tanner, 1965).

Kucinski and coworkers presented clinical data from ischemic stroke patients who were imaged with CT and DWI. They measured ADC and x-ray attenuation

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changes in infarcted tissue (Kucinski et al., 2002). In a cohort of 25 patients they observed mean ADC changes of 170×10^{-6}mm^2/s in the infarcted tissue 1.3–5.4 hours after symptom onset. This ADC decrease caused a strong contrast between infarcted and unaffected brain tissue (ADC 803×10^{-6}mm^2/s) on DWI. In contrast to the ADC changes, Kucinski observed a time-dependent x-ray attenuation decrease of 0.4 HU/hour. Based on these data CT appears to be less sensitive for early brain infarction compared to DWI.

A stroke MRI protocol consists of T2-, T2*-, diffusion- and perfusion- weighted images and magnetic resonance angiography (MRA). On T2-weighted and FLAIR images ischemic infarction appears as a hyperintense lesion seen at the earliest 6–8 hours after stroke onset (Mohr et al., 1995).

DWI allows the demonstration of ischemic tissue changes within minutes after vessel occlusion with a reduction of the ADC (Mohr et al., 1995). A net shift of extracellular water into the intracellular compartment (cytotoxic edema) with a consecutive reduction of free water diffusion is the main underlying mechanism for the ADC decrease (Röther et al., 1999). DWI leads to a significantly improved detection of early infarction compared to CT (91% versus 64%) (Fiebach et al., 2002; Saur et al., 2003).

PWI allows the measurement of capillary perfusion of the brain. The contrast bolus passage causes a nonlinear signal decrease in proportion to the perfused cerebral blood volume. It is not yet clear which PWI parameter gives the optimum approximation to critical hypoperfusion and allows us to differentiate infarct from penumbra and penumbra from oligemia (Rosen et al., 1990). Most authors, however, agree that in clinical practice mean transit time gives the best results. Calculation of the quantitative cerebral blood flow requires knowledge of the arterial input function, which in clinical practice is estimated from a major artery such as the middle cerebral or internal carotid artery. Thijs et al. (2004) evaluated the impact of different arterial input function (AIF) measured at 4 different locations in 13 ischemic stroke patients. The curves of AIF were measured near both middle cerebral arteries, in branches adjacent to the largest DWI abnormality and in the contralateral tissue to the DWI lesion. The largest PWI lesion was measured based on the AIF of the unaffected middle cerebral artery. The other three AIFs led to an underestimation of the infarct size on follow-up images.

The attempt to differentiate infarction from penumbra by imaging techniques was made by introducing DWI and PWI into the clinical setting. Using a simplified approach it has been hypothesized that DWI more or less reflects the irreversibly damaged infarct and PWI the complete area of hypoperfusion (Jansen et al., 1999). The volume difference in between these two (termed the PWI/DWI-mismatch; i.e. PWI- minus DWI-volume) would therefore be the stroke MRI correlate of the ischemic penumbra (Fig. 49.1). On the other hand, if there is no difference in PWI and DWI volumes or even a negative difference (PWI $<$ DWI) this is termed a PWI/DWI-match (Fig. 49.2) and, according to the model, equivalent to a patient who does not have penumbral tissue because of normalization of prior hypoperfusion or completion of infarction and total loss of penumbra (Parsons et al., 2002; Schellinger et al., 2003). One criticism is that this model does not take into account that the PWI lesion also assesses areas of oligemia which are not in danger and that DWI abnormalities do not necessarily turn into infarction (Kidwell et al., 2003).

Fiehler and coworkers analyzed the frequency of ADC normalization in 68 acute stroke patients: 19.7 % of their cohort had ADC normalization in more than 5 ml brain tissue. In those patients imaged within 3 hours after symptom onset, ADC normalization was seen in 35.5% while in patients imaged between 3 and 6 hours it was 7.5%. ADC normalization was predominantly seen in the basal ganglia and white matter in patients with distally located vessel occlusions and it was associated with a trend towards a better clinical outcome (Fiehler et al., 2004).

Thus, patients presenting with a PWI/DWI match within 3 hours after symptom onset might have salvageable tissue at risk and would benefit from fibrinolysis. However, it is still not known whether the absence of hyperintensities on follow-up T2-weighted images indicates neuronal integrity in humans. DeLaPaz et al. (1991) and Li et al. (2000) observed neuronal damage in histological examinations of tissue showing ADC normalization after reperfusion in a rat stroke model).

Stroke MRI was investigated under clinical routine setting. Based on an open, non-randomized patient cohort of 139 patients treated at 6 different academic hospitals, Röther et al. (2002) compared the results of 76 recombinant tissue plasminogen activator (rtPA) treated patients with 63 control subjects. Presenting with a slightly more severe stroke score, similar DWI lesions, and larger mismatch ratios, the treated patients showed early vessel recanalization more frequently and had better clinical outcome after 90 days (Röther et al., 2002).

The recently published DIAS and DEDAS trials (Desmoteplase in acute stroke) used a new fibrinolytic drug similar to a peptide from the saliva of *Desmodus rotundus,* a bat vampire. Patient screening was based on clinical examination, medical history and guided by Stroke-MRI. Only patients presenting a clear DWI/PWI mismatch were randomized. Those patients that received placebo or ineffective dosage

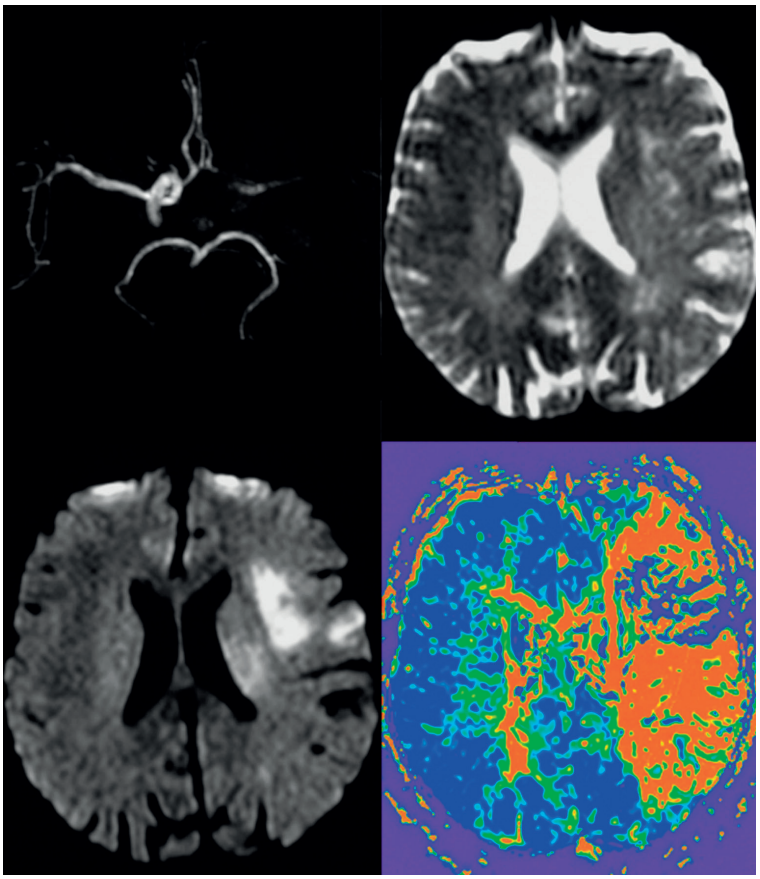

Fig. 49.1. Patient presenting 3.5 hours after symptom onset with aphasia and right hemiparesis. There is distal occlusion of the internal carotid artery and proximal middle cerebral artery occlusion on the left (upper left). On T2-weighted images (upper right) mild hyperintensity is seen in the deep left frontal white matter. The DWI abnormality is much more prominent (lower left). The PWI shows disturbed perfusion in the entire left middle cerebral artery territory (lower right). Following intravenous thrombolysis, the middle cerebral artery became patent again. The final infarction was slightly larger than the DWI abnormality. The neurologic symptoms improved.

showed a low recanalization rate and an unfavorable outcome. In patients who achieved an early vessel recanalization and a reperfusion of penumbra tissue a significant clinical benefit was observed and 60% of the patients from the most effective dose tier had an excellent clinical outcome (Hacke et al., 2005). In the DIAS 2 study, patients were enrolled based on a mismatch diagnosed either by MR (PWI/DWI) or perfusion computed tomography (PCT). Intention-to-treat analysis found no significant difference between the groups in clinical response rates, with numbers that contrasted sharply with their previous findings with this agent in the DIAS and DEDAS trials. Clinical response rate was 46.0% in the placebo group, 47.4% in the 90 µg/kg group, and 36.4% in the 125 µg/kg group.

Hyperacute stroke imaging demands the differentiation between ischemic stroke and intracranial hemorrhage, which is impossible by clinical means only. The diagnosis of intracranial hemorrhage is still only possible with CT. The need to perform both CT for exclusion of ICH and stroke MRI to guide therapeutic efforts is time-consuming, and medico-economically questionable (Powers and Zivin, 1998). The appearance of intracranial hemorrhage at MRI depends primarily on the age of the hematoma and the type of magnetic resonance contrast. The key substrate for early MRI visualization of hemorrhage is deoxyhemoglobin, a blood degradation product with paramagnetic properties due to unpaired electrons. The typical appearance of intracranial hemorrhage on MRI images was a heterogeneous focal lesion. With increasing susceptibility weight, the central area of hypointensity became more pronounced. On T2*-weighted images, few if any areas of hyperintensity are visible in the lesion core, which is surrounded by a hypointense rim. There is a surrounding hyperintensity on T2-weighted and T2*-weighted images (hypointense on T1-weighted images) that represents perifocal vasogenic edema. One randomized, blinded prospective multicenter trial recently investigated the role of stroke MRI in intracranial hemorrhage (Fiebach et al., 2004). Images from 62 intracranial hemorrhage patients and 62 non-hemorrhagic stroke patients all imaged within

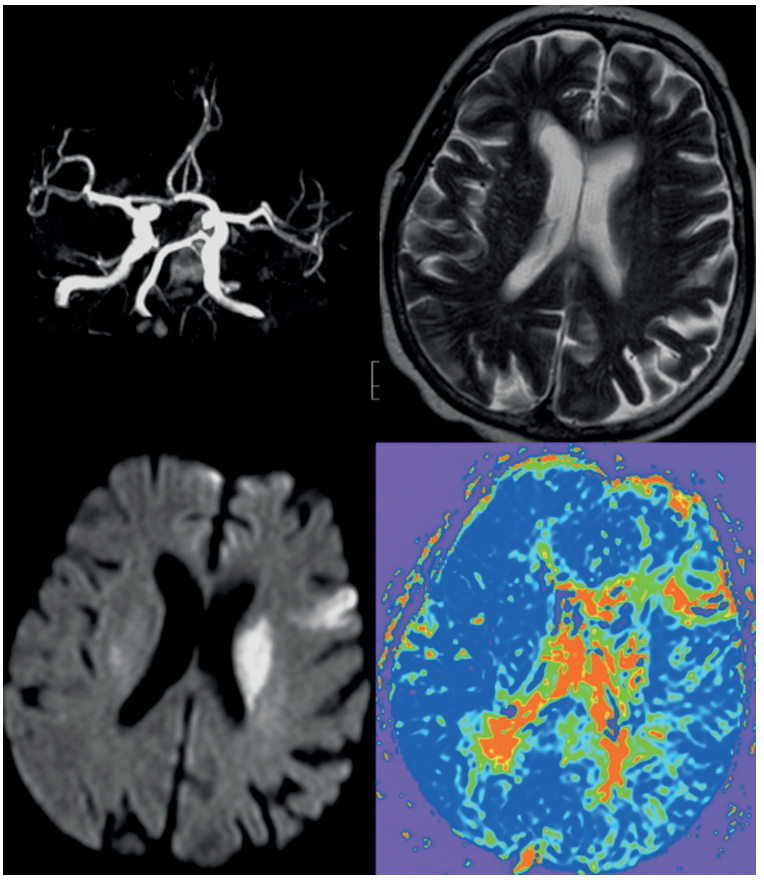

Fig. 49.2. Four hours after acute onset of motor aphasia and right-sided hemiparesis MRA findings and T2-weighted images are normal (upper left and right), although MRA as part of a fast stroke MRI protocol does not allow the evaluation of the M3 and M4 segments reliably. A mild cortical hyperintensity at Broca's region and the corona radiata is visible on DWI. The perfusion disturbance is of about the same size as the DWI abnormality. As there is no mismatch and thus no "tissue at risk" (lower left and right), thrombolysis is not indicated.

the first 6 hours after symptom onset (mean 3 hours 18 min) and were analyzed after randomization for the order of presentation. The size of intracranial hemorrhage ranged from 1–101.5 ml (mean 17.3 ml). Three readers experienced in stroke imaging and three final-year medical students each separately evaluated sets of diffusion-, T2- and T2*-weighted images unaware of clinical details. The experienced readers identified intracranial hemorrhage with 100% sensitivity (confidence interval: 97.1–100%) and a 100% overall accuracy. The medical students achieved a mean sensitivity of 95.16% (90.32–98.39%). Thus hyperacute intracranial hemorrhage is detectable with excellent accuracy even if the raters have only limited experience.

49.3. Stroke CT

A modern CT survey, including non-contrast CT (NCT), perfusion-CT (PCT), and CT-angiography (CTA) (Nabavi et al., 2002; König, 2003; Tomandl et al., 2003; Wintermark and Bogousslavsky, 2003) fulfills all the requirements for hyperacute stroke imaging (Latchaw et al., 2003).

NCT has classically been used as the standard initial imaging examination for acute stroke patients because of its convenience and its high sensitivity for the detection of intracranial hemorrhage, which represents an absolute contra-indication to thrombolytic therapy. Occasionally, NCT can provide information supportive of the diagnosis of evolving infarction (e.g. the hyperdense artery sign, indicating arterial thrombus), even when ischemic changes in the brain parenchyma such as hypodensity are not visible. Unfortunately, NCT provides solely anatomical—and not physiological—information and has thus very low sensitivity for acute stroke detection (Barber et al., 1999; Symons et al., 2002).

There exists sensitive—and specific—functional CT imaging, encompassing CTA and PCT (Fig. 49.3),

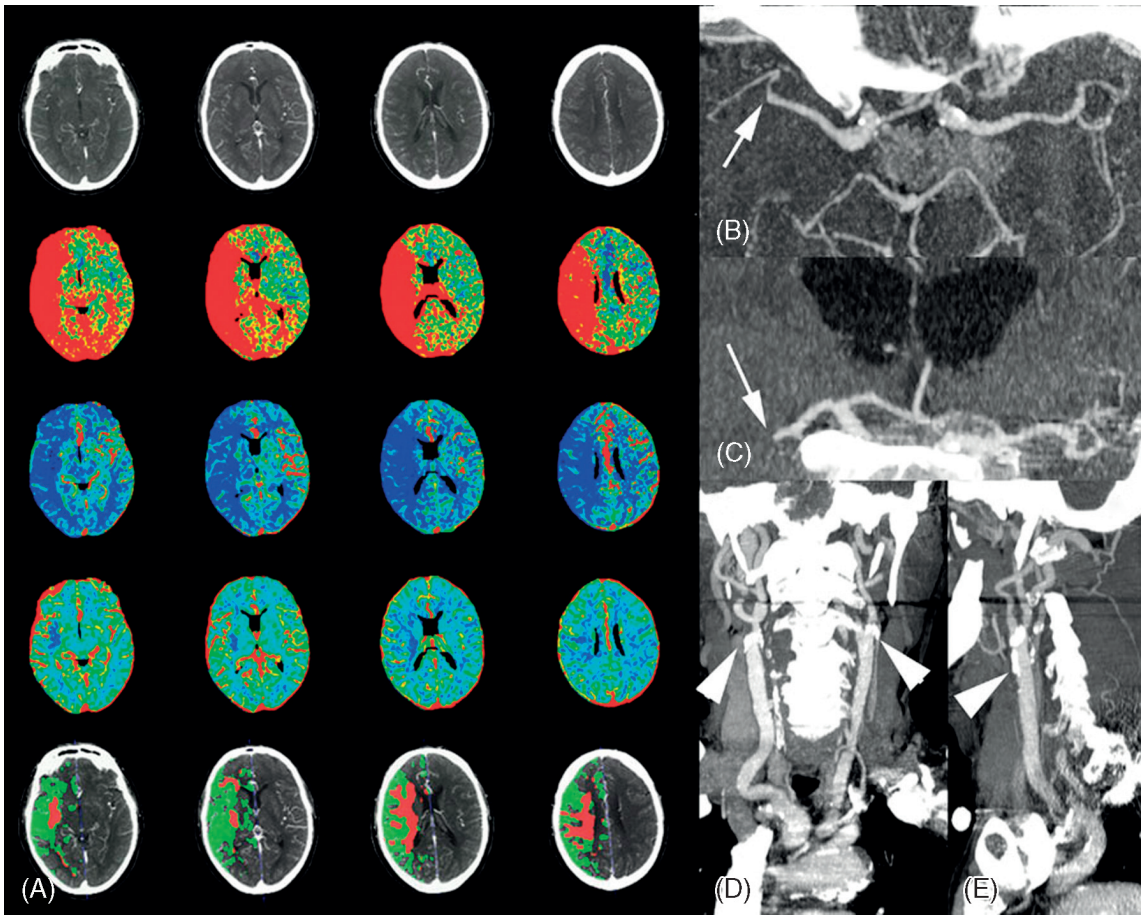

Fig. 49.3. Modern CT survey in a 62-year-old male patient admitted in our emergency room with a left hemisyndrome, including (A) perfusion-CT and (B–E) CT-angiography (CTA). (A) From the perfusion-CT raw data (first line), three parametric maps can be extracted, relating to mean transit time (MTT, second 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 *(arrowheads)*.

which provides complementary information about vessel patency and the hemodynamic repercussions of a possible vessel occlusion, respectively. PCT and CTA can be obtained immediately after NCT, during the same CT examination, obviating moving the patient to another imaging device for physiological information needed for making treatment decisions. The total duration of an NCT, two series of PCT, and a CTA is around 10 min (Wintermark and Bogousslavsky, 2003).

PCT imaging, using standard nonionic iodinated contrast, relies on the speed of modern helical CT scanners, which can sequentially trace the entry and washout of a bolus of contrast injected into an arm vein through an IV line (Eastwood et al., 2003). The relationship between contrast concentration and signal intensity of CT data is linear. Thereby, analysis of the signal intensity increasing then decreasing during the passage of the contrast provides information about brain perfusion. More specifically, PCT description of brain perfusion consists of three types of parametric maps, relating to regional cerebral blood volume (rCBV), mean transit time (MTT), and regional cerebral blood flow (rCBF), respectively. rCBV reflects the blood content of each pixel, MTT designates the average time required by a bolus of blood to cross the capillary network in each pixel, and rCBF relates to the amount of blood flowing through each pixel during a time interval of 1 minute (Wintermark et al., 2001; Eastwood et al., 2003). Recently, CBF values from PCT imaging have been shown to be highly accurate in humans when compared to the gold standard, positron emission tomography (Kudo et al., 2003).

By combining MTT and rCBV results, PCT has the ability to reliably identify the ischemic reversible penumbra and the irretrievable infarct core in acute stroke patients, immediately on admission. In the infarct core, both MTT and rCBV values are lowered, whereas in the penumbra, cerebral vascular autoregulation attempts to compensate for decreased rCBV by a local vasodilatation, resulting in increased rCBV values (Wintermark et al., 2002a,b). Commercial PCT software currently allows real-time automatic calculation of infarct and penumbra maps according to the above-mentioned principles.

49.4. PCT/CTA or MRI: Which one?

CT and MRI provide similar information. As a reminder, the DWI lesion corresponds to the infarct core, whereas the DWI-PWI mismatch is representative of the ischemic penumbra (Rordorf et al., 1998). The infarct core and the ischemic penumbra, as demonstrated by DWI/PWI and PCT, respectively, are comparable (Fig. 49.4A-E) (Wintermark et al., 2002a,b). Similarly, CTA and MRA results are very much alike (Fig. 49.3), but have respective advantages and drawbacks to be considered in the special settings of acute stroke.

Stroke MRI is still available only in a limited number of hospitals. Despite the advantages of stroke MRI there are still doubts whether it is a safe approach in severely affected patients and depending on each individual setting it is hard to conduct stroke MRI without losing too much time before treatment onset.

The main advantages are (1) direct visualization of the full extent of infarction on DWI, and (2) whole brain coverage can be achieved with PWI at a time resolution of 1.4 seconds per frame, thus even small but clinically relevant hypoperfusion can be visualized. Visualization of the circle of Willis can be performed within 3 minutes with a time-of-flight MR-angiography. If a patient moves the head during image acquisition a sequence can be easily repeated. No additional x-ray dosage or iodinated contrast agent is needed and therefore no nephrotoxicity or relevant allergic reactions are expected. In contrast to iodinated

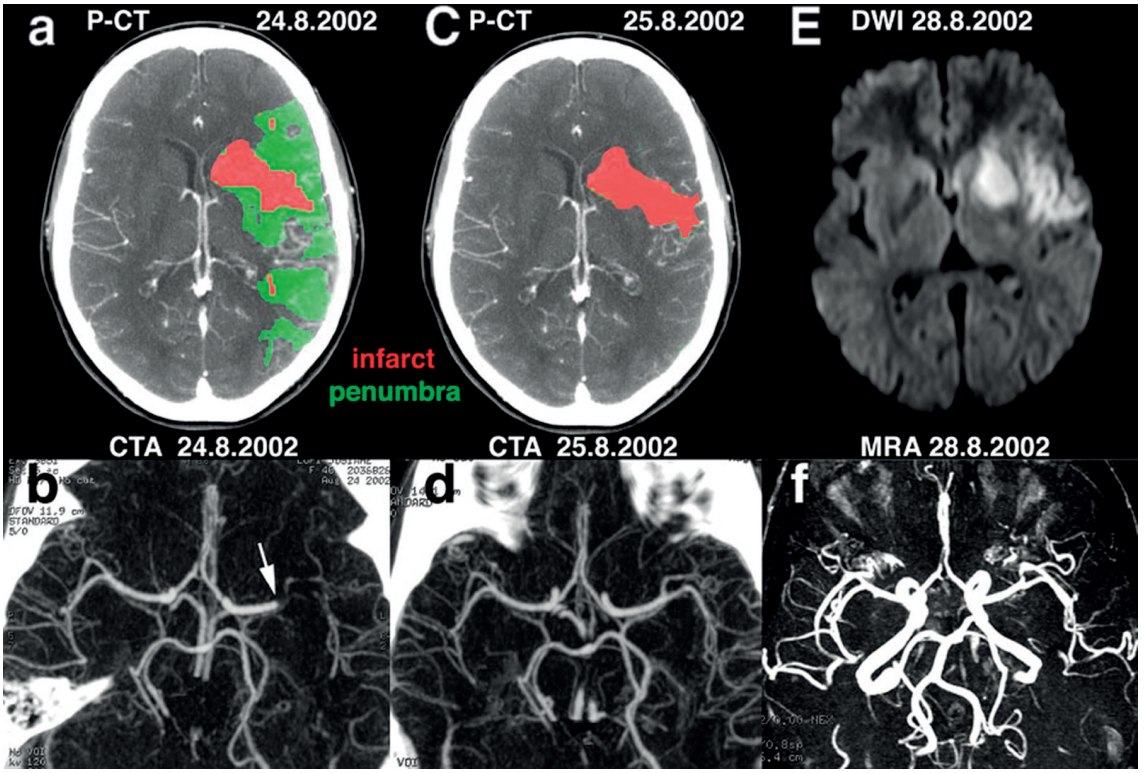

Fig. 49.4. (A) Admission perfusion-CT demonstrates mixed infarct and penumbra in the left sylvian territory in a patient with a right hemisyndrome, whereas (B) CT angiography (CTA) relates it to an occlusion at the left M1–M2 junction *(arrow)*. The patient underwent intravenous thrombolysis and his clinical condition evolved favorably. Twenty-four hours after admission, (D) follow-up CTA features a recanalization of the left sylvian artery, later confirmed on the (F) 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 (E) delayed DWI trace image.

contrast media, MRI perfusion measurement does not cause a feeling of heat and therefore movement artifacts are less likely during perfusion imaging. However, the control of vital signs and access to the patient during the 10-minute scan procedure is limited by the magnet. In addition, it takes some effort to train staff and technicians to conduct stroke MRI in a short period of time to establish an adequate work flow during the hyperacute phase of ischemic stroke.

CT is often objected to without reason for its use of x-rays and iodinated contrast material. However, the radiation dose involved in PCT imaging is less than a conventional cerebral CT examination (Wintermark et al., 2000) and no renal failure has yet been reported following a PCT examination (Smith et al., 2003).

Because of a limited spatial resolution, PCT cannot detect small lacunas, whereas NCT is not as sensitive to microbleeds as gradient-echo MRI. PCT has a limited spatial coverage (20–48 mm thickness). However, the issue of spatial coverage will be addressed in the near future through the development of larger multidetector CT scanners with greater arrays of elements. Even at present, PCT has demonstrated 95% accuracy in the delineation of the extent of supratentorial strokes, despite its limited spatial coverage (Wintermark et al., 2005). PCT has also been demonstrated as useful in the evaluation of vertebro-basilar ischemia (Nagahori et al., 2004).

The low requirements for performing PCT/CTA technology and its wide availability are keys to its overtaking of MRI as the imaging method of choice for acute stroke patients. Indeed, due to their relatively low cost and utility in other areas of medicine, particularly emergency medicine and trauma, CT scanners are becoming very widely available and, as opposed to MRI, it is foreseeable that every major emergency center will eventually be able to complete this form of imaging within minutes of the patient presenting to the emergency department.

Another major advantage of PCT over MRI relates to its quantitative accuracy. MRI perfusion imaging affords only a semiquantitative comparison of one hemisphere with the other. Quantitative accuracy of PCT makes it a potential surrogate marker to monitor the efficiency of acute reperfusion therapy, which is a decisive element when it comes to finding and validating new individualized therapeutical strategies for acute stroke patients.

49.5. Conclusion

Both CT and MRI fulfill all the requirements for hyperacute stroke imaging. CTA and MRA can define the occlusion site, depict arterial dissection, grade collateral blood flow, and characterize atherosclerotic disease. PCT and DWI/PWI accurately delineate the infarct core and the ischemic penumbra. CT and MRI both have their own advantages and drawbacks. The selection of one over the other depends upon the intrinsic characteristics pertaining to each imaging technique, but also upon the settings and on the knowledge and experience of the institutions' staff.

Controversies regarding the superiority of either CT or MRI technique for acute stroke imaging should not obscure the ultimate goal, which is to increase the availability and improve the efficiency of thrombolytic therapy. From that standpoint, CT and MRI must be considered as equivalent tools. Hopefully, using CT and/or MRI to define new individualized strategies for acute reperfusion will allow the number of acute stroke patients benefiting from thrombolytic therapy to be significantly increased.

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Chapter 50

Imaging intra- and extracranial vessels: computed tomography angiography and magnetic resonance angiography

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50.1. Computed tomography angiography

Remarkable advances in computed tomography (CT) scanner technology over the last decade have enabled CT angiography (CTA) to become the first-line imaging study for a majority of neurovascular applications, most notably those of acute stroke and subarachnoid hemorrhage. Indeed, at many centers, CTA has entirely replaced catheter arteriography as the "gold standard" for a growing number of clinical indications.

The increasing clinical impact of CTA over the past decade can largely be attributed to the development of helical scanners with increasing numbers of detector rows. By acquiring numerous image slices simultaneously from a single rotating x-ray source, these multidetector row CT (MDCT) scanners enable acquisition of CTA with greatly increased speed and quality. Given the dramatic increase in image slices per study, as well as the challenges of depicting the complex neurovasculature, three-dimensional (3D) post-processing has become essential for diagnostic review of CTA. Powerful tools for image manipulation are utilized in stand-alone 3D workstations or are increasingly incorporated into CT scanner consoles and diagnostic review workstations (PACS, Picture Archive and Communication System). CTA acquisition parameters and standardized 3D views are specifically tailored to best demonstrate the relevant pathology for various CTA indications.

50.1.1. CTA fundamentals

50.1.1.1. Evolution of multi-detector row CT

The great CT advance in the early 1990s was from step-and-shoot axial imaging to *helical* CT in which an unbroken stream of data was acquired as an x-ray source-and-detector combination spun continuously around the patient (Flohr et al., 2004). While this advance first enabled clinically useful volumetric imaging, the subsequent introduction of scanners with progressively more detector rows has enabled significantly larger coverage in a shorter amount of time and now true isotropic resolution (image voxels of comparable size in all three dimensions) (Hu et al., 2000). The latest 16- and 64-slice CT units can scan *entire vascular territories* in 15 to 30 seconds, well within the time course of the dynamic administration of a single bolus of intravenous contrast agent (Fox et al., 1998; Rydberg et al., 1998). These capabilities are especially advantageous for the challenging demands of new applications in cardiac imaging and neurovascular CTA.

With MDCT, each channel of the detector array generates a *separate* helix of imaging data. The reconstruction algorithms that merge these data channels to create MDCT image slices are complex and relate to the particular detector configuration (Taguchi and Aradate, 1998). Depending upon the clinical indication, detector rows of equal or varying thickness are activated in particular combinations to produce a certain number of image slices

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of a given thickness and resolution. Thus, a 4-slice scanner (i.e. able to acquire 4 image slices simultaneously) actually may have up to 16 detector rows. Hence the confusion of coexisting terminologies, with "multi-detector row CT" (MDCT) and "multi-slice CT" (MSCT) are both correct descriptors for modern CT scanners (Flohr et al., 2004). The total length of the detector array along the long axis of the patient direction (z-axis) in 16-slice scanners is typically 20 mm. The latest MDCT scanners can acquire up to 64 image slices simultaneously with most manufacturers utilizing a 40-mm-long array of 64 equally sized detector rows.

50.1.1.2. Intravenous contrast issues in CTA

Nonionic CT contrast agents have been shown to be generally safe, even in the setting of cerebral ischemia. In an animal model of MCA stroke, no significant neuronal toxicity from non-ionic contrast agents was observed, even to already ischemic neurons (Kendell and Pullicono, 1980; Doerfler et al., 1998). However, some patients are at higher risk for contrast-induced nephropathy (CIN) at baseline, especially those who have diabetes, pre-existing renal dysfunction, or both. Factors such as serum creatinine level and creatinine clearance help determine whether iodinated contrast can be safely administered. Creatinine clearance is an easily calculated estimate of glomerular filtration rate (GFR). It is recognized as more accurate than serum creatinine for assessing renal function as it also takes into account the patient's body weight and gender (Bettmann, 2004).

Multiple strategies to reduce the risk of CIN are available. Since nephrotoxicity from contrast media is dose-dependent (Morcos, 1998; Morcos et al., 1999), CTA protocols are designed to use the least amount of contrast possible. The use of denser contrast agents and innovative strategies enabled by the latest generation of power injectors may increasingly result in reduced contrast loads (Cademartiri et al., 2002). Recently, Aspelin et al. (2003) demonstrated the potential benefit of using an iso-osmolar agent, iodixanol, in patients with diabetes and borderline renal function. This agent, however, is more expensive and more viscous at room temperature compared to standard nonionic agents. Adequate pre- and post-procedure hydration is considered by most experts to be the most important factor in preventing CIN.

For those patients who are allergic to iodinated contrast media, premedication with antihistamines and steroids can blunt the anaphylactoid response. In the setting of an acute stroke, where there is insufficient time to complete a course of steroid administration, a gadolinium MR contrast agent may be used as a clinically effective alternative for CT (Henson et al., 2004). It should be noted that though the scans are usually diagnostic (Fig. 50.1), peak vessel opacification is much less than with iodinated contrast agents, even at gadolinium doses several times higher than typically used for MRI. Since gadolinium at these concentrations may theoretically be even more nephrotoxic than iodinated contrast, gadolinium should be used with caution when the contraindication to iodinated contrast administration is renal insufficiency rather than allergy.

50.1.2. CTA in specific neurovascular clinical scenarios

50.1.2.1. CTA in stroke imaging

According to the National Stroke Association Website, "stroke is our nation's third leading cause of death, killing nearly 160,000 Americans every year." Death or severe disability can be prevented or diminished if thrombolytic treatment is administered within a short time period after onset of embolic stroke. By helping to rapidly identify intracranial thrombus, vascular stenosis, and parenchymal ischemia, CTA in combination

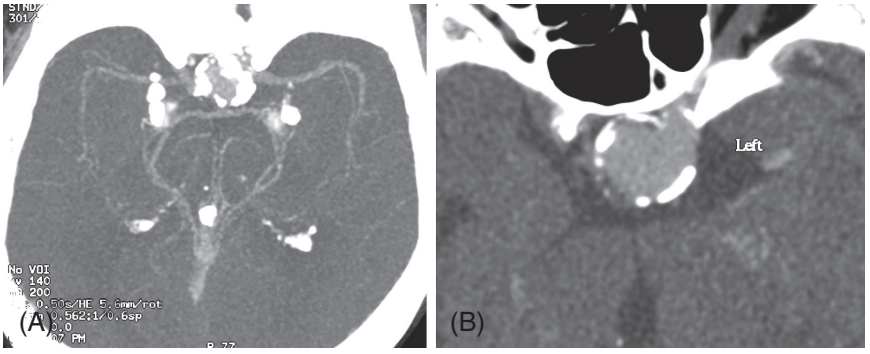


Fig. 50.1. Gadolinium CTA performed in a patient with severe iodinated contrast allergy: Despite suboptimal vascular opacification relative to iodinated contrast (A), the diagnosis of a 1.9 cm left PCOM aneurysm is still clear (B).

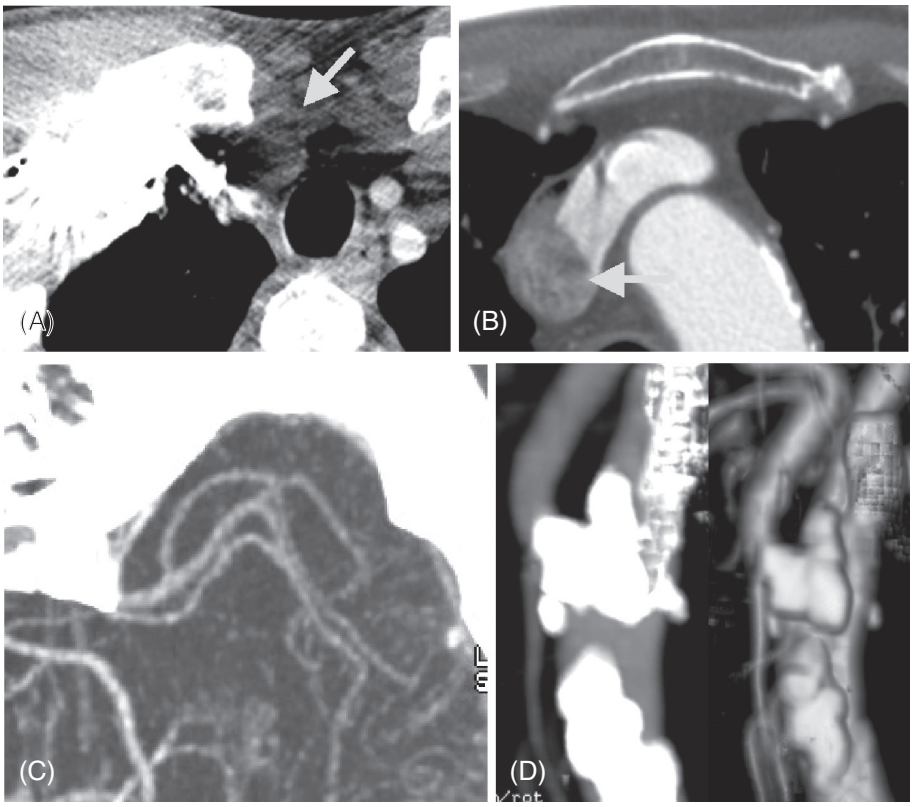


Fig. 50.2. Pitfalls in CTA imaging and post-processing: Streak artifact from undiluted inflowing contrast can obscure proximal great vessel segments (A, arrow). "Pseudo-thrombus" appearance from incomplete contrast mixing of unopacified and opacified blood can occur in the superior vena cava (B, arrow). "Pseudo-beading" artifact can occur due to superimposition of background noise on poorly opacified vessels on maximum-intensity projection views (C). Thick atherosclerotic calcification overlying lumen can preclude residual lumenal diameter measurement on maximum-intensity projection and volume-rendered (VR) views (D).

with CT perfusion (CTP) analysis has become a critical part of the early management of such patients in many institutions. A combined CTA/CTP study in patients suspected of having embolic stroke facilitates their diagnosis and, very importantly, the triage to appropriate therapy. MRI techniques such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have also revolutionized stroke imaging; DWI clearly delineating infarcted brain tissue within minutes and PWI defining areas of cerebral hypoperfusion (Röther, 2001). The choice of whether to use CT or MR techniques may depend on which modality is more readily available. At least one study in acute stroke patients has demonstrated equal accuracy of CTA and MRA for vessel delineation and close to equal accuracy of CTA source image analysis compared to DWI in determining infarct volumes (Schramm et al., 2002). When both are available, the modalities are complementary with CTA providing excellent assessment of proximal and collateral vessel status and DWI/PWI providing conspicuous identification of the infarct core and whole brain perfusion analysis. In this section, we will focus on the rationale and efficacy of a CTA/CTP imaging approach for acute stroke and how such studies are acquired and analyzed.

50.1.2.2. "Time is brain": rationale of CTA/CTP as a triage tool for acute stroke

Typically, patients with acute ischemic stroke symptoms undergo an unenhanced head CT scan as their first imaging test in order to determine if contraindications to thrombolytic treatment exist. Such contraindications include hemorrhage (an absolute contraindication) or a "large" parenchymal hypodensity. The hypodensity corresponds to already infarcted tissue. "Large" is defined as greater than one-third of the vascular territory (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Von Kummer et al., 1997). However, findings of early infarction on unenhanced CT are often very subtle and may go undetected, even by experienced physicians (Lev et al., 1999). Also, unenhanced CT scanning alone, although of some value

in predicting patients most likely to be harmed by thrombolysis, is of little value in predicting patients most likely to benefit from thrombolysis, specifically those with proximal large-vessel vascular occlusions.

Because unenhanced CT and clinical exam alone are limited in their ability to detect large vessel thrombus, CTA has become the first-line diagnostic test for patients presenting with signs and symptoms of acute stroke at many institutions. Due to the narrow time window available to initiate the thrombolytic agent, rapid triage is crucial. Therefore, the rationale in the evaluation of an acute stroke patient is to identify as quickly as possible those patients who may benefit from IV or IA thrombolysis or other acute stroke treatments. Importantly, CTA excludes from treatment patients with stroke mimics such as complex migraine and seizure. These patients will not benefit from and may be harmed by such therapies.

Because helical CT scanners are less expensive and more readily available at most hospital emergency departments than MRI scanners, performing CTA/CTP can be a quick and natural extension of the unenhanced head CT exam—an exam that is routinely obtained as part of the prethrombolysis workup at most institutions (Lev and Nichols, 2000; Lev et al., 2001a,b). The addition of a CT angiographic study seldom adds more than 10 minutes of scanning time to that of the conventional CT examination. Required post-processing can typically be performed in minutes, during which time the patient could be prepared for thrombolysis, should the decision to proceed with treatment be made (Koroshetz and Gonzales, 1999; Lev et al., 2001a).

50.1.2.3. CTA, CTA source images, and CTP: stroke detection and prognosis

Multiple studies have confirmed the ability of CTA to reliably detect large-vessel intravascular clot with an accuracy approaching 99% (Knauth et al., 1997; Shrier et al., 1997; Wildermuth et al., 1998; Lev et al., 2001a) (Fig. 50.3A). CTA has also been shown to be useful for the evaluation of collateral circulation distal to an occlusion, as well as for improving the conspicuity of acute cerebral ischemia (Barest et al., 1997; Ponzo et al., 1998). CTA has been shown to have higher sensitivity and less inter-operator variability than magnetic resonance angiography (MRA) for intracranial steno-occlusive disease and was found superior even to digital subtraction angiography (DSA) for detecting posterior-circulation involvement when slow flow is present (Bash et al., 2005). Since CTA through the neck is included in the CTA evaluation of patients with acute stroke, an embolic source of infarct, such as thrombus or occlusion at the carotid bifurcation, can often be identified (Fig. 50.3C,D).

CTA can also be used for risk stratification and prognosis. Among patients treated with intravenous tissue plasminogen activator (tPA), those who had patent vasculature or only occult distal occlusion on pretreatment CTA had better prognosis characterized by fewer hemorrhages, better National Institutes of Health (NIH) Stroke Scale score, and better early improvement (Sims et al., 2005). Risk stratification can also be accomplished by evaluating the parenchyma on CTA source images. Assuming an approximate steady-state level of contrast enhancement during scan acquisition, the source images from the CTA dataset can be considered whole-brain perfused blood volume images, generally referred to as "CTA source images" or CTA-SI. Hypodensity on CTA-SI helps facilitate detection of subtle parenchymal ischemic changes associated with distal embolic occlusions (Lev and Nichols, 2000) and can be used for risk stratification (Fig. 50.3B). A recent retrospective study from our institution has positively correlated the degree of parenchymal hypoattenuation on initial CTA source images with likelihood of hemorrhagic transformation and poor clinical outcome after intra-arterial reperfusion therapy (Schwamm et al., 2005).

Following CTA-SI, a dedicated CTP study acquisition can be acquired using the first-pass cine slab technique. Following very rapid bolus infusion of contrast material ($\sim$7 cm^3/second), image slices are acquired once per second over a total period of 45–60 seconds. This time period is sufficient to track the first pass of the contrast bolus through the intracranial vasculature without recirculation effects. More coverage with a second cine-CTP slab may be accomplished if renal function and total contrast dose limitations permit a second bolus injection. Following acquisition, cine-CTP images are processed into maps of cerebral blood flow, cerebral blood volume, and mean transit time. These maps help outline the region of "ischemic penumbra," which is understood as the abnormally perfused tissue surrounding a core of infarcted tissue. The penumbra, though potentially viable, is felt to be at risk for imminent infarction and may benefit from thrombolysis (Fig. 50.4). Alternatively, CTP maps may indicate that all or a large majority of the abnormally perfused tissue is already inevitably progressing to infarction. In this situation, initiating thrombolytic treatment could significantly worsen the outcome by precipitating intracranial hemorrhage. First-pass CTP is currently limited in the extent of coverage that can be obtained during a single bolus injection of contrast. This limitation is sometimes clinically restricting, but should be less so with the 40-mm maximum collimation available for each CTP slab on 64-slice scanners.

The acute stroke protocol is a multi-sequence scan consisting of the following components: (1) routine

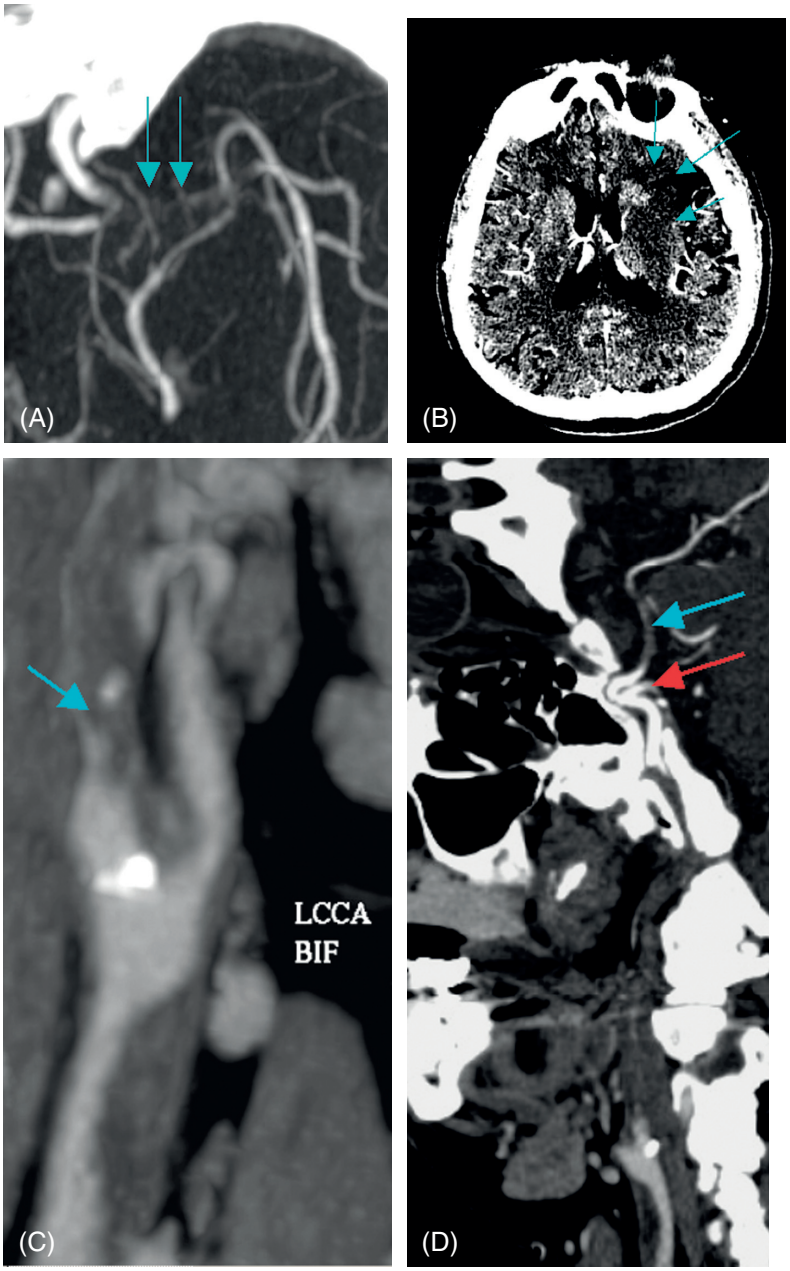


Fig. 50.3. CTA of the head and neck and CTA-SI analysis: Left proximal middle cerebral artery segmental occlusion is demonstrated on head CTA (A, arrows). Hypoperfused and possibly ischemic brain tissue is most conspicuous on CTA source images (CTA-SI) as hypo-attenuated region (B, arrows). Maximum-intensity projection of the carotid bifurcation demonstrates source of embolic infarct with clot occluding the proximal left internal carotid artery (C, arrow). CR view demonstrates absence of flow through the occluded cervical internal carotid artery, reconstitution of flow within the cavernous/supraclinoid carotid segments (D, red arrow) and again more distal obstruction of proximal middle cerebral artery segment (D, blue arrow).

unenhanced head CT, (2) CTA of the head and neck, and (3) an optional single- or two-slab cine CT perfusion study (Lev and Nichols, 2000). Depending on the MDCT scanner generation, high-resolution CTA coverage of the complete neurovascular system, from aortic arch to the vertex, can be performed in 15–35 seconds.

Since short-segment thrombo-embolic occlusions and small aneurysms can be virtually undetectable when scrolling through the thin axial source images, reformatted views that display vessels in an "angiographic" manner are an essential component of CTA diagnosis (Fig. 50.5). At Massachusetts General Hospital, we utilize dedicated technologists in a 3D-imaging lab to

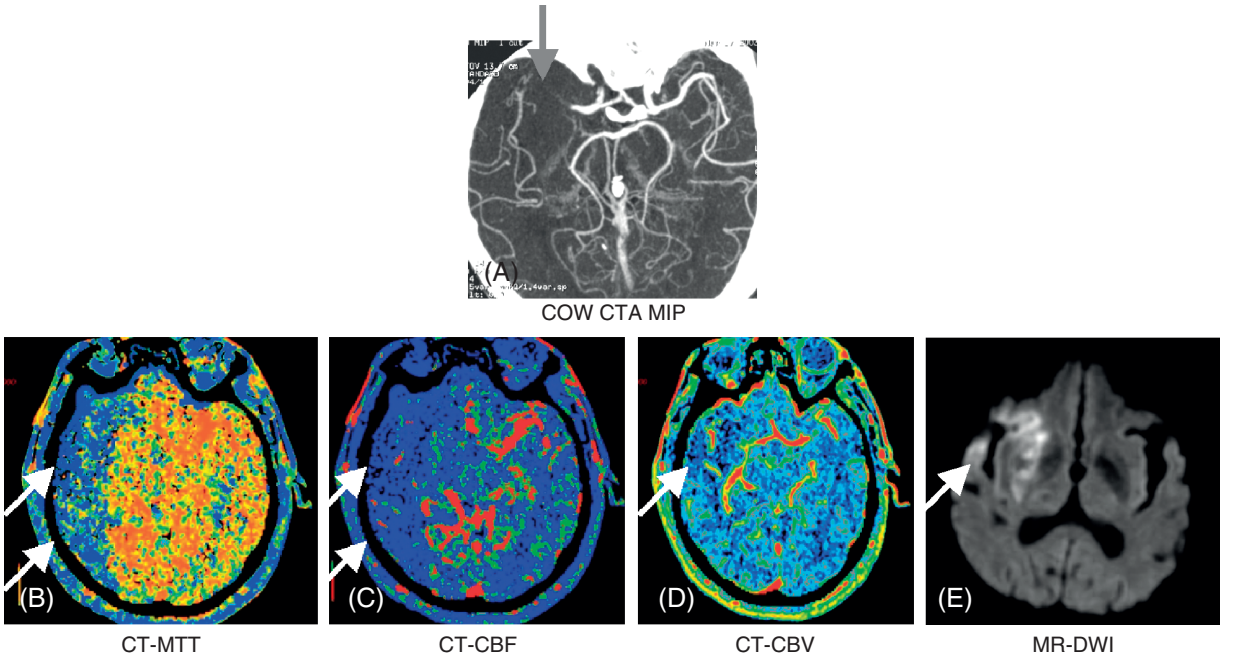


Fig. 50.4. Cine-CT perfusion analysis in acute stroke: middle cerebral artery stem occlusion is clearly visualized on CTA (A, arrow). Mismatch is present between large territorial perfusion abnormality on MTT and CBF maps (B and C, arrows) and small area of decreased perfusion on cerebral blood velocity map (D, arrow). The final infarct on DWI after successful thrombolysis is confined to an area of abnormality on the cerebral blood velocity map suggesting successful salvage by thrombolysis of larger penumbra (E, arrow).

create standard views of each vascular segment in a timely fashion. However, for emergent triage, angiographic maximum intensity projection (MIP) views can be reformatted at the scanner console in a semi-automated fashion in less than 1 additional minute after scan acquisition. They allow confident diagnosis of circle-of-Willis proximal branch vessel occlusion even before the patient has been removed from the scanner. Since MIP images are of arbitrary thickness, they can be used to quickly exclude overlapping bone from the angiographic views. A pitfall to be aware of is when a tortuous vessel segment loops out of the MIP slab plane, mimicking an occluded segment.

50.1.3. CTA of the neck

50.1.3.1. Chronic carotid artery steno-occlusive disease

CTA measurements of residual lumenal diameter have compared favorably with those of DSA, unenhanced MRA, and Duplex ultrasound (Schwartz et al., 1994; Lev et al., 1995a, 1997; Leclerc et al., 1996; Link et al., 1996; Anderson et al., 2000; Josephson et al., 2004; Berg et al., 2005). However, the user must pay careful attention to appropriate window and level display settings. Beam hardening artifact from heavy circumferential calcifications can result in overestimation of the degree of stenosis in both axial and longitudinal views. For measurement of small lumen diameters, even without calcified plaque, the accuracy of CTA measurement is limited by the pixel size—typically 0.4–0.5 mm (assuming a 20–25 cm field of view and a 512 × 512 imaging matrix). In serial examinations, differences in window settings, level settings and contrast density from one CTA study to another can produce large differences in the measured lumen size (Lev et al., 1995b; Dix et al., 1997; Liu et al., 2000). Software solutions for semi-automated detection of cross-sectional area and true lumenal diameters (D_{min},D_{max},D_{mean}), orthogonal to a computer-generated centerline, are now available and promise great utility for reducing interobserver variability and increasing post-processing efficiency (Zhang et al., 2004) (Fig. 50.6). Dense contrast opacification throughout the entire vascular segment evaluated is a prerequisite for success with such semi-automated techniques.

Degree of carotid stenosis can be expressed in terms of percent stenosis, residual lumen area, or residual lumen diameter. Percent stenosis, the ratio of maximal lumenal narrowing to the normal internal carotid artery distal to the bulb, was the severity index in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and is the most commonly used measure by practitioners in North America. However, the

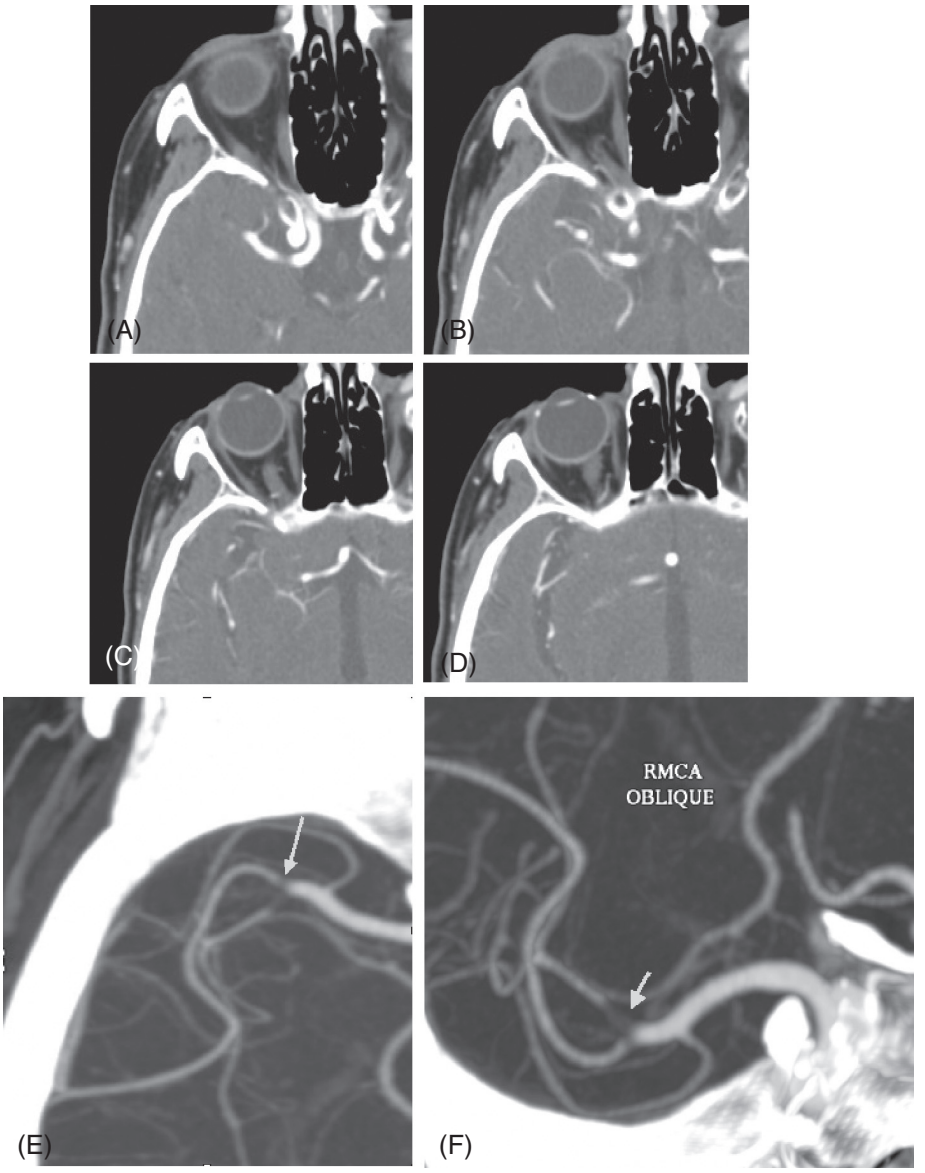
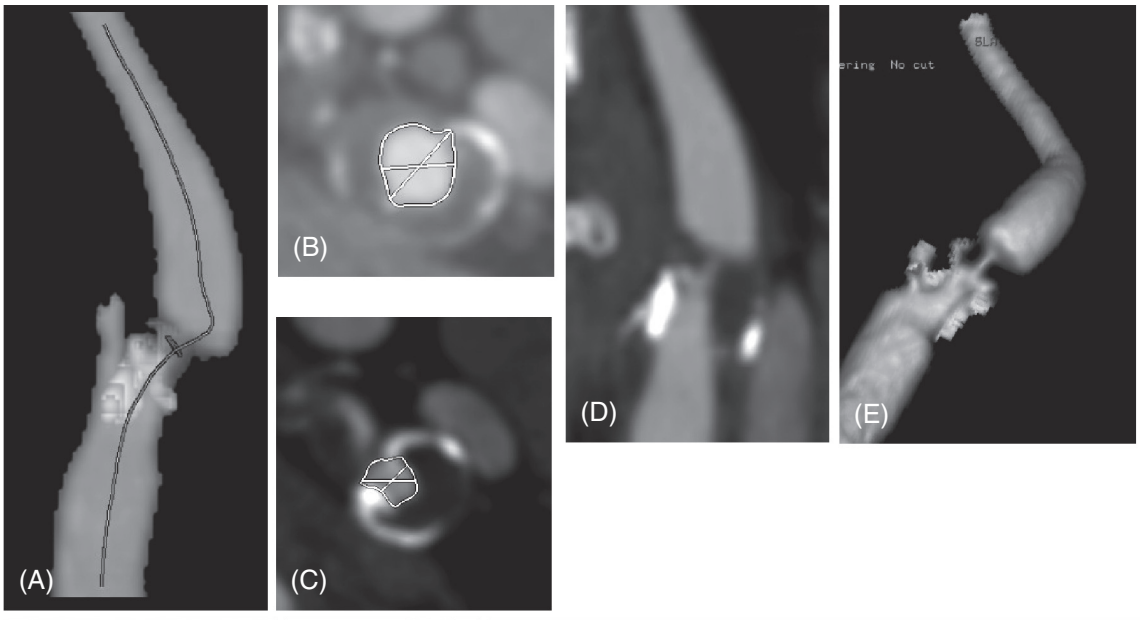


Fig. 50.5. Importance of maximum-intensity projection images for detection of small segmental occlusions. Occlusive thrombus at right middle cerebral artery bifurcation is very difficult to detect on sequential axial source CTA images (A–D) though very conspicuous on maximum-intensity projections (E, F arrows). Good opacification of vessels distal to occlusion by collateral flow is noted.

reference diameter of the distal ICA typically ranges from 5 to 8 mm, which can significantly alter the calculated percent stenosis. At Massachusetts General Hospital, we report the degree of vascular stenosis based on residual lumen diameter (RLD) using 1.5 mm as the cut-off for hemodynamically significant stenosis. An RLD of 1.5 mm correlates approximately to ultrasound peak systolic velocity of >250 cm/s and a NASCET measurement of 70% stenosis (Suwanwela et al., 1996). Plaque characteristics such as ulceration, amount of calcification, thin fibrous cap, lipid core, and hemorrhage have been evaluated as potential predictors of stroke risk. These features can sometimes be identified on CTA but not consistently (Oliver et al., 1999; Walker et al., 2002).

Prior to performing CTA of the neck it is important to review prior non-invasive ultrasound, MR, CT, and angiographic studies to determine what questions are to be answered. Our CTA neck protocol is very similar to the stroke CTA protocol except coverage extends only from the circle of Willis through the aortic arch. An optional *delayed* series helps detect the slow opacification of a hairline residual lumen and thus distinguish it from complete occlusion. The distinction is critically important



Point Name	Mean (mm)	Min (mm)	Max (mm)	Area (mm2)
Ref.	4.2 ± 0.6	4.0 ± 0.6	4.3 ± 0.6	13.6 ± 3.9
Sten. st.	7.5 ± 0.5	6.9 ± 0.5	8.1 ± 0.5	44.8 ± 5.6
Sten. End.	6.8 ± 0.5	6.5 ± 0.5	7.1 ± 0.5	36.7 ± 5.6
Stenosis	1.7 ± 0.6	1.5 ± 0.6	1.9 ± 0.6	2.3 ± 1.9

Fig. 50.6. Semi-automated carotid stenosis evaluation software. A vascular center-line is automatically generated (A). Cross-sectional area and true lumenal diameters (D_{min},D_{max},D_{mean}), orthogonal to the centerline are then calculated. Software must distinguish between lumenal contrast opacification and soft plaque (B) and mural calcification (C). Once the centerline model has been segmented, multiple post-processing options are available including maximum-intensity projection (D), VR (E), and endolumenal navigation (F). Analysis options include volume of stenosis (G) and automated generation of residual lumenal diameters and percentage stenoses for surgical decision-making (H).

since those with a hairline residual lumen are still at risk of embolic stroke and thus candidates for carotid endarterectomy (CEA) or stenting, whereas those with complete occlusion are usually treated medically (Lev et al., 2003). Curved reformatted images, prepared in our 3D lab, facilitate the survey of long tortuous vascular segments in the neck and cavernous sinus region for rapid identification of arterial stenoses and occlusion (Figs. 50.2 and 50.3D).

50.2. Magnetic resonance angiography

50.2.1. Introduction

Magnetic resonance angiography (MRA) has rapidly evolved to a widely applied clinical tool for the non-invasive imaging of the extra- and intracranial vasculature. Recent technical improvements applying parallel imaging and higher magnetic fields achieved higher spatial resolution, faster acquisition times, and reduced artifacts. For the extracranial arteries, MRA has developed from a screening tool towards the first-line technique to assess carotid artery disease and has replaced intra-arterial digital subtraction angiography (DSA), especially in combination with Duplex ultrasound studies (Röther et al., 1993; 1994).

Since the original publications on the feasibility of imaging flowing blood by the use of MR techniques, little has changed in our basic understanding of the underlying physics of moving spins within a magnetic field (Macovski and Nishimura, 1985; Dixon et al., 1986; Dumoulin, 1986; Wehrli et al., 1986; Dumoulin et al., 1988). Technical innovations have optimized imaging protocols, hardware, and reconstruction techniques.

While intra-arterial angiography displays the morphology of the filled vessel lumen, MRA shows the blood flow by means of flow-sensitive MR sequences. Therefore, the biophysical principles of MR flow phenomena must be considered when reading MR angiograms in order to properly judge abnormal flow findings. Additionally, direct information of the vessel wall disease is available from dedicated pulse sequences or the MRA source images itself. The principle drawback of MRA; that is, the reduced sensitivity to slow flowing blood and signal loss due to turbulent blood flow has been resolved by the development of contrast-enhanced MRA (CE-MRA). Even the assessment of the intracranial vascular disease is mainly a domain of MRA now, although diagnostic DSA is still the gold standard to address specific questions such as cerebral vasculitis.

50.2.2. Basic principles of magnetic resonance angiography

MRA is the heading for different techniques that image flowing blood non-invasively. These techniques can be divided into two main approaches: time-of-flight (TOF) and phase contrast (PC) MRA. Both techniques rely on the signal differences between moving spins (blood) and stationary tissue and aim to enhance flow-related signals while suppressing the background tissue. Contrast-enhanced MRA (CE-MRA) overcomes typical drawbacks of TOF-MRA especially in the evaluation of extracranial arteries such as exaggeration of the grade of a stenosis due to signal loss with turbulent flow after high-grade stenosis or due to in-plane saturation.

50.2.2.1. Time-of-flight MR flow-imaging method

The basic principle of TOF-MRA is the saturation of the stationary tissue background while enhancing moving, unsaturated spins flow into the acquisition slice (2D) or volume (3D) (Dixon et al., 1986; Wehrli et al., 1986). Saturation of the stationary tissue is achieved by applying repeated radio-frequency pulses with a short repetition time (Laub, 1988) and additional presaturation pulses. Moving spins from flowing blood in the vessels entering the acquisition slice have not experienced this repetitive exciting radio-frequency pulses. They are unsaturated and produce a flow-related enhancement when entering the excited slice.

Since MRA is insensitive to the flow direction (a method to overcome this shortcoming is described later in this chapter), images will display arteries as well as veins. The diagnostic value of these images is limited because of a disturbing overlay of arteries and veins that makes analysis of the vessel anatomy difficult. To solve this problem, an additional saturation slab is added: if the goal is to image, for instance, the neck arteries, then the saturation slab is placed distal to each slice, so that the venous blood is saturated before it flows into the measured slice. Similarly, if the venous structures are of interest, the saturation slab is placed proximal to the acquisition slice to presaturate the inflowing arteries (Edelman et al., 1989; Keller et al., 1989). TOF-MRA does not require any IV contrast media; however, in certain cases (e.g., arteriovenous malformations and fistulae) TOF after contrast enhancement is useful to get a better impression of the arterial as well as venous structures involved.

The raw data or "source images" that are received from 2D or 3D MRA sequences are a series of 2D sections. To create a 3D display of the vessel geometry, the source images are subjected to a volumetric post-processing method. Usually a "maximum intensity projection" (MIP) algorithm is performed to process 3D presentations that can be viewed in user-defined projections. The visual 3D impression can be enhanced by surface rendering methods like shaded surface display (SSD).

50.2.2.2. Two-dimensional or three-dimensional TOF techniques

Two- or three- dimensional TOF-MRA refers to whether a series of thin slices (2D) or a three dimensionally defined data volume is acquired. The advantages of 2D TOF-MRA is its higher sensitivity to slow blood flow compared to 3D techniques. Two-dimensional TOF-MRA was preferably used for the imaging of the carotid bifurcation and is still applied in venous MRA of the dural sinuses. The disadvantages however are its sensitivity to motion. In carotid imaging, 2D TOF-MRA is nowadays mainly substituted by CE-MRA.

In 3D TOF-MRA, a thick tissue slab (volume) is excited and a second, 3D Fourier transform is used to reconstruct the source image. The application of 3D Fourier transform (3DFT) sequences allows for extremely thin slices with voxel dimensions of about 0.5 mm and a high signal-to-noise ratio, thus contributing to the reduction of unwanted signal loss because of motion-induced phase changes (Laub, 1988).

50.2.2.3. Phase-contrast MRA

Phase-contrast (PC-MRA) is based on velocity-induced phase shifts of moving spins in the presence of a magnetic field gradient. The difference in signal intensity between flowing blood and stationary tissue is proportional to the blood flow velocity and quantitative flow information, therefore velocity, direction, and vessel display are possible (Dumoulin et al., 1989). The advantages of PC-MRA with respect to TOF-MRA are a higher sensitivity to slow-flowing

blood, a better suppression of the background tissue, and the potential of flow quantification. A major drawback of PC-MRA is the prolonged acquisition time if compared to TOF techniques with subsequent motion artifacts and the vulnerability to higher motion artifacts in stenoses. Due to advances in TOF-MRA and the need for short acquisition times PC-MRA is rarely used in clinical routine.

50.2.2.4. Contrast-enhanced MRA

Contrast-enhanced MRA (CE-MRA) is the preferred imaging technique for the evaluation of the extracranial arteries. CE-MRA typically employs a 3D gradient echo sequence and relies on the IV bolus injection of the T1 shortening contrast agent gadolinium. In contrast to TOF-MRA, a contrast bolus applied by a power injector is followed during its first pass through the arteries. Timing of the arrival of the contrast bolus is critical for CE-MRA in order to follow the peak of the arterial bolus passage. On-line monitoring of the vessels of interest supports adequate timing to launch the acquisition sequence. Background noise can be reduced by subtracting pre- and post-contrast images (Laub, 1999; Ozsarlak et al., 2004).

Since CE-MRA is less susceptible to signal loss due to turbulent or low blood flow than TOF-MRA, it is the preferred technique for the delineation of carotid stenoses and for non-invasive follow-up of coil-occluded intracranial aneurysms (Remonda et al., 1998; Carr et al., 2002; Gottschalk et al., 2002). Since acquisition time is critical in CE-MRA, parallel imaging techniques together with higher field strength may further improve extra- and intracranial applications (Tintera et al., 2004; Riedy et al., 2005). Newer, more relaxing contrast agent preparations like 1 M gadobutrol (Gadovist) (Goyen et al., 2001; Clevert et al., 2006) or gadobenate dimeglumine (MultiHance) (Anzalone et al., 2006) have further improved signal-to-noise ratio and established CE-MRA as first line diagnostic of carotid artery disease (Barth et al., 2006).

Time-resolved MRA can be done either by following the passage of contrast media through the tissue volume of interest or as a non-contrast arterial spin labeling method. Both techniques greatly profit from higher field strength and parallel imaging. The spin labeling method applies a labeling pulse to spins flowing through the vessel of interest and can be followed in a slab downstream from the labeling slice. This allows the investigation of brain perfusion from different arteries, the contribution to the basal anastomoses of the circle of Willis (van Osch et al., 2006), and the reconstruction of a functional vascular tree. So far, current limitation of MR hardware and a high workload of computation makes this technique mainly investigational.

50.2.3. Artifacts in MRA

Based on the physics of MR signal evolution, signal loss in TOF-MRA can be due to: (1) in-plane saturation, and (2) motion-induced phase changes.

50.2.3.1. In-plane saturation

The longer unsaturated spins reside in the excited slice (2D) or volume (3D), the more they are exposed to repeated radio-frequency pulses that intend to saturate the background tissue. This exposition to the radio-frequency pulses results in unwanted signal loss and consequently reduction in vessel-to-background contrast. This "in-plane saturation" is favored by large acquisition volumes and slow blood flow.

An elegant method to reduce signal loss due to in-plane saturation is to linearly increase the flip angles over the acquisition slab starting with low flip angles at the inflow side and ending up with a high flip angle at its outlet. This ramp of spatially varied flip angles or "tilted optimized non-saturated excitation" (TONE) results in a better visualization of blood vessels with low flow velocity and in-plane flow direction (Purdy et al., 1992; Nägele et al., 1994).

50.2.3.2. Motion-induced phase changes

Though the sensitivity of MRA to vessel obstructions is high, the specificity is low. This is in part due to the fact that pulsatile and turbulent flow occurs in curving vessels, at dividers and even more so in severe stenosis. Turbulent blood flow goes along with a dephasing of the protons resulting in signal loss. Although flow-compensation gradients, short echo times, and small voxel elements reduce this motion-induced phase shift, it must still be considered as a major drawback for the proper evaluation of vessel abnormalities. As detailed above, CE-MRA helps to reduce these artifacts and is successfully applied in the evaluation of carotid arteries and intracranial vessel pathology.

50.2.4. Image processing

The source images acquired during the excitation of a 2D MRA slice or 3D volume are commonly post-processed using a maximum intensity projection (MIP) algorithm. This software is based on a ray-tracing algorithm and creates angiogram-like images from the source images by tracing only the highest signal intensities along its path. The images can be three-dimensionally displayed in user-defined orientations and may be viewed in form of

a cine-angiography. This 3D presentation allows for the separation of overlying vessels and a visuospatial orientation to anatomical landmarks. Several problems may arise with the use of MIP projections and these are outlined below.

50.2.4.1. Vessel overlay

Although user-defined viewpoints of the vessel anatomy encompass a more direct view, the overlay of vessels can hamper the diagnostic value of the projections. Limiting the source images to the vessels of interest reduces the background noise (Lin et al., 1991).

50.2.4.2. Loss of vessel-to-background signal

The signal of small vessels may get lost during the MIP procedure due to volume-averaging artifacts and variations in the background signal intensities (Anderson et al., 1990). The source images therefore usually contain more precise information than the MIP projections and should be referred to whenever conspicuous signal loss is seen.

50.2.5. Clinical application of MRA

50.2.5.1. Extracranial examination

Atheromatous plaques of the aortic arch are a well-known source of embolism (Amarenco et al., 2006). Unfortunately, neither ultrasound nor TOF-MRA are suited to screening the aortic arch for plaque morphology. Long acquisition times of TOF-MRA and the pulsation of the aortic arch in combination with breathing artifacts make the aortic arch a *terra incognita* for non-invasive vessel imaging.

High-resolution CE-MRA together with breath-holding during MRA acquisition offers an approach for imaging the entire carotid circulation including the aortic arch (Carr et al., 2002). However, studies that evaluate the sensitivity and specificity of CE-MRA for the evaluation of the aortic arch are still missing.

50.2.5.2. Carotid and vertebral artery disease

The assessment of carotid stenosis is a domain of ultrasound and MRA. Doppler and Duplex ultrasound have a high sensitivity and specificity for the detection of carotid stenosis (Steinke et al., 1990); however, most surgeons and interventionalists ask for confirmation of the vessel pathology by a second imaging technique. CE-MRA is well suited to confirm the ultrasound diagnosis of carotid disease: It is non-invasive, has a high resolution, and reliably rules out tandem stenosis proximal and distal to the carotid bifurcation. Typical limitations of time-of-flight techniques such as signal loss due to turbulent blood flow and in-plane saturation are prevented. Additionally, the entire carotid circulation from the aortic arch to the circle of Willis is depicted (Fig. 50.7A).

Comparisons of the diagnostic accuracy of CE-MRA with digital subtraction angiography (DSA) (Fig, 50.7B,C) showed that the morphology of the

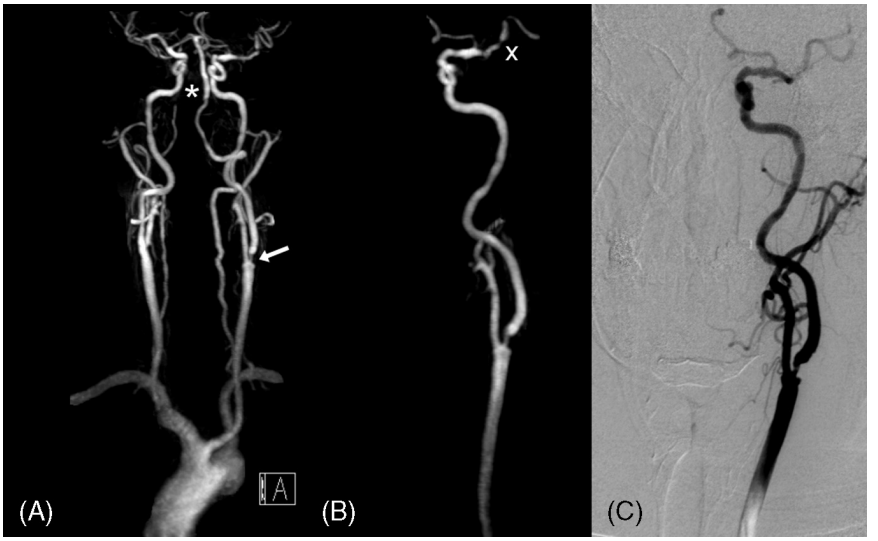


Fig. 50.7. Imaging of the supra-aortal vessels from the aortic arch to the intracranial basal arteries by CE-MRA (A). A left sided stenosis of the internal carotid artery (arrow) is visible, as well as an occlusion of the intracranial right vertebral artery (*). (B) Selective maximum intensity projection reveals lumen narrowing of about 70 % and intracranial arteriosclerotic changes of the middle cerebral artery (x). (C) Perfect accordance with intra-arterial angiography.

stenosis is reliably depicted by CE-MRA (Fellner et al., 2000; Cosottini et al., 2003). The grading of the vessel obstruction is obscured by intra-voxel dephasing effects leading to an overestimation of the stenosis by high-grade stenosis (Fig. 50.8A,B), although recent advances showed good correlations with rotational angiography (Anzalone et al., 2005; Wright et al., 2005). Therefore, the combined information of ultrasound and CE-MRA are used to approximate the grade of stenosis non-invasively (Friese et al., 2001). Diagnostic DSA is subjected to rare cases of near occlusion (pseudo-occlusion), where CE-MRA may falsely demonstrate vessel occlusion due to local turbulences and post-stenotic slow blood flow. However, adequate technical parameters will usually show at least a discontinuous residual lumen of the internal carotid artery (Fig. 50.8C,D). CE-MRA is also accurate in the vertebrobasilar circulation (Fig. 50.7A), and has the potential to provide a comprehensive and non-invasive evaluation of the head and neck arteries in a single study (Yang et al., 2005).

50.2.5.3. Carotid and vertebral artery dissection

The diagnosis of carotid artery dissection is a domain of Duplex ultrasound, MRA and axial MRI (Röther et al., 1995; Schievink, 2001; Bassi et al., 2003). Axial MRI slices with fat suppression typically show a semilunar vessel wall hematoma (Fig. 50.9). CE-MRA is superior in depicting the morphology and length of the dissected vessel wall (Lanczik et al., 2005). Duplex ultrasound is suited to follow the healing of the vessel wall. The diagnosis of vertebral artery dissections is more complex, since the typical wall hematoma is rarely detectable due to the smaller vessel lumen (Röther et al., 1995). Conventional angiography is still considered the gold standard and shows tapering stenosis/occlusion, abrupt occlusion, lumenal irregularity,

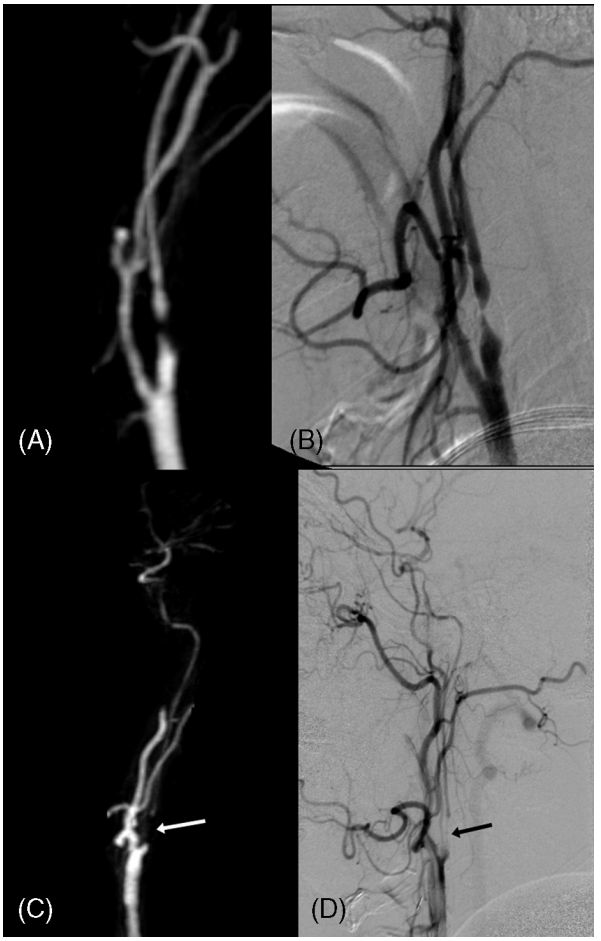


Fig. 50.8. Overestimation of an internal carotid artery stenosis by CE-MRA (A) compared to angiography (B). However, the anatomic details are sufficient for treatment planning and indication. The lack of a visible lumen in CE-MRA always indicates a stenosis of more than 70%. Pseudo-occlusion of the internal carotid artery with collapsed lumen of the internal carotid artery (C) and the residual lumen visible by angiography only (arrow, D).

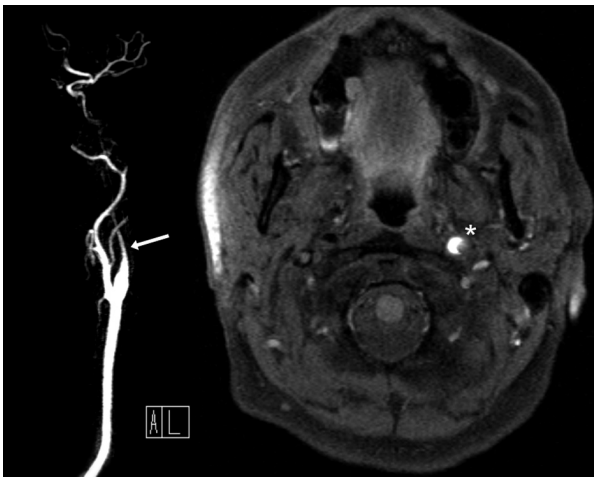


Fig. 50.9. Dissection of the internal carotid artery with typical appearance as a smooth, but rapid narrowing lumen (A) and the hematoma (*) of the arterial wall detected as a bright signal on fat-suppressed T1-weighted images (B).

intimal flap, lumenal filling defects and pseudoaneurysms (Tay et al., 2005).

50.2.5.4. Intracranial vascular disease

MRA is an important screening technique for visualizing the basal intracranial vessels. TOF-MRA is usually performed and delivers high-quality images of the basal arteries. Depending on the acquisition time and the field strength, even peripheral branches are delineated. Thrombo-embolic occlusion and atherothrombotic stenosis of basal intracranial arteries (Fig. 50.10A) shows a good correlation with transcranial Doppler ultrasound (Röther et al., 1994), and DSA is usually not required. MRA is especially valuable in the evaluation of the intracranial carotid artery, specifically the siphon, the vertebral artery, and in cases of calcified artery stenosis. Since MRA is inherently insensitive to bone structures, it is superior to other imaging techniques such as ultrasound and CT angiography that are hampered by bone superposition. However, the pitfalls are the same as described previously: overestimation of stenoses due to turbulent blood flow and in plane saturation. Pathologies such as vasculitis or vasospasm of the basal arteries may be detected; however, DSA is mandatory to delineate the complex morphology especially in the peripheral branches.

50.2.5.5. Aneurysms and arteriovenous malformations

Although high field strength improves the spatial resolution (Willinek et al., 2003), and TOF-MRA (Fig. 50.10B) can identify aneurysms (at least 3 mm in size) with a sensitivity of 74–98% (White et al., 2003), small aneurysms may go undetected. A second problem could be the high T1 signal of subarachnoid blood after several days, which might obscure an aneurysm. Therefore, the detection of intracranial aneurysms is still best-suited to DSA, preferably 3D rotational DSA. MRA is ideal for screening of cerebral aneurysms and TOF or CE-MRA is applied after endovascular therapy to exclude aneurysm regrowth (Leclerc et al., 2002).

Arteriovenous malformations and dural arteriovenous fistulae have a complex vessel architecture and DSA is the gold standard to analyze the nidus and the feeding vessels, and for the planning of the therapy. Nevertheless, MRA can deliver important information on the location of the arteriovenous malformations and the anatomical relations (Fig. 50.11). Time-resolved CE-MRA provides dynamic angiographic images and

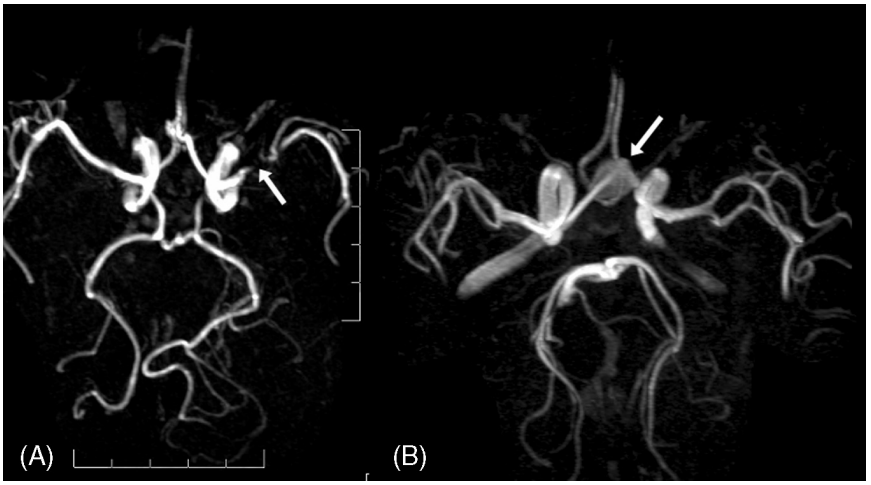


Fig. 50.10. TOF-MRA of the circle of Willis showing a middle cerebral artery stenosis (A). In the case of an occlusion, the distal vessel segments of the middle cerebral artery would become invisible. Anterior communicating artery aneurysm (B).

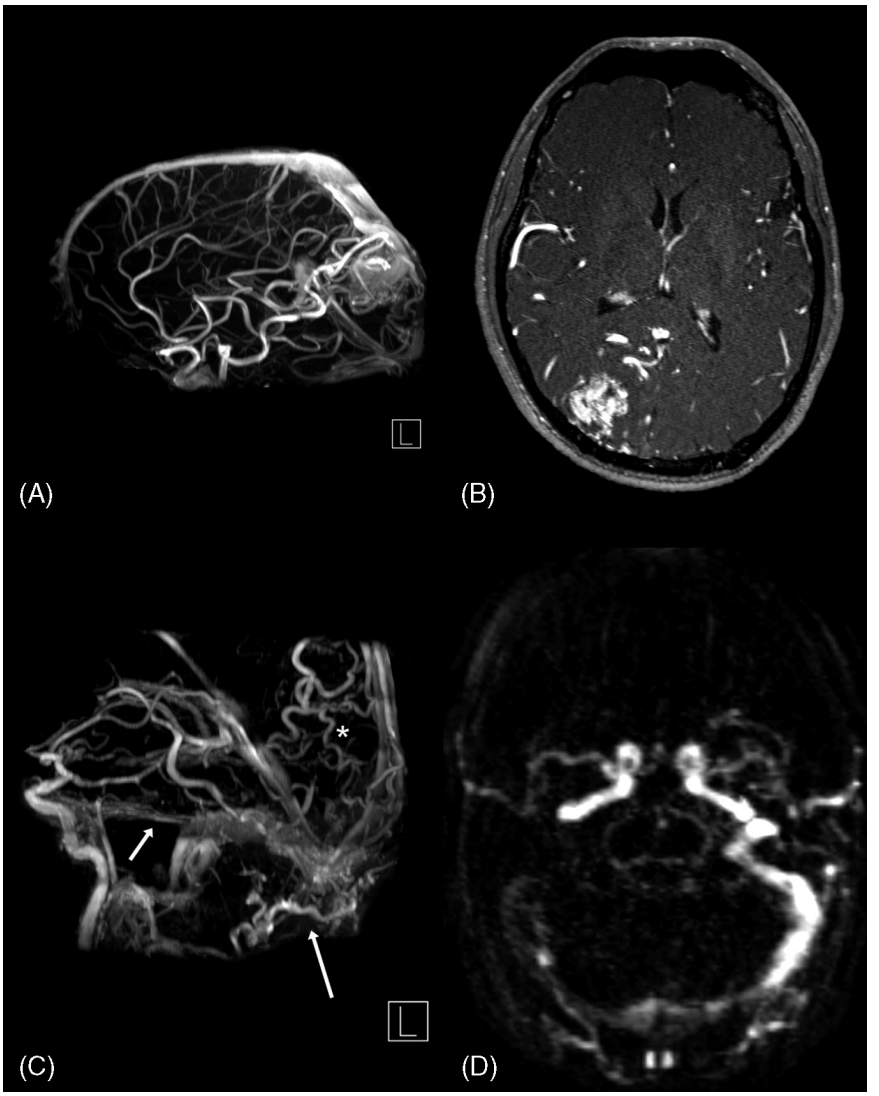


Fig. 50.11. An occipital arteriovenous malformation imaged by contrast enhanced TOF-MRA and selective maximum-intensity projection for an improved visualization of high flow vessels and venous structures (A). Intra-arterial angiography is always necessary for treatment planning, but source images of MRA are useful to locate the arteriovenous malformation in relation to eloquent brain regions (B). Dural AV fistula (C) by the same technique: Feeding arteries (the external occipital artery and the meningohypophyseal trunk) may be identified as well as the draining sinus and dilated cortical veins (*). Time-resolved MRA (D) reveals rapid shunting into the transverse and sigmoid sinus—otherwise a fistula may be missed on conventional MRI or even MRA.

may be a reasonable tool to screen for dural arteriovenous fistulae, although the spatial resolution is still low (Carroll, 2002).

50.2.5.6. Sinus and venous thrombosis

Cerebral sinus and venous thrombosis is a domain of MRA, since diagnosis can be made in most cases without contrast media or applying x-rays, significant when treating pregnant women. Two-dimensional TOF-MRA is usually sufficient to show the occluded sinus or deep venous system, but sometimes the short T1 of the thrombus itself may mimic flow. In questionable cases a PC-MRA is useful because of its unique sensitivity to flowing spins, but the flow parameters must be adjusted carefully. Every time, the reading of perpendicular T1 (with fat suppression) and PD/T2 images is necessary for direct visualization of the thrombus (Fig. 50.12). However, cortical vein thrombosis may be missed frequently and require DSA (Lafitte et al., 1997; Bousser, 2000).

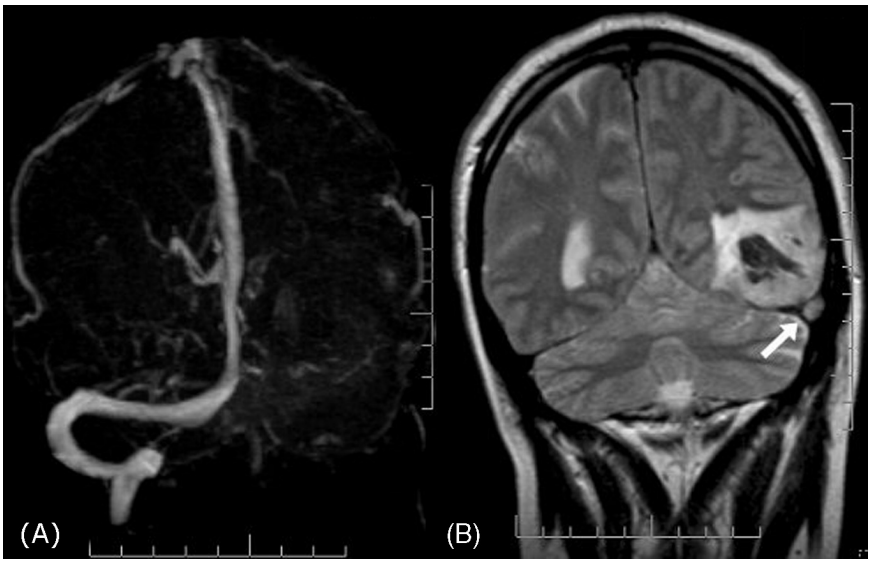


Fig. 50.12. Transverse and sigmoid sinus thrombosis in TOF-MRA (A) and T2-weighted imaging (B). No flow signal within the region of the left sinus and direct visualization of the thrombus (arrow). Conventional sequences also reveal congestive edema and hemorrhage.

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Chapter 51

The interactions between cardiovascular and cerebrovascular disease

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The interactions between cardiovascular and cerebral disease have been widely developed over the last 20 years (Furlan, 1987; Di Pasquale and Pinelli, 1992; Wilterdink et al., 1998; Guillot, 1999; Di Pasquale and Pozzati, 2000; Warlow et al., 2001). The recent widespread diffusion of stroke units have significantly enhanced our knowledge about pathophysiology of acute cerebrovascular disease and the role of cardiac disease, while multidisciplinary teams including neurologists, neurosurgeons, angiologists, and cardiologists, are currently involved in the evaluation and treatment of patients with cerebrovascular disease in many hospitals (Evans et al., 2002; Langhorne et al., 2005).

The two main topics on heart–brain interactions are: (1) association of carotid, intracerebral and coronary artery disease, and the identification of the prognostic markers for a long-term follow-up; and (2) cardioembolic cerebral ischemia and cardiologic work-up and treatment after a cerebrovascular event.

51.1. Association of cerebrovascular and coronary artery disease

51.1.1. Epidemiology and pathophysiology

sAtherosclerosis is a progressive, multifocal disease secondary to complex relationships among genetic traits, acquired cardiovascular risk factors, endothelial dysfunction, inflammation, and platelet aggregation. The clinical consequences of acute complications of atherosclerotic lesions, as acute coronary syndromes, stroke, transient ischemic attacks (TIAs), rupture of aortic abdominal aneurysms or acute ischemia from peripheral artery disease, represent the leading cause of disability or death in the Western world (Bakhai, 2004).

During the development of atherosclerotic lesions, inflammation may play a pivotal role both in the early phase of plaque growth, when monocytes adhere to the vascular endothelium and accumulate in lesion-prone arterial sites; and in the late phase, when plaque erosion or rupture occur, and a systemic inflammatory reaction may "activate" vulnerable plaques (Ross, 1999; Goldstein et al., 2000; Rothwell et al., 2000; Blann et al., 2002; Libby et al., 2002; Fuster et al., 2005; Hansson, 2005).

The pathophysiology of atherosclerotic disease is different in arterial sites. Most coronary events are secondary to acute thrombosis from ulcerated plaques, while most cerebrovascular events are secondary to embolism from carotid, aortic, or cardiac lesions; and abdominal atherosclerotic disease develops toward aneurysmatic dilatation.

The long-term follow-up of patients with carotid or peripheral artery disease is strongly influenced by a coexisting coronary artery disease. After a long-term follow-up period, patients with carotid artery intima and media thickness, TIA, or minor stroke have a higher incidence of cardiac than cerebrovascular deaths (O'Leary et al., 1999; Touzè et al., 2005). Even among patients with peripheral artery disease, after a long-term follow-up period, more than half of deaths are secondary to coronary events (Sutton-Tyrell et al., 1998; Cotter et al., 2003).

51.1.2. Algorithm for the detection of coronary artery disease in patients with carotid artery disease

Almost all patients with multiple cardiovascular risk factors or with carotid artery disease should be evaluated

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for a coexisting coronary artery disease. A possible algorithm includes exercise ECG testing, a well-established, safe, low-cost test followed (if positive and asymptomatic) by a second marker of myocardial ischemia obtained by myocardial perfusion scintigraphy or stress echocardiography. In patients unable to exercise, stress (dypiridamole, adenosine, or dobutamine) echocardiography or myocardial perfusion scintigraphy may be performed. These tests are safe and show adequate sensitivity and specificity for the detection of coronary artery disease.

A routine use of coronary angiography was routinely suggested more than 20 years ago for patients with carotid artery disease, candidates to carotid endarterectomy showing a coexisting coronary artery disease in more than half of cases, severe in one-quarter of them (Hertzer et al., 1985). Nevertheless, a routine use of non-invasive evaluation for identifying a silent coronary artery disease in patients undergoing carotid endarterectomy was considered cost-effective. Di Pasquale et al. (1986) suggested an algorithm including exercise ECG testing and perfusion myocardial scintigraphy in 190 consecutive patients with cerebral ischemia undergoing carotid endarterectomy, identifying a coexistent silent coronary artery disease in 28% of cases. Patients unable to exercise submitted to pharmacological stress testing showed a coexisting coronary artery disease in >40% of cases (Di Pasquale et al., 1991). Urbinati et al. confirmed the prognostic usefulness of this algorithm, even in patients without a history of coronary artery disease (Urbinati et al., 1992, 1994). After a mean follow-up period of 5.4 years, among the 25% of patients with silent coronary artery disease the occurrence of coronary events was 29%, whereas among those with normal exercise ECG testing was only 1.2%. The prognosis of patients with silent coronary artery disease was similar to the prognosis of cerebrovascular patients with previous myocardial infarction.

51.1.3. Simultaneous activation of atherosclerotic plaques in remote arterial sites

Recently, the classification of atherosclerotic arterial lesions shifted from a quantitative to a qualitative approach, and a new concept of "vulnerable patients" and "vulnerable plaques" has been developed (Naghavi et al., 2003). Several clinical findings, cardiovascular risk factors, morphological markers (echolucent or dishomogenous plaques), and laboratory findings such as elevated serum C-reactive protein (or other inflammatory markers), may identify "vulnerable patients" who should be carefully monitored and aggressively treated (Ridker et al., 1997; Fayad and Fuster, 2001; Honda et al., 2004; Libby, 2005; Nighoghossian et al., 2005).

On the other hand, in patients with recent acute cardiovascular events it may be useful to search for complicated lesions in remote arterial sites. Rioufol et al. (2002) showed that in patients with acute coronary syndromes, angiographic and intravascular ultrasound studies may identify plaque ruptures in non-culprit coronary arteries. Other reports showed that patients with acute myocardial infarction have multiple plaque ruptures and elevated serum inflammatory markers (Goldstein et al., 2000; Mauriello et al., 2005; Tanaka et al., 2005).

A "systemic" activation (involving infective agents or immunological activation) of atherosclerotic lesions may be the trigger of acute coronary syndromes. Urbinati et al. (1998) studied the morphology of carotid lesions in patients with unstable or stable coronary artery disease. Carotid echotomography showed that dishomogenous and irregular ("active") plaques were significantly more numerous in patients with unstable than in those with stable coronary artery disease. After a 1.2-year follow-up, most patients with "active" plaques developed "quiescent" plaques. Recently, Honda et al. (2004) showed that patients with acute coronary syndromes had a higher incidence of complex or echolucent carotid lesions and Komorowsky et al. (2005) observed that complex coronary and hard carotid plaques identify a subset of patients with very high risk of cardiovascular events. Finally, Watanabe et al. (2005) showed that a stabilization of carotid lesions may be obtained with intensive cholesterol-lowering therapy.

The simultaneous activation of coronary and carotid lesions may produce relevant clinical events. In patients with severe angina or acute coronary syndromes a very high incidence of cerebrovascular events occur within 90 days. The more frequent pathophysiological mechanisms are embolism from ventricular mural thrombi, left atrial or auricular thrombi during paroxysmal atrial fibrillation, ulcerated aortic plaques during catheter manipulations, and also activation or thrombosis of aortic or carotid plaques (Kassem-Moussa et al., 2004).

Left ventricular thrombosis cannot explain most strokes occurring in patients with acute myocardial infarction (Mooe et al., 1999). Bodenheimer et al. (1994) observed that the occurrence of ischemic stroke is similar in patients with anterior and inferior myocardial infarction, while left ventricular thrombosis occurs more frequently in those with anterior myocardial infarction. Modrego-Pardo et al. (1998) investigated a series of patients with or without angina pectoris by cerebral magnetic resonance imaging (MRI) showing that those with acute coronary syndromes have a higher prevalence of silent brain

infarcts. Tanne et al. (2002) observed that the risk of stroke is higher in patients with unstable than stable angina suggesting that patients with unstable angina may have coexisting "active" carotid or aortic lesions. Similar results were reported also by Budaj et al. for the GRACE Investigators (Budaj et al., 2005). Finally, Giele et al. (2004) showed that patients with overt vascular disease are at risk for silent brain infarcts. Overall, these studies suggest that a simultaneous activation of carotid, aortic, and coronary plaques may occur in many cases.

An intriguing question may develop—can an "active" atherosclerotic lesion trigger a systemic inflammatory reaction? Recent studies support the hypothesis that active coronary lesions may release several cytokines developing a "vicious" circle toward activation lesions in remote arterial sites. Lombardo et al. (2004) showed that multiple complex stenosis, plaque fissures, and widespread coronary inflammation are common in patients with acute coronary artery disease. Schillinger and Exner (2005) showed that a substantial increased risk for neurological events occurs in patients with rapid progression of atherosclerotic lesions in the carotid arteries, with 2-year stroke risk exceeding 10%. Rost et al. (2001) showed that high level of serum C-reactive protein identifies patients with carotid disease at high risk of stroke. Finally, Hansson (2005) observed that activated coronary lesions may release several factors (i.e., interleukines) inducing the liver to produce C-reactive protein for sustaining a systemic activation of arterial atherosclerotic plaques.

51.1.4. The treatment of patients with coronary and carotid artery disease

Patients with coronary and carotid artery disease should be aggressively monitored and treated because of their "very high" risk of cardiovascular events. Non-pharmacological treatment should include programs for modification of the lifestyle; that is, diet, smoking cessation, regular exercise, and weight control. Such programs should be performed in dedicated settings with a multidisciplinary approach for secondary prevention, including nurse-directed educational programs. Evidence-based pharmacological interventions for preventing cardiovascular events include:

1. *Anti-thrombotic treatment*. Aspirin is the first choice, and ticlopidine or clopidogrel are the second choice. Recent studies suggest that association of aspirin and clopidogrel could be proposed in high-risk patients (Antithrombotic Trialists Collaboration, 2002).
2. *Statins*. Statins are very effective for preventing cardiovascular events in patients with hypercholesterolemia, both in primary and secondary prevention. Recent studies suggest that statins may prevent coronary and cerebrovascular events also in patients with normal cholesterolemia, probably for alternative mechanisms, such as plaque stabilization (Chapman, 2005).
3. *ACE inhibitors*. In recent studies, ACE inhibitors were able to reduce cardiovascular events in "high risk" patients, probably because of endothelial protective effects (Fox, 2003).

In patients with severe coexisting coronary and carotid disease candidates to surgical revascularization, the choice between "staged" or combined operations is determined by assessment of the relative severity of carotid and coronary disease, and by the experience of the centers. The development of percutaneous coronary interventions and, more recently, of percutaneous carotid interventions challenged the previous guidelines. In most cases, a "hybrid" treatment including both surgical and percutaneous interventions may be feasible (Graor and Hertzer, 1988; Hu et al., 2003; Naylor et al., 2003); nevertheless, no evidence-based recommendations on this new approach is available.

51.2. Cardio-embolic sources of cerebral ischemia

Nearly one-third of all ischemic strokes are cardioembolic. Non-valvular atrial fibrillation accounts for about 50%, and probably more, of cardio-embolic strokes (Cerebral Embolism Task Force: Cardiogenic Brain Embolism, 1989; Hart, 1992; Palacio and Hart, 2002). In patients with recent TIA or stroke, the diagnosis of cardio-embolic cerebral ischemia should be always considered, because in these cases the early use of anticoagulants may strongly influence the prognosis of the patients (Albers et al., 2004).

In recent years, the widespread use of transesophageal echocardiography (TEE) allows a more frequent identification of potential cardiac sources of embolism in patients with cryptogenetic stroke, particularly in young adults, but even in elder patients who frequently showed large and complicated plaques in the ascending aorta. TEE is able to show lesions undetectable by transthoracic echocardiography (TTE), such as: left atrial auricular thrombosis and spontaneous echocontrast, occurring mainly in patients with mitral stenosis or atrial fibrillation; ascending aorta atherosclerotic lesions, occurring in the aged population; and patent foramen ovale (PFO) and atrial septal aneurysm, often occurring in young patients with cryptogenetic stroke (Kronzon and Tunick, 1993; O'Brien et al., 1998; Kizer and Devereux, 2005).

51.2.1. Algorithm for diagnosis of cardio-embolic cerebral ischemia

The diagnosis of cardio-embolic cerebral ischemia may be difficult and may remain uncertain. To date, diagnosis of cardio-embolic stroke is often made by exclusion, in the absence of significant carotid disease. Neurological symptoms of stroke and neuroimaging findings may be suggestive, but are not specific, for the diagnosis of cardio-embolic stroke. Also lacunar strokes, usually attributed to small-vessel disease, have been associated with cardio-embolic disease (Kizer and Devereux, 2005). The cardiac lesions more frequently involved in cerebral embolism are:

1. *Lesions at high embolic risk*. Ventricular thrombi (mainly in acute myocardial infarction and dilatative cardiomyopathies), left atrial appendage thrombi (in patients with non-valvular atrial fibrillation [AF], sick sinus syndrome and atrial flutter) often associated with spontaneous echo contrast and left atrial appendage dysfunction, endocarditic vegetations (both infective and degenerative or marantic), rheumatic mitral valve disease, thrombosis of prosthetic heart valves, cardiac tumors, and aortic atherosclerotic plaques.
2. *Lesions at low or uncertain embolic risk*. Atrial septal aneurysm, PFO, mitral annular calcification, aortic valve calcification or calcified aortic valve stenosis, and mitral valve prolapse.

Although transthoracic echocardiography and TEE are the gold standard for the detection of cardiac sources of embolism, other imaging techniques such as cardiac ultrafast CT, MRI, and indium-111-labeled platelet scintigraphy have been proposed if echocardiographic studies are non-diagnostic. Indium-111-labeled platelet scintigraphy allows evaluation of thrombus activity, particularly in unstable conditions such as prosthetic cardiac valve thrombosis and acute myocardial infarction. The high cost and long duration of the test are the main limits of this technique.

ECG Holter monitoring, in patients with TIA or stroke, may be useful to detect paroxysmal atrial fibrillation or sick sinus syndrome. Although the mechanism of stroke in patients with sick sinus syndrome is yet to be elucidated, episodes of transient atrial fibrillation or severe bradycardia, in the presence of critical atherosclerotic carotid lesions, can be involved.

Patient history, clinical evaluation, and transthoracic echocardiography allow the detection of cardiac sources of embolism in most cases of cardio-embolic cerebral ischemia. The following algorithm may be proposed:

1. The cardiac evaluation should be reserved to patients potentially eligible for oral anticoagulant treatment or cardiac surgery.
2. In patients aged less than 45 years and with unexplained stroke TEE is always warranted.
3. In patients aged more than 45 years without history of cardiac disease and with unexplained stroke, TEE is warranted; whereas in those with history of cardiac disease, TTE is often sufficient, possibly followed by TEE in selected patients.
4. In patients with atrial fibrillation, echocardiography may be redundant because the indication for oral anticoagulant treatment after stroke is definite. TTE is occasionally needed to clarify underlying structural cardiac disease. TEE is appropriate in selected cases, mainly when a causal relationship between atrial fibrillation and stroke is debatable (Di Pasquale et al., 1993).

51.2.2. Cardio-embolic disorders

In recent years, many studies have defined the embolic risk of most cardiac diseases and updated guidelines on diagnostic algorithms and treatments are available.

51.2.2.1. Atrial fibrillation/atrial flutter

Non-valvular atrial fibrillation is the most frequent cardiac cause of cerebral ischemia accounting for half of cardio-embolic strokes (Hart et al., 2003). Non-valvular atrial fibrillation in particular carries a high risk of systemic stroke, but is only weakly associated with TIAs (Hart et al., 2004). The occurrence of atrial fibrillation as a cause of cardio-embolic stroke is probably underestimated. In a recent study an event-loop recorder identifies patients with atrial fibrillation, which remained undetected with standard ECG and with Holter, in a further 5.7% of cases (Jabaudon et al., 2004). Overall, the risk of stroke widely ranges from 0.4% to 12% per year with an average of 4.5% per year (Stroke Prevention in Atrial Fibrillation Investigators, 1992; Hart et al., 2002). Most strokes associated with atrial fibrillation are large and disabling, and the overall mortality associated with stroke in non-valvular atrial fibrillation is two-fold that of stroke from other causes (Gage et al., 2004).

51.2.2.1.1. Cardiac sources of embolism in non-valvular atrial fibrillation

The pathogenic mechanism of most strokes is embolism due to large emboli from atrial or auricular thrombi. Nevertheless, a minority of cases of cerebral embolism in this aged, hypertensive population may

be caused by coexisting lesions, such as carotid or ascending aorta plaques, or intracerebral artery disease. The different pathophysiology of stroke and TIAs in patients with atrial fibrillation could account for different prognosis and response to antithrombotic treatment in patients with non-valvular atrial fibrillation with stroke than those with TIA. Nevertheless, a recent report from the EAFT and SPAF III trials revealed no evidence that atrial fibrillation patients did not respond to anticoagulant therapy (Hart et al., 2004).

51.2.2.1.2. Predictors of embolism in non-valvular atrial fibrillation

Among patients with non-valvular atrial fibrillation, clinical and echocardiographic risk factors for embolism have been identified and prospectively validated (Stroke Prevention in Atrial Fibrillation Investigators, 1992). The SPAF III criteria for identifying patients at high risk of embolism include recent congestive heart failure or left ventricular dysfunction, previous thrombo-embolism, systolic blood pressure $\geq$160 mmHg and advanced age (Hart et al., 2003). In the presence of any of these risk factors, patients with non-valvular atrial fibrillation should be treated with adjusted-dose warfarin with a target international normalized ratio (INR) ranging from 2 to 3. Moreover, TEE allows the detection of further markers of thrombo-embolic risk, such as left atrial and left atrial appendage thrombi, spontaneous echo contrast, and left atrial appendage dysfunction (Di Pasquale et al., 1995; Manning and Douglas, 1998; Zabalgoita et al., 1998). The prevalence of these findings is significantly higher in atrial fibrillation patients who have suffered stroke or systemic embolism. Patients without any of these risk factors have a low to moderate risk of stroke when treated with aspirin.

51.2.2.1.3. Anticoagulant treatment versus aspirin

The efficacy of oral anticoagulant treatment for the prevention of stroke in non-valvular atrial fibrillation was definitely assessed in the early 1990s by large randomized clinical trials (Go et al., 2003; Aguilar and Hart, 2005) and confirmed by recent guidelines (Singer et al., 2004). Overall, of 2,313 participants without previous cerebral ischemia from five randomized trials, warfarin decreased the incidence of all strokes odds ratio (OR) >0.26–0.59, and the risk of bleeding was not significantly increased in warfarin-treated patients. Nevertheless, patients included in these trials represent only 7–39% of the screened patients. Conversely, aspirin alone reduces the risk of stroke by nearly 20%, and warfarin reduced the risk of 45% when compared with aspirin. Warfarin is recommended in all patients with a high to moderate risk of stroke, while aspirin may be used in patients at low risk of stroke (<2% per year).

51.2.2.1.4. Antithrombotic treatment after acute stroke

A particular issue concerns when warfarin should be initiated for secondary prevention. After acute stroke, early recurrence of stroke occurred in nearly 5% of atrial fibrillation patients during the initial 2 weeks. So far, the issue of the timing of warfarin initiation is not clearly addressed. In EAFT, among patients who commenced oral anticoagulant treatment within 2 weeks of ischemic stroke or TIA there was no reported secondary hemorrhagic evolution. It seems reasonable to begin warfarin as soon as possible after the patient is medically and neurologically stable, ideally achieving therapeutic anticoagulation 7–10 days after stroke onset (Hart et al., 2002).

51.2.2.1.5. Aged population

The safety of long-term oral anticoagulant treatment (maintaining INR between 2 and 3) has not been completely defined among patients older than 75 years. In patients aged 65–75 years, with diabetes mellitus or ischemic cardiomyopathy without left ventricular dysfunction, oral anticoagulant treatment should be preferred if at least two risk factors are present.

51.2.2.1.6. Other treatments

51.2.2.1.6.1. PLAATO

Recently, in patients with non-valvular atrial fibrillation who could not undergo oral anticoagulant treatment, percutaneous occlusion of left atrial appendage may be safe and feasible. First, Sievert et al (2002) reported the results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device. The device consists of a nitinol cage covered with a polymeric membrane and has a series of hooks to help anchor it to the mouth of left atrial appendage. In their first 15 patients at 6 months' follow-up, Sievert et al. reported no complications and no strokes. Later, the study extended the series to 87 patients: implantation was successful in 86 of the 87 patients, and after a mean follow-up of 10 months, only 1 minor stroke and 2 TIAs occurred (Sievert, 2003). Hanna et al. (2004) and Ostermayer et al. (2005) confirmed the safety of surgical closure of the left atrial appendage, and more recently in the LAAOS study left atrial appendage closure was performed in patients undergoing coronary artery bypass graft intervention, when they were at high risk of stroke (Healey et al., 2005).

51.2.2.1.6.2. Rhythm control versus rate control strategy

Recent studies compared rhythm control versus rate control strategy showing that rhythm control does not reduce stroke occurrence. A possible explanation of these results is that people who appeared to be in sinus rhythm were not really in sinus rhythm all the time. Overall, the trial shows that oral anticoagulant treatment protects against stroke, but sinus rhythm does not (Wyse et al., 2002). When electrical cardioversion of non-valvular atrial fibrillation is planned, oral anticoagulant treatment should be performed at least 4 weeks before sinus rhythm has been restored. Recently, several studies suggest that in patients with recent non-valvular atrial fibrillation, if left atrial thrombosis or echocontrast are absent at TEE, electrical cardioversion may be feasible and safe even after a 24–48 hour period of heparin treatment (Manning et al., 1995; Sherman et al., 2003). Patients with asymptomatic atrial fibrillation have less serious heart disease, but more often a coexisting cerebrovascular disease may be present (Flaker et al., 2005).

51.2.2.1.6.3. ACEI or angiotensin II receptor blockade

Recently, several studies showed that ACE inhibitors may prevent recurrences of atrial fibrillation. In the trandolapril cardiac evaluation (TRACE) study, trandolapril reduces the incidence of post-myocardial infarction atrial fibrillation by 47% (Pederson et al., 1999), in the studies of left ventricular dysfunction (SOLVD) study in patients with ejection fraction (EF) <35% enalapril reduces the incidence of atrial fibrillation by 77% (Vermes et al., 2004). Also angiotensin II (AT II) antagonists may reduce new onset atrial fibrillation (Bourassa, 2005). In the losartan intervention for endpoint (LIFE) study, which included hypertensive patients, losartan reduces new cases of atrial fibrillation by 33% and, compared to atenolol, reduces the incidence of stroke by 51% (Wachtell et al., 2005). A large ongoing Italian study, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISS)-Atrial Fibrillation Trial, is assessing the role of angiotensin receptor blockade in reducing the recurrence of atrial fibrillation (Disertori et al., 2006).

51.2.2.2. Atrial flutter and embolic risk

Only in recent years has it been established that in patients with atrial flutter the risk of stroke is not negligible. Similarly to atrial fibrillation, there is evidence of left atrial and left atrial appendage dysfunction either in persistent atrial flutter or after electrical cardioversion or radio-frequency ablation (Grimm et al., 1997; Omran et al., 1997). Moreover, a prevalence of left atrial thrombi and spontaneous echo contrast of 10% and 30% respectively, has been documented in patients with atrial flutter by TEE (Sparks et al., 1998).

The prevalence of systemic thrombo-embolism and stroke in patients with atrial flutter is about 7% with an estimated risk of 1.8% per year which is only slightly less than that observed in patients with atrial fibrillation. Effective oral anticoagulant treatment determines a significant reduction of the embolic risk. In the absence of controlled clinical trials the indications for oral anticoagulant treatment should be the same as established in the guidelines for atrial fibrillation (Singer et al., 2004).

51.2.2.3. Acute myocardial infarction

Since the 1980s, several studies have focused on the risk of stroke and systemic thrombo-embolism in patients with recent myocardial infarction. Echocardiographic studies have reported a high incidence of left ventricular thrombi following myocardial infarction. In a meta-analysis of echocardiographic studies including 2,018 patients with recent myocardial infarction the prevalence of left ventricular thrombosis was 27% (Van Dantzig et al., 1996). This finding is almost exclusive of patients with anterior myocardial infarction (39%), whereas for the inferior location the prevalence of thrombus is very low (0–5%). About 90% of mural thrombi occur when the ventricular apex is involved. In most cases thrombus occurs within 48 hours from the acute myocardial infarction, although it may be found even after 1–2 weeks.

The risk of stroke is high when left ventricular thrombus is detected. Indeed, the rate of embolic events was 18% in a pooling of 921 patients with thrombus, in comparison with 2% in patients without. Furthermore, a meta-analysis from 11 echocardiographic studies performed in patients with acute myocardial infarction showed a five-fold increase of the embolic risk in the presence of left ventricular thrombosis (Vaitkus and Barnathau, 1993). The morphologic characteristics of thrombi have a clinical importance because thrombi with mobility and protrusion into the left ventricular cavity have higher embolic potential. The prevalence of embolic events is 55% for mobile thrombus versus 10% for stratified thrombus, and 47% for protruding thrombus versus 7% for stratified thrombi. Most embolic events, including stroke, occur within 3 weeks of acute myocardial infarction (Loh et al., 1997). It has been shown that oral anticoagulant treatment is able to reduce the prevalence of intracardiac thrombus, as well as to decrease the risk for systemic embolism. In the previously mentioned pooled review of echocardiographic studies, patients with left ventricular thrombosis who were on oral anticoagulant treatment exhibited only a relative risk of 0.3% to suffer an embolic event.

Unfortunately, most studies focusing on myocardial infarction and stroke show data from short-term

follow-up periods. Recently, Witt et al. (2005) performed a large survey conducted in Olmstead County, Minnesota, to examine the rate of stroke after incident myocardial infarction, during a long-term follow-up. The results of this large study on 2,160 patients with myocardial infarction hospitalized between 1979 and 1998 showed: (1) the incidence of stroke is very high in the first 30 days (44-fold increased risk of stroke) followed by a rapid decline toward a stable risk over the following 4–5 years; (2) factors independently associated with increased risk for stroke are older age, history of stroke, and diabetes, but no association was seen between stroke and localization of myocardial infarction; (3) no reduction in the risk of stroke was detected during the two decades of the study, showing that the current treatments of acute myocardial infarction does not affect the embolic risk.

According to current guidelines, the use of oral anticoagulant treatment is only recommended following myocardial infarction in patients at high risk for embolic events. Patients with large anterior myocardial infarction or with apex involvement, those with significant heart failure, those with intracardiac thrombus on echocardiography, or with history of previous thrombo-embolic events should receive oral warfarin (INR between 2 and 3). Oral anticoagulant treatment has to be continued for at least 3 months; anticoagulation has to be continued in patients with chronic atrial fibrillation or other documented risk factors, such as left ventricular dysfunction (Harrington et al., 2004).

Long-term trials with antiplatelet agents or oral anticoagulant treatment following myocardial infarction show a significant reduction in the occurrence of stroke. Because of the low embolic risk after 3 weeks from myocardial infarction, it is conceivable that antithrombotic therapy prevents atherothrombotic stroke due to carotid artery disease, rather than from cardio-embolic sources. In particular, aspirin is able to reduce non-fatal stroke by 25% at 27 months showing that the pathophysiological mechanism of stroke after myocardial infarction could be secondary to activation of carotid or aortic plaques. Association between aspirin and fixed regimen low-dosage oral anticoagulant treatment has been recently investigated in randomized clinical trials, but this strategy did not prove better than aspirin alone for preventing stroke. Conversely, a meta-analysis showed that moderate- to high-intensity oral anticoagulant treatment associated with aspirin proved better than aspirin alone for reducing mortality, recurrences of myocardial infarction, and stroke (Anand and Yusuf, 1999).

In 2002, three studies compared aspirin versus the association of high-dose oral anticoagulant treatment and aspirin. Antithrombotics in the secondary prevention of events of coronary thrombosis II (ASPECT II) (Van Es et al., 2002) showed that the association of aspirin and warfarin (INR target 3–4) is better than aspirin alone. Antithrombotics in the prevention of reocclusion in coronary thrombosis II (APRICOT II) (Brouwer et al., 2002), performed in patients undergoing thrombolysis, showed that event-free survival was 83% in patients who assumed the association of aspirin and oral anticoagulant treatment and 70% in patients with aspirin alone. Finally, warfarin, aspirin reinfarction study II (WARIS II) (Hurle et al., 2002) showed that the association of oral anticoagulant treatment and aspirin significantly reduced the occurrence of reinfarction and thrombo-embolic stroke. Nevertheless, in warfarin, aspirin reinfarction study II (WARIS II), nearly 30% of patients receiving oral anticoagulant treatment was below the target range, nearly 30% discontinued oral anticoagulant treatment during the 80-month study period, 5–7% were withdrawn for hemorrhagic complications, and 2–3% were deemed non-compliant.

Long-term oral anticoagulant treatment is not recommended in patients with left ventricular post-infarction aneurysm. Indeed, prevalence of intracardiac thrombus is quite high (48–66% in surgical series, 49% at autopsy), but risk of systemic embolism is low (0.35 per 100 patients per year), presumably because the thrombus is contained within the non-contractile aneurysmal cavity. Oral anticoagulant treatment is only recommended in patients with thrombus presenting any previously described high-risk morphologic findings.

51.2.2.4. Valve disease, prosthetic cardiac valves, and endocarditis

51.2.2.4.1. Prosthetic cardiac valves

Patients with prosthetic cardiac valves are at high risk of systemic embolism and stroke is the most common clinical presentation. In patients with a mechanical valve the incidence of major embolic events is even more than 4% per year in the absence of antithrombotic treatment, whereas it is 2% during antiplatelet therapy, and 1% with anticoagulants (Vongpatanasin et al., 1996).

51.2.2.4.2. The embolic risk according to the prosthetic model and the position

Embolism is two-fold higher for a mechanical mitral prosthesis when compared to the aortic position. Moreover, embolic risk is higher for the old caged-ball type (e.g., Starr–Edwards) than for the single tilting disk (Bjork–Shiley) or the bileaflet model (e.g., St. Jude Medical). Patients at highest embolic risk are those with multiple prosthetic valves, atrial fibrillation, advanced age (>70 years), and poor left ventricular function.

In patients with bioprosthetic valves the embolic risk is moderately high during the first 3-month period

following operation. Thereafter, endothelialization of the bioprosthetic ring has a protective role and the risk of thrombo-embolism is approximately that of patients with mechanical prosthetic valves who are receiving oral anticoagulant treatment. Patients with mechanical prosthetic valves always require long-term oral anticoagulant treatment, which has to be initiated as soon as possible following surgery (within 6–12 hours) (Salem et al., 2004).

Prevalence of major bleeding during oral anticoagulant treatment is 1.4% per year. In selected patients with aortic valve replacement without additional embolic risk factors, low-intensity oral anticoagulant treatment (INR 2.0–3.0) is adequate for the prevention of thrombo-embolic events, while reducing the incidence of thrombo-embolic complications. The overall incidence of adverse events, either thrombo-embolic or hemorrhagic, is minimal when the INR is between 2.5 and 4.9 and between 2.5 and 3.6 according to a meta-analysis from 12 North American studies (Bloomfield et al., 1991; Hammermeister et al., 1993; Cannegieter et al., 1995).

51.2.2.4.3. The association of antiplatelet therapy with oral anticoagulant treatment

Dipyridamole has been associated with conflicting results (Chesebro et al., 1983; Pouleur and Boyse, 1995). The combination of high-dose aspirin (500–1000 mg per day) with low intensity oral anticoagulant treatment (INR 1.8–2.3) has decreased embolic events, but increased the incidence of gastroenteric bleeding. Otherwise, the combination of low-dose aspirin (100 mg per day) with warfarin (INR 3.0–4.5) has been beneficial in patients with prosthetic valves at high embolic risk (coexisting atrial fibrillation or previous embolism). Indeed, such regimen significantly decreased systemic embolism and death, but increased minor (but not major) hemorrhagic complications. Finally, the combination of low-dose aspirin (100 mg/day) plus lower-intensity oral anticoagulant treatment (INR 2.5–3.5) showed similar antithrombotic protection and less bleeds in comparison with high intensity oral anticoagulant treatment (INR 3.5–4.5) alone. In conclusion, the association of aspirin with oral anticoagulant treatment is advisable in patients who have suffered an embolic event during adequate oral anticoagulant treatment, in those with additional embolic risk factors (atrial fibrillation, previous thrombo-embolism, left atrial thrombosis, poor left ventricular function) or in patients with strong indication for aspirin treatment (i.e., coexisting coronary artery disease, previous TIA or stroke). In patients with bioprosthetic valves, low intensity anticoagulation (INR 2.0–3.0) is indicated during the first 3 months following surgery; thereafter, aspirin is a sufficient prophylaxis. Long-term oral anticoagulant treatment is warranted only in patients at high risk for embolism (Heras et al., 1995).

51.2.2.4.4. Valvular disease

Rheumatic mitral valve stenosis has the highest embolic risk in comparison with any other cardiac disorder. The embolic risk is even higher when atrial fibrillation is present, as well as in the elderly and in those with low cardiac output. The embolic risk is not related to the severity of stenosis, valvular calcification, or New York Heart Association (NYHA) class. During the long-term follow-up, the risk of cerebrovascular events was similar in patients with mitral or aortic stenosis.

Despite the lack of randomized trials, oral anticoagulant treatment is undoubtedly useful to reduce systemic embolism and stroke. Definite indications for oral anticoagulant treatment (INR 2.0–3.0) are previous thrombo-embolic event and atrial fibrillation, either paroxysmal or chronic. Oral anticoagulant treatment is recommended in patients with sinus rhythm and moderate left atrial enlargement (>5 cm) who are at high risk for atrial fibrillation. Oral anticoagulant treatment is also recommended in elderly patients and in those with severe stenosis (Salem et al., 2004). In patients suffering from embolism despite oral anticoagulant treatment two options are available: increase the intensity of anticoagulation (INR up to 3.5) or combine oral anticoagulant treatment with low-dose aspirin or dipyridamole.

51.2.2.4.5. Valve disease and systemic lupus erythematosus

In systemic lupus erythematosus, the incidence of stroke is high, affecting 52% of patients with different clinical manifestations as stroke, TIA, seizures, cognitive dysfunction, psychosis. When TEE is routinely performed in patients with systemic lupus erythematosus valve thickening or thrombotic valve vegetations may be detected in 53–61% of cases. The clinical implications of these evidences have a strong health and economic burden (Roldan et al., 2005).

51.2.2.4.6. Aortic valve calcification and calcified aortic stenosis

The incidence of calcified aortic valve disease is reported in about 1% of patients with TIA or stroke undergoing echocardiography (Stein et al., 1977). Case reports provide evidence of brain infarction, retinal ischemia, or peripheral vascular occlusion due to calcific emboli from aortic valves. Embolism can complicate cardiac catheterization and valvuloplasty. Primary oxalosis with calcium infiltration in aortic valve and left ventricle has been reported as a cause of cardio-embolic stroke. However, in a prospective controlled study on 815 patients with aortic valve calcification or calcified aortic valve stenosis, stroke was not significantly associated

with the severity of the aortic valve disease, but hypertension and carotid artery stenosis were frequently associated (Brockmeier et al., 1981; Davidson et al., 1988; Rancurel et al., 1989).

51.2.2.4.7. Infective endocarditis

The incidence of infective endocarditis is stable: 1.7–2 cases per 100,000 persons per year (Hart et al., 1990). Degenerative and prosthetic valve disease have become more common than rheumatic heart disease in recent surveys; moreover, patients with endocarditis and hemodialysis, diabetes mellitus, intravenous drug use, and nosocomial infections are common. Embolization from endocarditic vegetations may occur in 11–25% of cases and results in death in 24–50%. The risk is highest in the first 48 hours and the vegetations at high risk of embolization are those highly mobile, diameter >10 mm, associated with *Streptococcus viridans* and *Staphylococcus aureus* infections. Particularly at high risk are the vegetations of right-sided valves (Di Salvo et al., 2003; Heiro et al., 2000; Mylonakis and Calderwood, 2001).

The treatment for reducing the risk of embolization consists of accurate antibiotic therapy followed by surgery (Villacosta et al., 2002). The potential role of anticoagulant therapy or antiplatelet agents is controversial. In a recent study, Chan et al. (2003) showed no efficacy of aspirin for reducing the risk of clinical embolization in patients with infective endocarditis.

According to recent guidelines (Salem et al., 2004) in patients with a mechanical prosthetic valve and endocarditis who have no contraindications, long-term oral anticoagulant treatment is recommended. For patients with non-bacterial endocarditis and systemic or pulmonary emboli, and in those with disseminated cancer with aseptic vegetations, administration of full-dose heparin is also recommended.

51.2.2.5. Heart failure and cardiomyopathies

In 1994, Baker and Wright (1994) reviewed the incidence of arterial thrombo-embolism in patients with heart failure selecting 11 studies. The incidence of embolic events, ranging from 0.9 to 5.5 events per 100 patients per year (mean 1.9% per year), was significantly higher than the incidence in the general population aged 50–75 years (i.e., 0.5 events per 100 subjects per year). Nevertheless, the authors concluded that there is no subset of patients with heart failure that definitively has a higher embolic risk except those with atrial fibrillation. Moreover, among patients with non-valvular atrial fibrillation in the SPAF I study, left ventricular dysfunction and history of heart failure were independent predictors of thrombo-embolism.

According to recent guidelines, in patients with heart failure and atrial fibrillation, left ventricular thrombosis or history of embolic events, oral anticoagulant treatment is strongly recommended (Harrington et al., 2004). Sharma et al. (1998) showed that among patients with heart failure and left ventricular thrombosis, the history of recent myocardial infarction and severe left ventricular dilatation were predictors of embolic risk. Stratton et al. (1988), after a 2-year follow-up, showed that left ventricular thrombosis disappeared in 29% of patients without oral anticoagulant treatment and in 59% of those with oral anticoagulant treatment.

Even the occurrence of severe left ventricular dysfunction or left ventricular dilatation are considered possible indications to oral anticoagulant treatment. In the survival and ventricular enlargement (SAVE) study (Loh et al., 1997), which enrolled patients with recent myocardial infarction and left ventricular dysfunction, univariate analysis showed that patients with ejection fraction ≤28% had a two-fold increase in relative risk of stroke. In the studies of left ventricular dysfunction (SOLVD) (Al Khadra et al., 1998), which enrolled patients with ejection fraction ≤35%, with ischemic etiology in most cases, oral anticoagulant treatment showed a reduction of total mortality but failed to show a reduction of embolic events, probably because of the low incidence of embolic events.

The only recent controlled trial of oral anticoagulant (OAC) in patients with heart failure who were in sinus rhythm was the warfarin/aspirin study in heart failure (WASH) study (WASH Study, 1999). Two-hundred and seventy-nine patients were randomized to OAC (target INR 2.5) versus 300 mg aspirin per day, during a follow-up period of 2.5 years. There was no significant difference in the composite endpoint of death, myocardial infarction, and stroke between the two treatments (Jones and Cleland, 1999). In the USA, two other studies, the warfarin and antiplatelet therapy in heart failure (WATCH) trial and the warfarin vs aspirin in patients with reduced left ventricular ejection fraction (WARICEF) trial, evaluated the role of oral anticoagulant treatment in patients NYHA class II–IV and EF <40%. Unfortunately, the limited recruitment of patients in these trials did not allow conclusions to be reached on the original endpoint (BM Massie, pers. comm.). In patients with dilated cardiomyopathy the prevalence of ventricular thrombi is substantial, ranging from 11% to 60% among non-anticoagulated patients (Fuster et al., 1981; Yokota et al., 1989; Falk et al., 1992).

Stroke and systemic thrombo-embolism are reported in 8.4–18% of the patients. The embolic risk is significantly higher in the presence of atrial fibrillation and advanced congestive heart failure. There are no prospective studies of the risk/benefit ratio of oral anticoagulant treatment in patients with dilatative cardiomyopathy. However non-randomized observational studies show

efficacy of oral anticoagulant treatment for the prevention of embolism in these patients (Kyrle et al., 1985; Halperin, 1994).

In the absence of definite guidelines based on prospective randomized trials, oral anticoagulant treatment should be indicated in patients with dilated cardiomyopathy at higher embolic risk such as those with atrial fibrillation, advanced congestive heart failure and left ventricular thrombosis (Koniaris and Goldhaber, 1998).

In patients with hypertrophic cardiomyopathy, systemic embolism and stroke are possible complications during the natural history of the heart disease (Di Pasquale et al., 1990; Russel et al., 1991). Hypertrophic cardiomyopathy "per se" is not an embologenic heart disease. The embolic risk is almost related to the occurrence of one of three events: atrial fibrillation, infective endocarditis, and evolution toward a dilatative form with systolic dysfunction and congestive heart failure. The embolic risk is particularly high in the presence of paroxysmal or chronic atrial fibrillation with definite indication to oral anticoagulant treatment (INR 2.0–3.0).

51.2.2.6. Patent foramen ovale and atrial septal aneurysm

In about one-quarter of the adult population, a patent foramen ovale (PFO), commonly present in the fetus, may persist. PFO is a hemodynamically inter-atrial communication consisting of the persistence of the one-way flap valve overlying the fossa ovalis allowing right-to-left shunt when right atrial pressure exceeds left atrial pressure (Kernt et al., 2001). A PFO may be detected in about one-third of patients with history of cerebral ischemia (Adams, 2004; Hara et al., 2005).

After several case reports on a possible association between PFO and cerebral embolism, in 1988, Lechat et al. (1988) and Webster et al. (1988) firstly showed a higher prevalence of PFO (>50%) in young stroke patients versus controls. In the following years, large case-control studies confirmed these data (Hausmann et al., 1992; Louie et al., 1993; Schminke et al., 1995), while two studies (De Belder et al., 1992; Di Tullio et al., 1992) did not show a higher prevalence of PFO in adult patients with cryptogenetic stroke. Recently, a meta-analysis definitively confirmed the correlation between PFO and stroke (Overell et al., 2000), with stroke risk ranging from 1% to 17.5% (Meissner et al., 2006).

51.2.2.6.1. Criteria for diagnosis of PFO and stratification of the embolic risk

PFO is judged to be present if any microbubble is seen in the left-sided cardiac chambers within three cardiac cycles from the maximum right atrial opacification. Second, PFO may be associated with higher risk of paradoxical embolization in the presence of a large right-to-left shunt at rest and enhanced membrane mobility (Fox et al., 2003), larger defects (Schuchlenz et al., 2004). Finally, coughing during a Valsalva maneuver may increase the sensitivity for detecting PFO during contrast echocardiography (Stoddard et al., 2001).

51.2.2.6.2. Criteria for diagnosis of paradoxical embolism through the PFO

In several case reports, venous thrombi trapped in PFO have been detected in patients with central and systemic embolization. Diagnosis of paradoxical embolism through PFO should always include: (1) no evidence of other sources of embolism; (2) coexistence of deep venous thrombosis, venous thrombi trapped in PFO, or pulmonary embolism; (3) large PFO or larger amounts of inter-atrial shunting or both; (4) association of PFO with atrial septal aneurysm (25%) or with mitral valve prolapse, both potential cardio-embolic sources. Transcranial Doppler examination may improve the diagnosis of paradoxical embolism in the presence of microbubbles injected in a venous line in the cerebral circulation (Droste et al., 2002; Devuyst et al., 2004).

Several possible sources of embolism may be associated with PFO. They include atrial septal aneurysm, situations of enhanced atrial vulnerability and atrial arrhythmias (Berthet et al., 2000), persistence of the Eustachian valve and Chiari network (Schneider et al., 1995; Schuchlenz et al., 2004). The coexistence of stroke from paradoxical embolism and pulmonary embolism during air travel has been also reported (Lapostolle et al., 2003).

Because of the high prevalence of PFO in the general population caution is required for the diagnosis of paradoxical embolism. In many patients with stroke, the PFO is likely not to be etiologically related to cerebral ischemia. Also, in more than one-third of cases the PFO is only incidentally associated in patients with cryptogenic stroke. Current therapeutic options for secondary prevention include medical treatment with aspirin or oral anticoagulant therapy, percutaneous invasive or surgical procedures for the closure of the defect.

51.2.2.6.3. Medical therapy

Recently, Homma and Sacco (2005) considered nine studies including 943 patients, mean age 45 years, follow-up duration 33 months. In medical treatment the incidence of annual stroke was 1.98% and the cumulative incidence of stroke and death was 3.12%. The risk of recurrences was higher among younger patients. In the patent foramen ovale in cryptogenic stroke (PICCS) study (Homma et al., 2002), which compared head-to-head warfarin and aspirin, no differences were seen between these two treatments. In patients with cryptogenic ischemic stroke and PFO, recent guidelines recom-

mended antiplatelet therapy over no therapy and over warfarin (Albers et al., 2004).

51.2.2.6.4. Percutaneous closure of PFO

Homma and Sacco (2005) considered 12 studies including 1,430 patients with a mean age of 46 years and a mean follow-up period of 18 months. The stroke incidence was 0.19% and the cumulative incidence of stroke and death was 1.15%. The acute complications of the procedure were nearly 1.5%. Only Windecker et al. (2004) compared medical treatment and percutaneous closure of PFO finding a superiority of invasive treatment. Moreover, Wahl et al. (2005) showed that transcatheter closure of PFO removes the clinical relevance of atrial septal aneurysm.

Recently, Meissner et al. (2006) observed that methodological limits of many trials have resulted in potentially inaccurate conclusions regarding the association of PFO and stroke. In the stroke prevention: assessment of risk in a community (SPARC) study, in which TEE was performed in 585 subjects randomly sampled, 140 were found to have a PFO, in 6 cases associated to atrial septal aneurysm. After a 5-year period, 41 patients experienced a cerebrovascular event, but no correlation was found between PFO and the risk of stroke. Nevertheless, in this study only patients aged over 45 years were included and information on concomitant medications was not available.

51.2.2.6.5. Surgical closure of PFO

Homma and Sacco (2005) considered 5 studies including 161 patients, with a mean age of 43 years and a mean follow-up period of 22 months. The incidence of stroke was 0.34% and the cumulative incidence of stroke and death was 0.85%.

In the last 2 years, a debate has arisen on the role of percutaneous closure of PFO, because the wide diffusion of this new technique has been recently challenged (Adams, 2004; Donnan and Davis, 2004; Furlan, 2004; Tong and Becker, 2004). In order to establish the role of percutaneous closure of PFO, three randomized clinical trials are ongoing: the Randomized Evaluation of recurrent Stroke comparing PFO Closure to establish current standard of Treatment (RESPECT) trial, the CLOSURE I trial and the CARDIA PFO trial.

51.2.2.7. Atrial septal aneurysm

The prevalence of atrial septal aneurysm, a localized bulging of the inter-atrial septum, ranges from 1% in autopsy to 2.2% in TEE series, in about 10% of young patients with TIA or stroke (Messè et al., 2004). The prevalence in patients with cryptogenic stroke is even higher (range 16–28%). Nearly one-half of the atrial septal aneurysms detected by TEE are not visualized by routine TTE.

Cerebral ischemia in patients with atrial septal aneurysm could be secondary to embolism from thrombi of the aneurysmal sac or to paradoxical embolism through a PFO, coexisting in 60–75% of cases. Other potential mechanisms of embolism in patients with atrial septal aneurysm include coexistent myxomatous mitral valvulopathy, Chiari's network (which is the congenital residuum of the sinus venosus in right atrium), and the Eustachian valve. Chiari's network has been discovered incidentally in up to 4% of autopsy studies and in 2% of patients undergoing TEE, but it is more common in patients with cryptogenic strokes (Schneider et al., 1995). A prospective long-term study showed only a low incidence of embolic stroke in atrial septal aneurysm (Burger et al., 2000).

TEE studies suggested a strong association between interatrial septum thickness of more than 5 mm and cerebrovascular events (Schneider et al., 1990). A thickened interatrial septum was found in 75% of patients with a history of ischemic stroke and only in 24% of those without history of cerebral ischemia. Moreover, atrial septal aneurysm has been particularly associated with small lacunar infarcts (Albers et al., 1994), and with atrial vulnerability, consisting of a high occurrence of atrial fibrillation (Homma et al., 2003).

Overall, the risk of stroke in patients with atrial septal aneurysm has not been assessed and if atrial septal aneurysm is detected in a patient with stroke, the risk of cerebrovascular recurrences is unclear. Aspirin can prevent thrombo-embolism in these patients, but no long-term comparison between warfarin and aspirin for preventing stroke is available. Mas et al. (2001) previously showed that in patients with PFO and atrial septal aneurysm aspirin was insufficient to protect against recurrences.

Patients with an atrial septal aneurysm have a coexisting PFO in most cases. In these patients the embolic risk is higher because the atrial septal aneurysm may increase the PFO diameter, facilitating right-to-left shunting by redirecting flow from the inferior vena cava toward the PFO. Patients with PFO and atrial septal aneurysm have a 3- to 4-fold increased risk for recurrent events than those with PFO alone. Recently, Wahl et al. (2005) submitted to transcatheter treatment 141 patients with atrial septal aneurysm and PFO and 220 patients with PFO alone. All patients were symptomatic for cerebral ischemia. This study showed that the closure of PFO is safe and effective even in the presence of atrial septal aneurysm and that transcatheter treatment of PFO may reduce atrial septal mobility. The long-term risk of recurrent events after transcatheter treatment in patients with atrial septal aneurysm and PFO is comparable to those with PFO alone.

51.2.2.8. Aortic plaques

Since the 1990s, the association between protruding atherosclerotic plaques of ascending aorta and embolic events was seen in TEE studies, autopsy studies, and intra-operative epi-aortic evaluations during surgery (Tunick and Kronzon, 2000). Patients with aortic plaques frequently have associated carotid artery disease (Demopoulos et al., 1995), and coronary artery disease (Fazio et al., 1993). Moreover, a further intriguing association was seen between aortic plaques and atrial fibrillation. The SPAF Investigators detected complicated aortic plaques in 35% of patients, with a risk of stroke of 12–20%, suggesting that in patients with non-valvular atrial fibrillation cerebral embolism may be due to aorto-embolism in 10–20% of cases (Blackshear et al., 1999).

A routine TEE has shown the presence of aortic atherosclerotic plaques in nearly half of patients with ischemic stroke. Aortic plaques can be occasionally observed by TTE, but only the TEE approach can systematically detect aortic plaques, providing a detailed definition of the intimal surface of thoracic aorta. Aortic plaques are detected mainly in older patients.

In order to identify aortic plaques at high risk of embolism, Amarenco et al. (French Study of Aortic Plaques in Stroke Group, 1996) investigated the prevalence and the characteristics of high-risk aortic plaques. The authors observed that embolic risk was significantly higher if the atheroma was protruding or had a thickness of more than 4 mm. The same authors demonstrated an increased recurrence of embolic events (nearly four-fold) in patients with ischemic stroke and aortic plaques.

Even morphologic findings are highly predictive of embolic risk. The prevalence of mobile lesions and of ulceration greater than 2 mm was found to correlate with cryptogenic stroke (Stone et al., 1995). Cohen et al. (1997) followed up 338 patients, aged $\geq$60 years, for 2–4 years. Hypoechoic plaques, calcifications, and ulcerations were common in plaques $\geq$4 mm; the highest embolic risk was found in non-calcified plaques, which may be considered "vulnerable" plaques.

An emerging issue concerns the risk of embolism from aortic plaques during left heart catheterization and cardiac surgery. The high prevalence of elderly patients undergoing coronary angiography significantly enhances the risk of these complications. In nearly 50% of cases, guiding catheters may scrape the aortic debris, with a high risk of embolization. Frequently, visible atheromatous material is retrieved from the guiding catheter that had been passed up the aorta from the femoral artery (Keeley and Grines, 1998).

The risk of aorto-embolic events during cardiac surgery is even greater, occurring in 2–7% of patients. During cardiac surgery in patients with aortic plaques, cross-clamping, cannulation and manipulation of the ascending aorta make the risk of embolic complications very high. In elderly patients and in those with aortic valve disease, a preoperative TEE or intraoperative TEE should be routinely performed in order to identify the site of a safe cannulation and cross-clamping or to perform an alternative minimally invasive direct coronary artery bypass graft.

Sometimes after left heart catheterization an "atherothrombotic syndrome" consisting of renal failure, skin lesions, blue toes, and other signs of peripheral embolism may be observed. The probable cause of this syndrome is cholesterinic embolism from aortic atherosclerotic lesions (Coy et al., 1992; Davila-Roman et al., 1997).

Recently, the role of aortic atheroma as a risk factor for embolism has been challenged (Meissner et al., 2004), and the need for a better definition of the high risk findings is suggested (Yahia et al., 2004). An intriguing debate on the systematic need for TEE evaluation in patients with stroke and normal carotid arteries is ongoing (Harloff et al., 2005).

Possible treatments in patients with aortic plaques for preventing stroke include aspirin, statins, oral anticoagulant treatment, and surgical removal. While early reports claimed that oral anticoagulant treatment is harmful and can precipitate systemic embolism, more recently three studies investigated the role of oral anticoagulant treatment in patients with aortic plaques. Dressler et al. (1998) observed a high incidence of vascular events in patients non-treated with oral anticoagulant treatment (45%) versus patients treated with oral anticoagulant treatment (5%). The SPAF investigators re-evaluated the results of the study by the results of TEE (Blackshear et al., 1999). Among patients with aortic plaques and non-valvular atrial fibrillation, oral anticoagulant treatment was protective against the risk of stroke. Finally, Ferrari et al. (1999), in a prognostic non-randomized study, showed a better outcome with less embolic events among patients treated with oral anticoagulant treatment versus antiplatelets. Oral anticoagulant treatment is mainly effective in patients with aortic plaques greater than 4 mm, with ulcerations and with soft morphology. Only prospective randomized studies of comparison between aspirin and warfarin in patients with stroke and aortic plaques could indicate the optimal treatment for the prevention of recurrences.

51.2.2.9. Other cardio-embolic diseases

Although only a minority of ischemic strokes affects younger adults, as many as half of these patients are less than 65 years old. In these patients other less

frequent cardiac sources of embolism could be detectable (Bougusslavsky et al., 1989).

51.2.2.9.1. Mitral valve prolapse

Since the early 1970s, mitral valve prolapse was postulated to be a possible source of cerebral emboli. Several reports, mainly concerning stroke in young adults, have firstly suggested a high prevalence of mitral valve prolapse in stroke (Nishimura et al., 1985). Nevertheless, if restrictive echocardiographic criteria are adopted, mitral valve prolapse is less frequently identified, its prevalence rate being approximately that observed in a healthy population (4–6%). Indeed, the prevalence of cerebral ischemia in patients with mitral valve prolapse is low, approximately 0.5% per year (Marks et al., 1989).

Thickening of the mitral leaflets with myxomatous findings and mitral insufficiency may increase the risk of systemic emboli, although these data were not recently confirmed (Gilon et al., 1999). The risk is further increased in patients with atrial fibrillation or endocarditis. Data concerning the occurrence of thrombi on the leaflets are scarce. Mitral valve prolapse can be associated with an atrial septal aneurysm, PFO, or rarely with idiopathic lesions of cerebral arteries caused by systemic connective tissue disorders or with abnormalities of platelet activity and clotting disorders.

51.2.2.9.2. Mitral annular calcification and valvular strands

Mitral annular calcification, which is detectable by TTE, has been reported in association with ischemic stroke resulting in an independent risk factor (Nair et al., 1989; Aronow et al., 1990, 1992; Benjamin et al., 1992). The presumed mechanism for stroke is the detachment of small calcific emboli from the degenerated mitral annulus. However, a causal relationship between mitral annular calcification and stroke is difficult to demonstrate because mitral annular calcification is often associated with advanced age, congestive heart failure, and particularly with atrial fibrillation. Valvular strands are mobile filamentous strands of the cardiac valves which have been associated with stroke and systemic embolization (Orsinelli and Pearson, 1995; Tice et al., 1996; Roberts et al., 1997). The association with cerebral ischemia has been reported for strands on both the mitral and aortic valves.

51.2.2.9.3. Cardiac tumors

Atrial myxomas represent more than 50% of primary cardiac tumors. Seventy-five percent of the myxomas occur in the left atrium (Reynen, 1995). Systemic embolism and stroke occur in 40% of cases. Emboli are of two types: platelet-fibrin and tumor fragments (Knepper et al., 1988). Most atrial myxomas can be detected by TTE, but only TEE and MRI allow a precise definition of the mass and its connections with the cardiac structures. Atrial myxomas are found in about 1 of 200 young adults with stroke/TIA, and in perhaps 1 of 750 older patients with cerebral ischemia.

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Chapter 52

Ultrasound investigations of the intra- and extracranial vessels

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In the past three decades, Doppler ultrasound investigation has replaced conventional angiography as the method of choice for the investigation of the intra- and extracranial brain supplying arteries. Further technical developments such as duplex sonography and the advent of ultrasound contrast agents have significantly broadened the applications of ultrasound in the clinical routine. Besides the established diagnostic features, new ultrasound-based treatment options, such as sonothrombolysis are emerging on the horizon. This chapter will summarize the state of the art of intra- and extracranial ultrasound and give a brief outlook on upcoming new ultrasound applications.

52.1. Ultrasound investigation of the extracranial vessels

About 50% of all symptomatic stenoses or occlusions of the anterior circulation are located in the proximal portion of the internal carotid artery (ICA). They typically result from atherosclerotic narrowing of the vessel lumen. Large clinical trials have shown the efficacy of surgical over medical treatment of carotid artery stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995). The risk of stroke and also the indication for carotid endarterectomy depend strongly on the degree of the stenosis. Thus screening for and reliable and valid quantification of the carotid stenosis is of utmost clinical importance and can be achieved by ultrasound investigation.

52.1.1. Examination techniques

Before the introduction of color-coded duplex sonography, the examination of the neck arteries was performed with the use of conventional Doppler ultrasound systems. Diagnosis was obtained by analyzing the Doppler waveform including the indirect evaluation of the periorbital arteries as well as compression tests. With the advent of color-coded duplex sonography, direct visualization of the vessels was possible. Duplex systems display blood flow in a color-coded fashion within the grayscale images of the vessel walls and thus facilitate vessel identification (Fig. 52.1). Evaluation of arterial hemodynamics, however, as in duplex sonography should be based on the careful analysis of the Doppler spectra waveforms and not on color imaging.

Duplex systems furthermore provide a number of additional features that are not available with conventional Doppler sonography, such as examination of the vessel walls and identification of atherosclerotic plaques before they lead to the significant lumen narrowing that results in hemodynamic disturbances. Vessel wall thickness (intima-media thickness—see section 52.1.10.1) serves as a morphological criterion for atherosclerosis and can be quantified with duplex systems.

52.1.2. Patient preparation

For ultrasound examination of the neck arteries the patient should be placed in a supine position. The examiner can sit behind the patient's head or on the right-hand side. The latter position is frequently preferred by cardiologists who perform carotid

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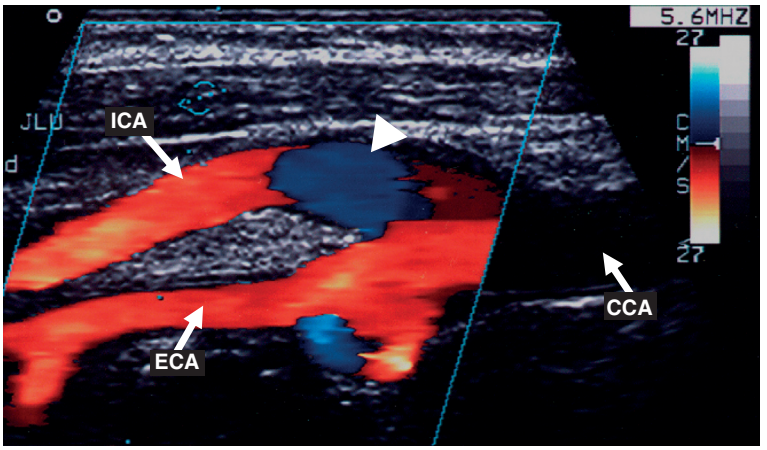

Fig. 52.1. Color duplex image of a normal carotid bifurcation. CCA = common carotid artery; ICA = internal carotid artery; ECA = external carotid artery (with some branches); arrowheads = carotid bulb.

examination in connection with echocardiography. Neurologists typically prefer to sit behind the patient's head since this position facilitates transcranial examination (see below).

52.1.3. Machine settings

Duplex ultrasound of the neck arteries is typically performed with linear transducers, operating between 5.0 and 7.5 MHz. Grayscale imaging needs to be optimized by adjusting the time-gain compensation that allows enhancement of signals that are reflected by deeper structures and that are thus more attenuated. For optimal color imaging, the pulse repetition frequency (PRF) should be adjusted to avoid excessive aliasing (color shift from red to blue). Color gain should then be tuned. Color display is satisfactory if the vessel lumen is almost completely filled with color pixels but excessive extraluminal color artifacts are avoided. It is generally agreed that blood flow away from the probe is coded blue and flow directed towards the probe is displayed in red.

52.1.4. Anatomic orientation

The topographical situation of the carotid arteries can be assessed quickly by imaging in transversal section. Position of the common, internal, and external carotid arteries can be depicted more easily by tilting the probe 45° downwards. This improves color filling of the vessels. The longitudinal scan plane should then be selected for further examination.

First the entire course of the common carotid artery should be displayed. Sometimes only sections of the vessel are visible. In these cases the probe should be tilted around the "cable axis" by some degrees. Then the probe should be slid upwards until the carotid bulb appears in the right half of the screen. The bulb can typically be identified by the "blue-to-red" color flap that represents the physiological swirl with some retrograde flow (blue) (Fig. 52.1). Now the two branches of the carotid artery can be displayed by tilting the probe around its lower edge. The internal carotid artery should then be carefully examined by sliding the probe further upwards.

For examination of the vertebral artery the pulse repetition frequency should be reduced since blood flow velocity is usually lower in the vertebrobasilar system. For topographical orientation we recommend displaying the common carotid artery and then tilting the ultrasound beam downwards until the cervical vertebra become visible. Parts of the V2 segment of the vertebral artery can then be examined between the shadows caused by the vertebra (Fig. 52.2). For the identification of the origin (V0) and the V1 segments, the probe should be slid downwards until the subclavian artery can be displayed. Correct vessel identification must be confirmed by compression tests (see below). The V3 segment can be examined by placing the probe behind the mastoid. Here the vessel typically runs in a semi-circled loop. The intradural part of the vertebral artery (V4 segment) can only be examined from the transnuchal approach (see section 52.2.1).

52.1.5. Doppler spectra analysis

Color coding of blood flow provides information regarding the flow direction (towards [red] or away from [blue] the probe). The presence of localized aliasing can be a sign of a higher graded stenosis. Artifacts, however, occur very frequently in color mode and suboptimal machine settings can lead to aliasing in

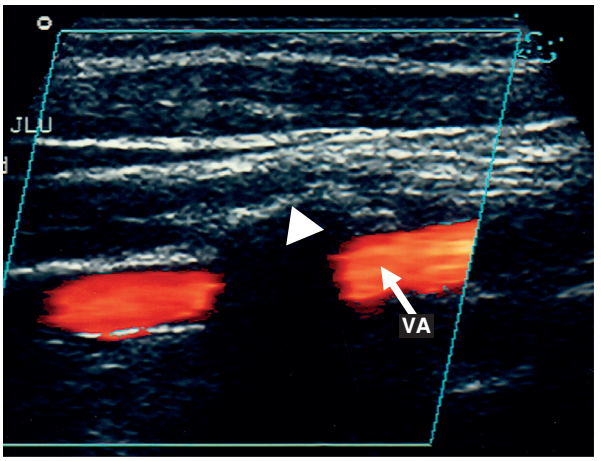

Fig. 52.2. Color duplex image of a normal vertebral artery (V2 segment). VA = vertebral artery; arrowhead = shadow caused by the cervical vertebra.

unimpaired arteries or even mask pathological findings. Thus diagnoses should always be based on Doppler spectra analysis and not on color imaging.

For Doppler spectra analysis, the sample volume should be placed into the center of each vessel and should be moved along the entire course of the artery. Abrupt changes of the flow pattern (particularly increase of the peak systolic flow velocity with turbulences) are indicative of stenoses and will frequently be overlooked if Doppler spectra analysis is performed only sporadically. For the purpose of documentation, one representative Doppler spectra sample of each vessel (and of all pathological findings) should be documented and peak systolic and diastolic blood flow velocity should be measured. Therefore careful correction of the insonation angle is required.

52.1.6. Compression tests

The advent of color-coded duplex sonography might have decreased the importance of compression tests since imaging facilitates vessel identification. Nevertheless, two compression tests should routinely be performed.

52.1.6.1. Identification of the external carotid artery

Doppler frequency analysis typically reveals a more pulsatile flow with low diastolic velocity. This pattern, however, is sometimes not very marked. Moreover, blood flow in the internal carotid artery, which should be more continuous, can be quite pulsatile in some patients. For correct identification both Doppler spectra should be compared and a compression test of the temporal artery must be performed. For this purpose the artery should be palpated 1 cm in front of the tragus of the ear and then tapped jerkily. This maneuver causes distinct rebound waves within the Doppler spectra of the external carotid artery and not (or only minimally) within the internal carotid artery (Fig. 52.3).

52.1.6.2. Identification of the vertebral artery

The anatomical feature of the V2 segment of the vertebral artery is almost unmistakable. However, the V1, V3, and particularly the V0 segments can be mixed up with branches of the subclavian or external carotid artery. A compression test should therefore always be performed by tapping the V3 segment behind the mastoid. The typical rebound waves prove the vessel in question to be the vertebral artery (Fig. 52.4).

52.1.7. Occlusion of the internal carotid artery

The following criteria need to be fulfilled for the valid diagnosis of an internal carotid artery occlusion:

1. Absence of a flow signal within the entire course of the vessel lumen (no color coding and no flow signal in the Doppler spectra analysis).
2. Slightly hyperechogenic thrombotic material within the vessel lumen (proximal occlusion only).
3. "Pre-occlusive flow pattern" within the distal common carotid artery (systolic spikes with partially reversed flow during the diastole) (Fig. 52.5).

The diagnosis is furthermore supported by indirect signs from the common carotid artery where blood flow pattern is normally determined by the resistance of the internal and external carotid artery territory. Occlusion of the internal carotid artery typically results in an "externalization" of the Doppler spectrum with increased systolic and decreased diastolic blood flow velocities and reduced pulsatility.

Examination of the branches of the ophthalmic artery, namely the supraorbital and supratrochlear artery, can support the diagnosis, since an occlusion (or a high-grade stenosis) of the proximal internal carotid artery results in a marked pressure drop with impaired flow pattern in the ophthalmic artery branches. An occlusion of the internal carotid artery typically results in a flow reversion in the supratrochlear artery. Occlusion or high-grade stenosis of the internal carotid artery furthermore often results in the recruitment of intracranial collateral pathways. However, if intracranial collaterals cannot be demonstrated this does not rule out severe steno-occlusive internal carotid artery pathology since the anterior or posterior communicating artery are sometimes hypo- or aplastic.

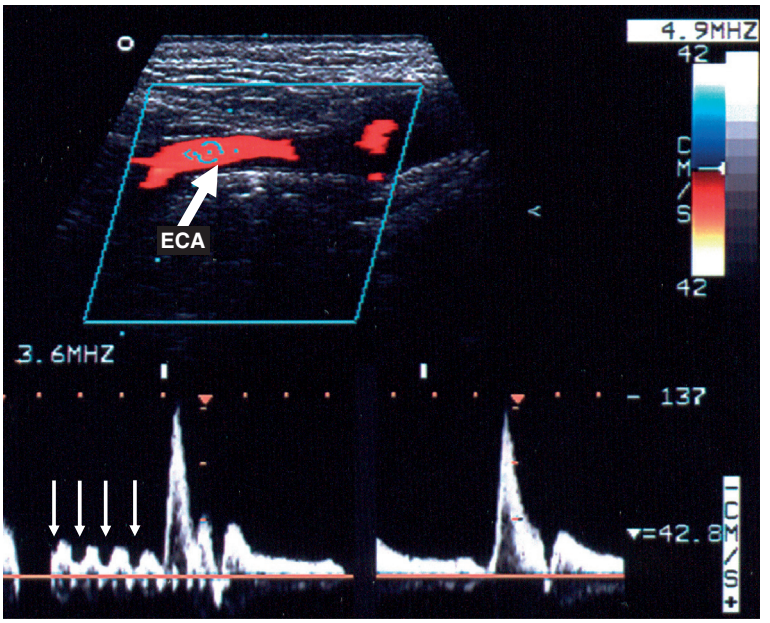

Fig. 52.3. Compression test confirms correct identification of the external carotid artery. ECA = external carotid artery; arrows = rebound waves caused by tapping onto the temporal artery.

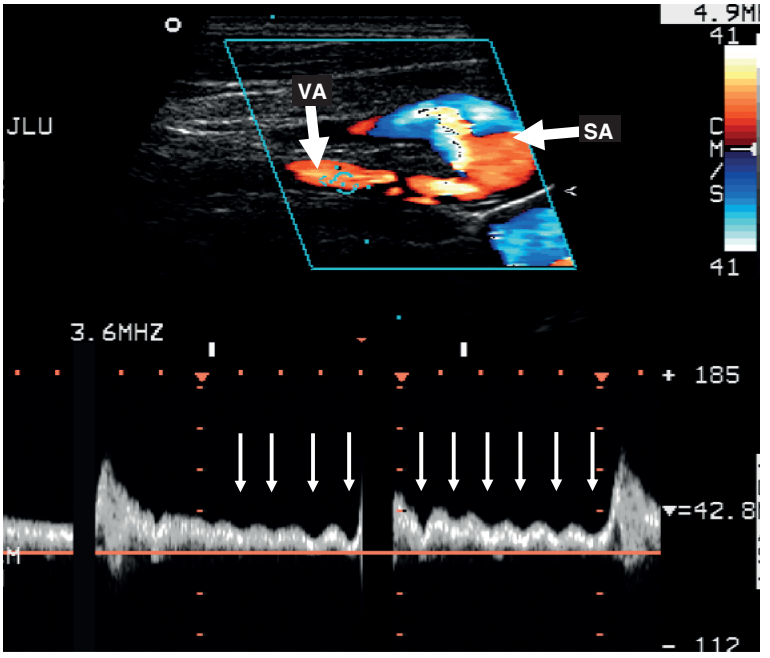

Fig. 52.4. Compression test confirms correct identification of the vertebral artery at its origin from the subclavian artery. VA = vertebral artery; SA = subclavian artery; arrows = rebound waves caused by tapping onto the V3 segment behind the mastoid.

52.1.8. Stenosis of the internal carotid artery

A stenosis is defined as a localized reduction of a vessel's inner diameter. While conventional imaging techniques (CT angiography, MR angiography or digital subtraction angiography) basically display the luminal narrowing, duplex sonography provides information regarding the vessel wall irregularity (grayscale imaging) and the resulting hemodynamic consequences (color mode and Doppler spectra analysis). Assessment

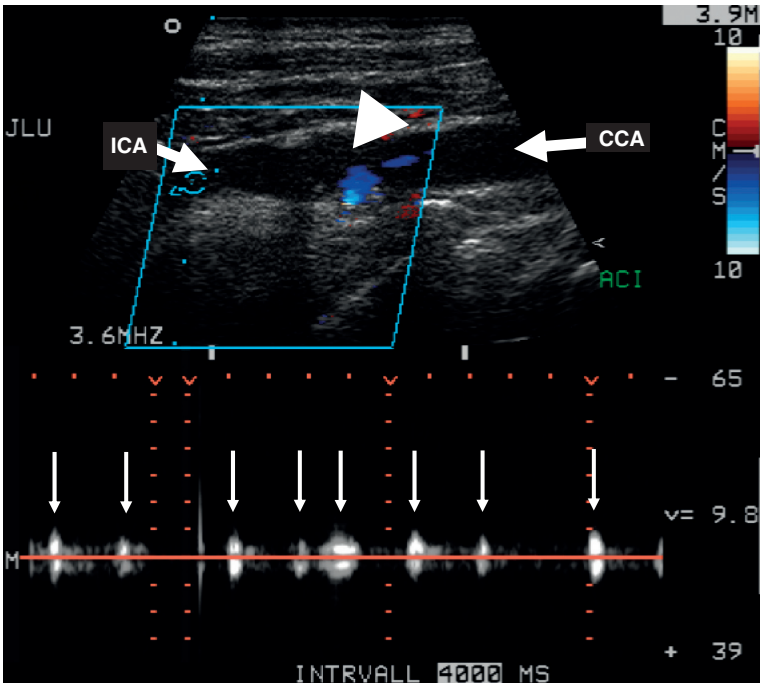

Fig. 52.5. Occlusion of the internal carotid artery. Doppler spectra analysis reveals a typical preocclusive flow pattern within the proximal part of the internal carotid artery (arrows). ICA = internal carotid artery; CCA = common carotid artery; arrowhead = carotid bulb.

of the Doppler spectra provides *direct* and *indirect* findings that help to make a diagnosis (see Table 52.1).

52.1.8.1. Direct findings

Systolic and diastolic blood flow velocity is increased within the stenosed segment of the artery. Blood flow velocity (or Doppler frequency shift) correlates with the extent of the lumen narrowing and is therefore important for the quantification of the stenosis (see below). Peak systolic blood flow velocity can increase up to 600 cm/s (20 kHz at 4 MHz) in high-grade stenoses, but then drops as luminal narrowing exceeds 90% (Fig. 52.6).

52.1.8.2. Indirect findings

Proximal to the stenosis, blood flow velocity is typically reduced with increased pulsatility (prestenotic signal). Distal to the stenosis blood flow velocity is likewise reduced. Pulsatility, however, is diminished, with decelerated systolic blood flow increase.

The literature reports numerous methods to quantify the degree of luminal narrowing. It can be expressed in terms of residual lumen area (mm^2), residual lumen diameter (mm) or—most commonly—in percentage stenosis (%). Quantification methods need to be evaluated by comparison with conventional angiography which serves as the gold standard. Definitions of angiographically determined percentage values, however, differ among the literature. While the European Carotid Surgery Trial (ECST) study made use of the *local* stenosis calculation (ECST method), the North American Symptomatic Carotid Endarterectomy Trial (NASCET) calculated the *distal* stenosis degree (NASCET method) (Barnett et al., 1998; Randomised Trial of Endarterectomy for Recently Symptomatic Carotid Stenosis, 1998). Calculation of the local degree with the ECST method is complicated by the fact that the original lumen (C) is difficult to determine on angiograms. Both methods differ particularly in low-grade stenoses but become increasingly comparable with higher degrees of stenosis. The following equation allows the conversion of ECST into NASCET percentage values:

$$\text{ECST stenosis (\%)} = 0.6 \times \text{NASCET stenosis (\%)} + 40\%$$

Although color duplex methods allow direct visualization of the stenosis, morphometrical techniques that rely on diameter or area measurements from grayscale (or even from color-coded) images should not be used any longer, since they are too susceptible to artifacts. Stenosis quantification in conventional Doppler sonography as well as by color-coded duplex sonography should be based on *direct* and *indirect* hemodynamic criteria that were determined from Doppler spectra frequency analysis. Blood flow velocity within the stenosis serves as a *direct* criterion for stenosis-quantification. It allows a rough calculation of stenosis degree.

Table 52.1

Criteria for the quantification of carotid artery stenoses (Kaps et al., 2005)

Degree of stenosis	≤60%	70%	80%	90%	>90%	Occlusion
Direct criteria						
Intrastenotic peak systolic BFV	<120 cm/s	200 cm/s	300 cm/s	>300 cm/s	Variable	0
Intrastenotic peak systolic frequency	<4 kHz	7 kHz	10 kHz	>10 kHz	Variable	0
Intrastenotic end-diastolic BFV	<40 cm/s	≥40 cm/s	≥130 cm/s	≥130 cm/s	Variable	0
Indirect criteria						
Ophthalmic artery (branches)	Orthograde	Flow reduced/ no-flow/ retrograde	Retrograde	Retrograde	Retrograde	Retrograde
Intracranial collateral pathways	No	No	Activated	Activated	Activated	Activated
ACI/ACC index	≥1.5	≥2.0	≥4.0	≥4.0	Not utilizable	Not utilizable

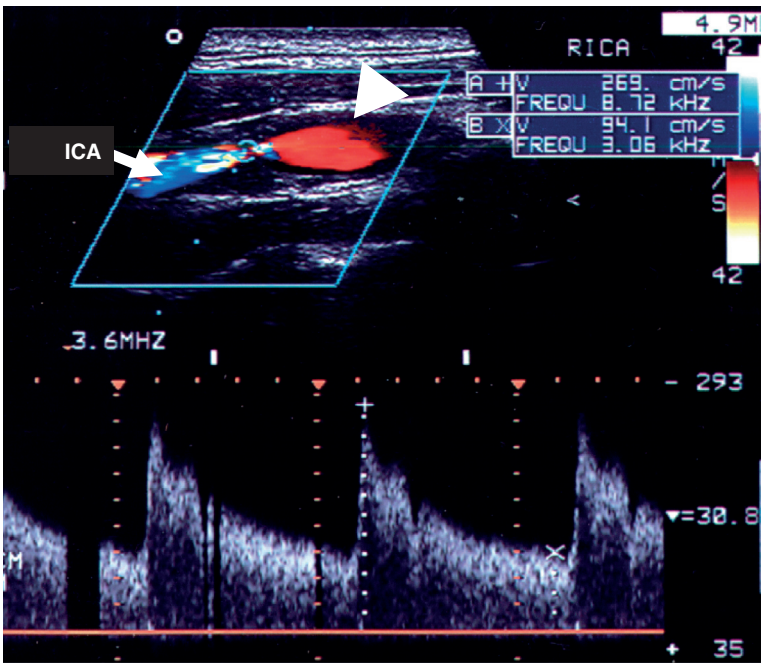

Fig. 52.6. Internal carotid artery stenosis with circumscribed acceleration of peak systolic blood flow velocity (269 cm/s). ICA = internal carotid artery; arrowhead = carotid bulb.

52.1.8.3. Intrastenotic peak systolic blood flow velocity

Intrastenotic peak systolic blood flow velocity increases when luminal narrowing exceeds 50%. Between 50% and 90% stenosis blood flow velocity (or Doppler frequency shift) increases exponentially but finally drops in filiform (>90%) stenoses.

52.1.8.4. Intrastenotic end-diastolic blood flow velocity

In high-grade stenoses only a small number of erythrocytes travel with maximum speed. This can lead to a break-off of the upper part of the frequency spectrum and peak systolic blood flow velocity sometimes is difficult to measure. In these cases, intrastenotic

end-diastolic blood flow velocity can be used for stenosis quantification. *Indirect* criteria allow a further specification of the degree of the internal carotid artery stenosis.

52.1.8.5. Flow-reversal within the branches of the ophthalmic artery

If the degree of an internal carotid artery stenosis exceeds 70%, the obstruction results in a pressure drop that causes flow-reversal in the ophthalmic artery and its branches (supraorbital and supratrochlear artery).

52.1.8.6. Internal carotid artery/common carotid artery index

The relation between peak systolic blood flow velocity in the internal and in the common carotid artery (carotid ratio) can additionally be used to quantify an internal carotid artery stenosis. A quotient of 1.5 is suggestive of a stenosis greater than 50%, a quotient of 4 indicates a greater than 70% stenosis.

52.1.8.7. Activation of intracranial collateral systems

Recruitment of intracranial collateral systems can be determined by examination of the anterior and posterior communicating artery. Flow reversal in the ipsilateral A1 segment is indicative for an activation of the anterior communicating artery collateral flow (cross-flow). Impaired blood flow patterns and "musical murmurs" indicate a functional overload of the anterior or posterior communicating artery and thus suggest an activation of intracranial collateral systems.

52.1.8.8. "Subtotal" internal carotid artery stenosis

Clear differentiation between internal carotid artery occlusion and high-grade stenosis is of the utmost importance for clinical management. While blood flow velocity is usually increased with increasing luminal reduction, blood flow is ebbing away in subtotal stenoses and velocity can be extremely low. The indirect criteria for the detection of internal carotid artery stenosis resemble those of an occlusion. Thus, subtotal stenoses can easily be mistaken for vessel occlusions. The criteria for a subtotal stenosis are as follows:

1. Reduced systolic and diastolic peak flow velocity.
2. Highly reduced post-stenotic blood flow.

Indirect criteria for the detection of internal carotid artery stenosis resemble those of an occlusion. Color duplex sonography can improve the sensitivity for the differentiation between subtotal internal carotid artery stenoses and occlusions. To enable the detection of highly reduced blood flow velocity, pulse-repetition frequency needs to be reduced and the color gain should be increased as high as possible ("low-flow detection"). Application of ultrasound contrast enhancers might further improve the significance of duplex sonography although they also enhance color artifacts.

Reliability of carotid ultrasound

Data regarding the reliability of carotid ultrasound vary strongly among the literature (Sabetai et al., 2000). Most studies compare ultrasound findings to intraoperative specimens (Cartier et al., 1993; Schulte-Altedorneburg et al., 2002) or to digital subtraction angiography (DSA), which is regarded as the gold standard in this context. While the majority of authors report good or excellent agreements between DSA and ultrasound (Hansen et al., 1996; AbuRahma et al., 1997; Furst et al., 1999; Borisch et al., 2003; Gaitini and Soudack, 2005), some groups report insufficient agreement regarding the degree of carotid stenoses (New et al., 2001; Jahromi et al., 2005). It should be pointed out that the reliability of carotid ultrasound relies strongly on the training and experience of the examiner (and to a lesser degree on the quality of the ultrasound equipment and the criteria for stenosis quantification) and thus some inaccuracy should be expected. However, this holds true for all imaging methods, including DSA, which likewise bears surprising inaccuracies if compared to planimetric assessment of post mortem specimens (Schulte-Altedorneburg et al., 2005). Carotid ultrasound is a sufficiently reliable and valid method if applied in a state-of-the-art fashion by a well-trained and experienced examiner who is aware of the limitations of the method.

52.1.9. Vertebral artery

52.1.9.1. Vertebral artery stenosis

For the detection of occlusions and stenoses in the vertebrobasilar system, similar principles apply as for the examination of the carotid arteries. The vertebral artery, however, cannot be displayed in its entire course by means of ultrasound, so indirect signs of hemodynamic impairment are of particular importance (Kaps et al., 1992; de Bray et al., 2001). Stenoses and occlusions of the vertebral artery are predominantly located at the origin of the vessel (V0 segment) and at the V4 segment (Fig. 52.3).

The origin of the vertebral artery can be displayed directly. Correct identification, however, must be confirmed by a compression test (see section 52.1.6). Locally increased blood flow velocity with peak systolic blood flow velocities typically exceeding 120 cm/s and post-stenotic turbulences are indicative for a stenosis. Indirect signs for a V0 stenosis can be detected in distal segments, such as a diminished pulsatility or (in high-grade stenoses) systolic decelerations. Stenoocclusive findings are uncommon at the V2 and V3 segments. The V4 segment can be examined using the transnuchal approach (see section 52.2.1).

52.1.9.2. Vertebral artery occlusion

Absence of any Doppler signal from the vertebral artery is suggestive for an occlusion of the vessel. Diagnosis of vertebral artery occlusion, however, is complicated by two special features of this vessel:

1. Side-to-side differences of the vessel diameter are common. *Hypoplasia,* defined as a diameter smaller than 2 mm, can complicate the detection of the Doppler or the color signal. Absence of a flow signal can be misinterpreted as a vessel occlusion. Grayscale imaging, however, allows the pinpointing of the anatomical position of the vessel in its V2 segment and to determine its diameter. Caliper differences, as the underlying cause for a missing signal or side-to-side differences of the Doppler frequency spectra, can be ruled out. Furthermore, identification of the V2 segment on grayscale images allows placement of the sample volume precisely into the lumen.
2. In chronic proximal vertebralis occlusion *cervical collaterals* can provide blood supply to a variable extent. In these cases blood flow can be detected within the lumen of the vertebral artery despite proximal occlusion. Blood flow velocity is typically low with reduced pulsatility and sometimes with systolic flow reversal. The V0 and V1 segments are not detectable. In cases with substantial collateralization blood flow appears normal within the V2–V4 segments. Direct visualization of cervical collaterals on the level of the V2 and V3 segment supports the diagnosis of a proximal vessel occlusion with collateral filling.

52.1.9.3. Subclavian steal syndrome

High-grade stenosis or occlusion of the subclavian artery or the brachiocephalic trunk proximal to the origin of the vertebral artery can lead to flow reversal in the ipsilateral vertebral artery. Particularly during exercise with the ipsilateral arm, post-stenotic perfusion pressure drops and blood supply to the arm is provided by the vertebrobasilar system (steal phenomenon), sometimes resulting in dizzy spells, diplopic images, headache, and other focal neurological symptoms. Clinical symptoms typically increase with exercise and subside when the arm is rested.

Since the subclavian artery and the brachiocephalic trunk are difficult to access with ultrasound, careful analysis of the Doppler spectral waveform in the vertebral artery helps to make a diagnosis. In mild subclavian steal syndrome, Doppler spectra show a midsystolic notch. With increasing pressure gradients, the flow pattern indicates partial then complete reversal of the flow direction within the vertebral artery (Fig. 52.7).

Compression of the ipsilateral upper arm (i.e., using a blood pressure cuff) attenuates flow reversal in the vertebral artery, and cuff release aggravates this. Performance of a compression test is important for the differentiation between an (incomplete) subclavian steal syndrome and a proximal high-grade vertebral artery stenosis or occlusion, since flow reversal can occur under both conditions. Obstruction of the vertebral artery, however, will not respond to the upper arm compression test.

52.1.10. Atherosclerosis of the vessel wall

Before the advent of color duplex sonography, atherosclerotic pathology of the vessel wall could only be detected if it led to luminal narrowing and thus to impaired Doppler spectra on conventional Doppler. Hemodynamic impairment, however, does not occur in stenoses of less than 50%, so minor atherosclerotic pathologies were not detectable. In modern color duplex sonography systems grayscale imaging allows careful examination of the arterial vessel walls (Fig. 52.8).

52.1.10.1. Intima-media thickness

Increased intima-media thickness is one of the earliest findings in cerebral macroangiopathy and is considered as a surrogate marker of generalized atherosclerosis. Although intima-media thickness cannot be regarded as an independent risk factor, it has been demonstrated to predict cardiovascular events such as stroke and myocardial infarction (Grobbee and Bots, 1994; Bots et al., 1997; O'Leary et al., 1999; Schulte-Altedorneburg et al., 2001; Touboul et al., 2004; Van Bortel, 2005).

Using high frequency ultrasound (>7 MHz), the vessel walls are delineated by two hyperintense margins that were separated by a hypointense layer (Fig. 52.8A). Although ultrasound cannot differentiate

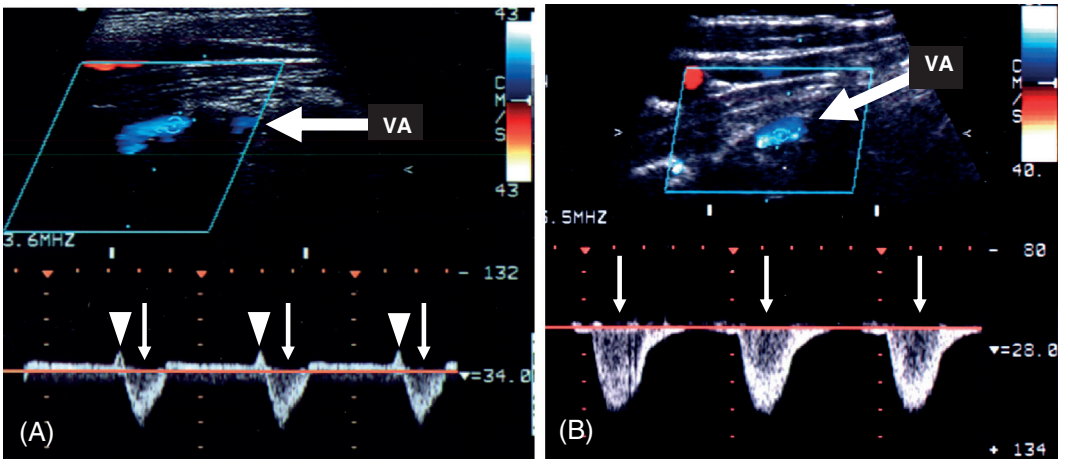

Fig. 52.7. Subclavian steal phenomenon caused by an occlusion of the subclavian artery. (A) Incomplete steal; blood flow direction changes during the cardiac cycle from orthograde (arrowhead) to retrograde (arrow). (B) Complete steal with retrograde blood flow (arrow). VA = vertebral artery (V2 segment).

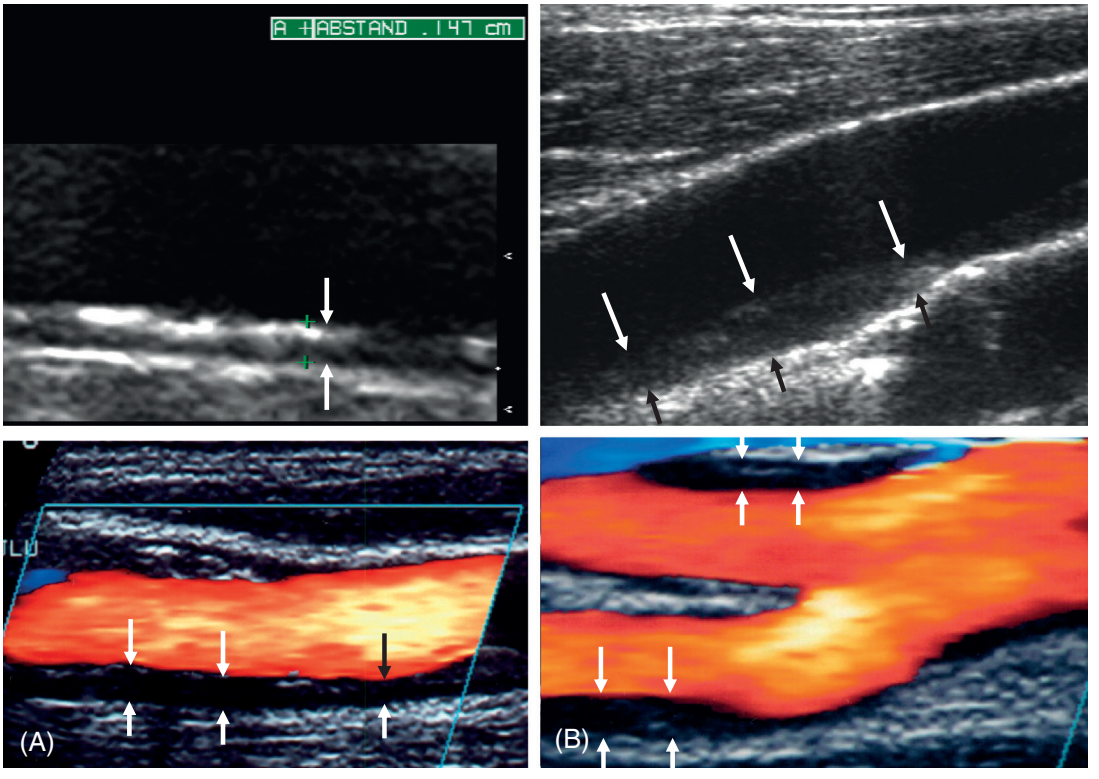

Fig. 52.8. Macroangiopathy without hemodynamic impairment. (A) Two examples for increased intima-media thickness. (B) Two examples of atherosclerotic plaque.

between intima and media histologically, comparative studies between ultrasound and histology indicated that the first hyperintense margin is caused by reflexion at the borderzone between the vessel lumen and the intima; the second hyperintense margin is caused by a reflection between the media and the adventitia. Thus the thickness of the first hyperintense and the second hypointense layer equals the intima-media thickness.

Reliable intima-media thickness measurements should be obtained from the far and not from the near wall since the latter measurement has to be performed at the trailing edge of the ultrasound pulse and thus may be inaccurate. The best site of carotid intima-media

Table 52.2

Normal values of IMT derived from a community population (n = 3,383) (Mackinnon et al., 2004)

Intima-media thickness (IMT)	Mean	SD
Common carotid artery	0.74 mm	0.15 mm
Carotid bifurcation	0.92 mm	0.33 mm
Internal carotid artery	0.77 mm	0.31 mm

thickness measurements is still a matter of debate. In many clinical trials intima-media thickness is measured at three different sites, the common carotid artery (1–2 cm proximal to the flow divider), the carotid bifurcation and the internal carotid artery. Intima-media thickness progression over time, however, appears to be most prominent at the internal carotid artery (Mackinnon et al., 2004). Normal values of intima-media thickness are presented in Table 52.2.

52.1.10.2. Atherosclerotic plaque

Atherosclerotic protrusions of the vessel wall that do not alter blood flow (or Doppler signals) are termed "plaques." They can be displayed by grayscale imaging and can be described according to their echogenicity as echogenic/echolucent and as homogeneous/heterogeneous (Fig. 52.8B). Several studies determining the correlation of ultrasonic plaque morphology with histopathologic findings and interobserver reliability of plaque evaluation provided only moderate results (Hartmann et al., 1999). The potential of sonographic plaque analysis for risk-stratification presently seems to be limited. However, the present literature allows the conclusion that plain shaped, homogeneous echogenic plaques appear to be rarely ulcerated and thus "stable" while echolucent; and inhomogeneous plaques more frequently tend to be hemorrhagic or ulcerated. Nevertheless, caution is warranted by deriving clinical decisions from ultrasonic plaque morphology.

52.2. Ultrasound investigation of the intracranial vessels

One-dimensional echo-encephalography was used in the 1960s to assess midline-shift non-invasively. This first application of transcranial sonography was forgotten after the advent of computed tomography. In 1982, Rune Aaslid and coworkers introduced transcranial Doppler sonography (TCD). This technique for the first time allowed the study of intracranial hemodynamics non-invasively using ultrasound. In the late 1980s, transcranial color-coded duplex sonography (TCCS) was introduced—a technique that combined conventional and color-coded Doppler sonography with grayscale imaging. Although TCD nowadays is still in use in the clinical routine (and still represents the method of choice for certain applications such as microemboli detection), the present chapter will focus on TCCS as a state-of-the-art method for the assessment of intracranial hemodynamics.

Several studies indicated that type and extent of intracranial steno-occlusive findings predict functional outcome early after acute ischemic stroke. Particularly patency of the middle cerebral artery has been identified as an independent predictor of early clinical improvement. Due to its non-invasive character and its bedside applicability, transcranial ultrasound is suitable in a setting of thrombolytic therapy. Knowledge of the intracranial vascular status may facilitate the indication for thrombolysis or other invasive therapeutic procedures in hyperacute stroke. Furthermore, transcranial ultrasound can be used to assess the effects of acute stroke treatment (revascularization, hemorrhagic complications) and to monitor the patient's further course (Martin et al., 1995; Goertler et al., 1998; Nabavi et al., 1998; Postert et al., 1999; Gerriets et al., 2002).

52.2.1. Examination techniques

For the examination of the circle of Willis and of the brain parenchyma, the transtemporal acoustic bone window above the tragus of the ear is commonly used. For standardization a transversal insonation plane that parallels the orbito-meatal line should be selected (Fig. 52.9A). For a first overview an examination depth between 14 and 16 cm should be selected that allows imaging of the contralateral hemisphere. Time-gain compensation should be adjusted to generate homogeneous grayscale intensity along the different examination depths. Holding the probe horizontally (0° plane), the butterfly-shaped mesencephalon which is surrounded by the echogenic basal cisterns can be visualized (Fig. 52.9B). By tilting the probe 10° upward (10° plane), the third ventricle comes into view as a hypoechogenic double reflex. The pineal gland and the choroid plexus within the lateral ventricle can be identified as echogenic structures (Fig. 52.9C). In the 30° plane, the cella media of the lateral ventricle can be detected (Fig. 52.9D). After screening the contralateral brain parenchyma for abnormalities, the examination depth should be reduced to 9–10 cm. The basal cerebral arteries can then be examined in the 0° plane (Fig. 52.10).

The distal segments of the vertebral artery (V4 segments) and the proximal part of the basilar artery can

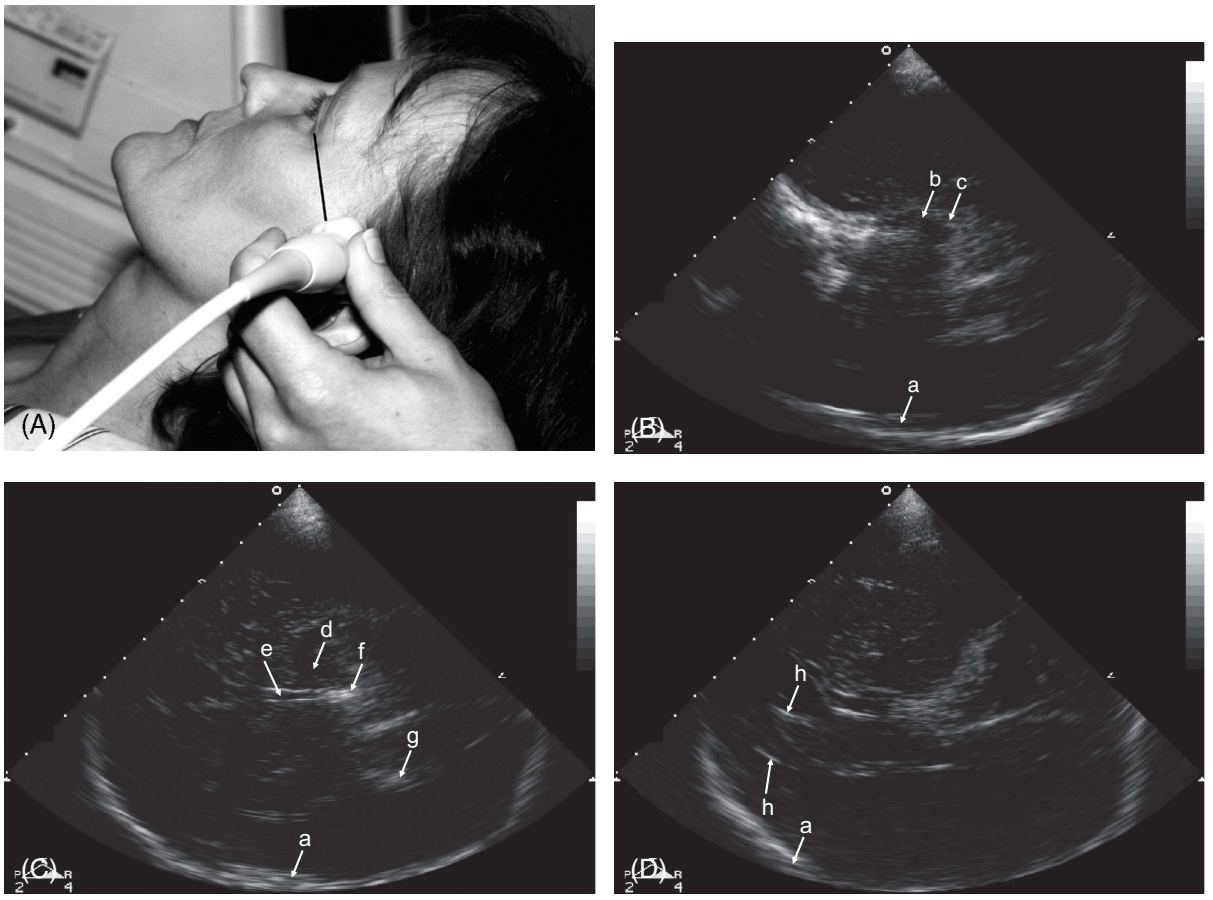

Fig. 52.9. (A) Insonation through the temporal bone window. The insonation plane parallels the orbito-meatal line. (B) 0° plane, brainstem. (C) 10° plane, third ventricle. (D) 30° plane, lateral ventricle. a = contralateral skull; b = brainstem; c = basal cisterns surrounding the brainstem; d = ipsilateral thalamus; e = third ventricle; f = pineal gland; g = choroid plexus within the contralateral ventricle; h = contralateral lateral ventricle.

be investigated from the transnuchal approach (Kaps et al., 1992; De Bray et al., 1997). The probe is attached horizontally to the neck, approximately 3 cm below the protuberantia occipitalis externa, so that the ultrasound beam points toward the root of the nose. Examination depth should be set to 10 cm. Grayscale imaging will then show the blurred hypointense shape of the foramen magnum. Further anatomic details are usually not visible from this approach. After switching on the color mode, the y-shaped image of the vertebral arteries merging to the basilar artery becomes apparent (Fig. 52.11).

In contrast to conventional TCD, simultaneous visualization of several vessels and the surrounding parenchyma allows fast and unequivocal identification of the individual arteries. Color gain should be increased until first extravasal color artifacts occur. Pulse repetition frequency can be adjusted to avoid aliasing effects. The entire course of the basal cerebral arteries should then be traced with the Doppler sample volume while observing the frequency spectrum continuously for pathologic blood flow changes. This detailed procedure is necessary because otherwise circumscribed stenoses with only minor pre- or poststenotic flow disturbances will frequently be overlooked. A representative Doppler frequency spectrum sample of each artery should then be selected and peak systolic and diastolic blood flow velocity should be documented. Careful correction of the insonation angle is recommended to avoid over- or underestimation of the real blood flow velocity. Since the measuring error increases with increasing correction angle, measurements should be performed preferably at unbowed segments of the vessel. Correction angles greater than 30° should be avoided if possible.

52.2.2. Bone window failure and ultrasound contrast agents

Temporal hyperostosis can lead to excessive ultrasound attenuation and thus to insufficient insonation conditions

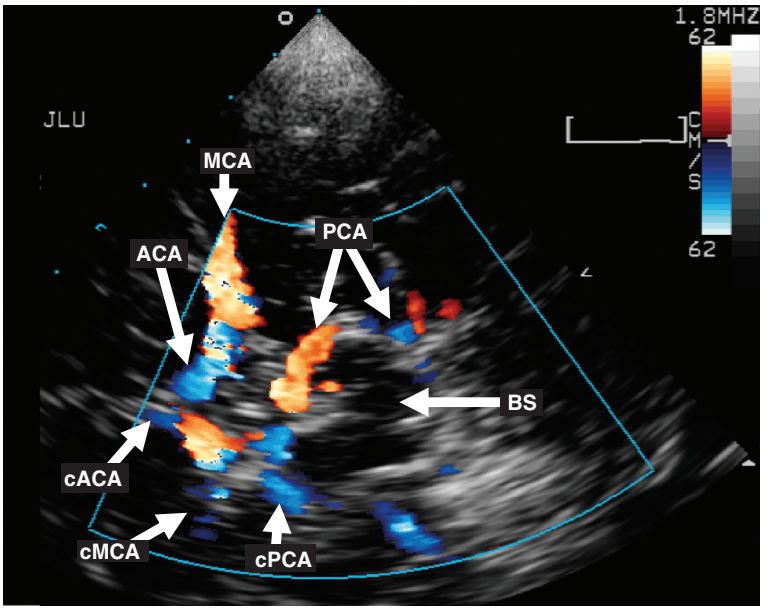

Fig. 52.10. Color coded duplex sonography: circle of Willis. BS = brainstem; MCA = middle cerebral artery; cMCA = contralateral MCA; ACA = anterior cerebral artery; cACA = contralateral ACA; PCA = posterior cerebral artery; cPCA = contralateral PCA.

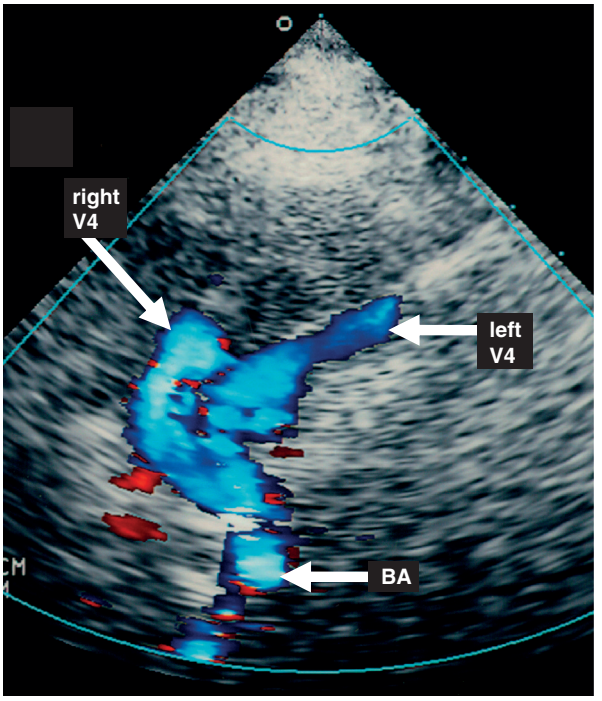

Fig. 52.11. Transnuchal insonation (normal finding). V4 = vertebral artery (V4 segment); BA = basilar artery.

through the temporal bone window. The incidence of temporal hyperostosis increases with age and is more problematic in women than in men. In representative collectives of stroke patients, window failures occur in 10–20% and make an examination impossible.

With the use of ultrasound contrast enhancers, insonation problems can be overcome in most of these patients (Fig. 52.12). Ultrasound contrast enhancers typically consist of a shell that is composed of albumin, palmitic acid, polymers, or other materials. The shells are filled with air or other gases, such as fluorocarbons. After intravenous injection, ultrasound contrast enhancers pass the pulmonary capillary bed and enter the left circulation. Because of the marked difference in acoustic impedance between gas bubbles and the surrounding blood, they strongly increase the reflectivity of blood and thus improve signal-to-noise ratio. Following contrast enhancement, most (75–93%) of the patients that were not investigatable due to hyperostosis can be examined sufficiently (Postert et al., 1999; Gerriets et al., 2002; Zunker et al., 2002; Droste et al., 2005).

52.2.3. Occlusion of intracranial arteries

Absence of color signals and the lack of a pulsed wave (pw)-Doppler spectrum are indicative of a vessel occlusion. However, in cases where a segment of the circle of Willis is not visible, it has to be considered whether this is due to vessel occlusion or Doppler signal attenuation that is, caused by temporal hyperostosis. For the differentiation of insufficient insonation conditions from true vessel occlusions, the presentability of other intracranial arteries is of importance. Thus the following diagnostic criteria for intracranial vessel occlusion have been proposed (Gerriets et al., 1999).

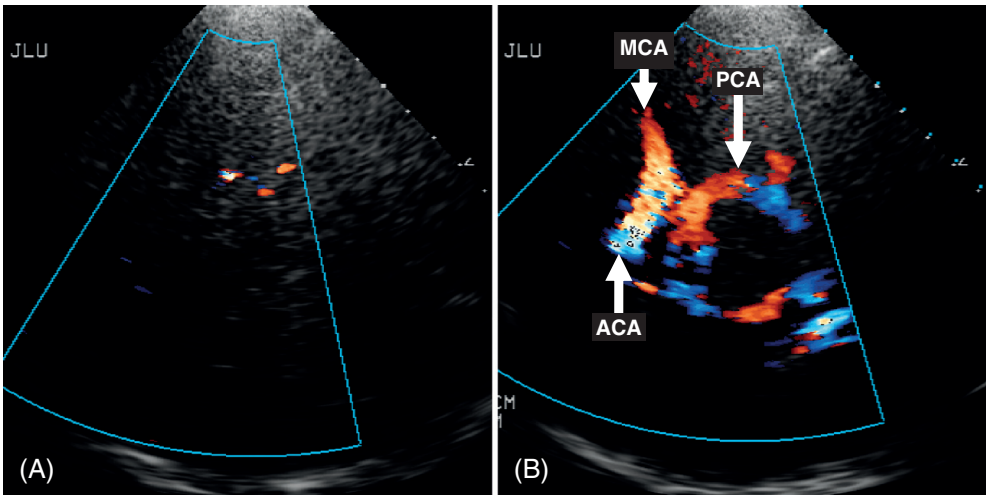

Fig. 52.12. Insufficient acoustic bone window. (A) Before injection of echocontrast enhancer the basal cerebral arteries cannot be identified. (B) Following injection of an echocontrast enhancer, the circle of Willis can be investigated (normal finding). MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery.

1. *Middle cerebral artery occlusion*. M1 segment not detectable (no color signal, no pw-Doppler spectrum) and A1 segment of the anterior cerebral artery, P1 and P2 segments of the posterior cerebral artery sufficiently assessable (Fig. 52.13); or M1 segment not detectable and the distal part of the internal carotid artery (carotid siphon) is occluded.
2. *Distal internal carotid artery occlusion*. Internal carotid artery siphon not detectable and the P1 and P2 segments of the posterior cerebral artery are adequately assessable while extracranial Doppler analysis reveals either a typical high resistance signal ("preocclusive signal") with absence of diastolic flow as a sign for a distal obstructive process or occlusion at the origin of the ipsilateral internal carotid artery.
3. *Posterior cerebral artery occlusion*. P1 and P2 segments not detectable; M1 and A1 segments adequately observable.
4. *Anterior cerebral artery occlusion*. A1 segment and ACI siphon not detectable; P1 and P2 segments of the posterior cerebral artery are adequately observable.

In all cases of doubt the application of ultrasound contrast enhancers are recommended to improve the differentiation between arterial occlusion and insufficient insonation conditions.

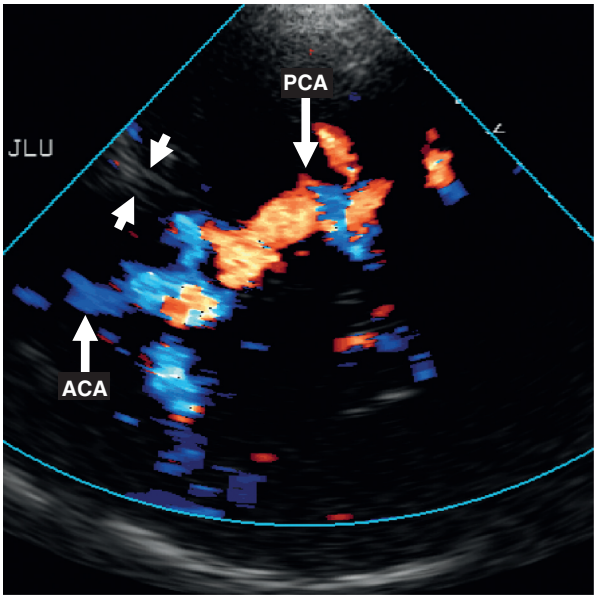

Fig. 52.13. Proximal middle cerebral artery occlusion (arrows). No Doppler signal could be detected where the middle cerebral artery should appear. The remaining arteries can clearly be identified. ACA = anterior cerebral artery; PCA = posterior cerebral artery.

52.2.4. Stenoses of intracranial arteries

Intracranial artery stenoses due to atherosclerosis are frequent findings among stroke patients. Stenoses moreover can be found in patients with subarachnoid hemorrhage (segmental spasms), large vessel vasculitis, or during the recanalization process following arterial occlusion.

Diagnostic criteria for the diagnosis of intracranial stenoses are similar to those of extracranial vessels. Aliasing in color mode can sometimes suggest the presence of a stenosis. Accurate diagnosis, however, requires Doppler spectra analysis, revealing a circumscribed acceleration of mean systolic blood flow velocity with spectral signs of disturbed flow. Prestenotic

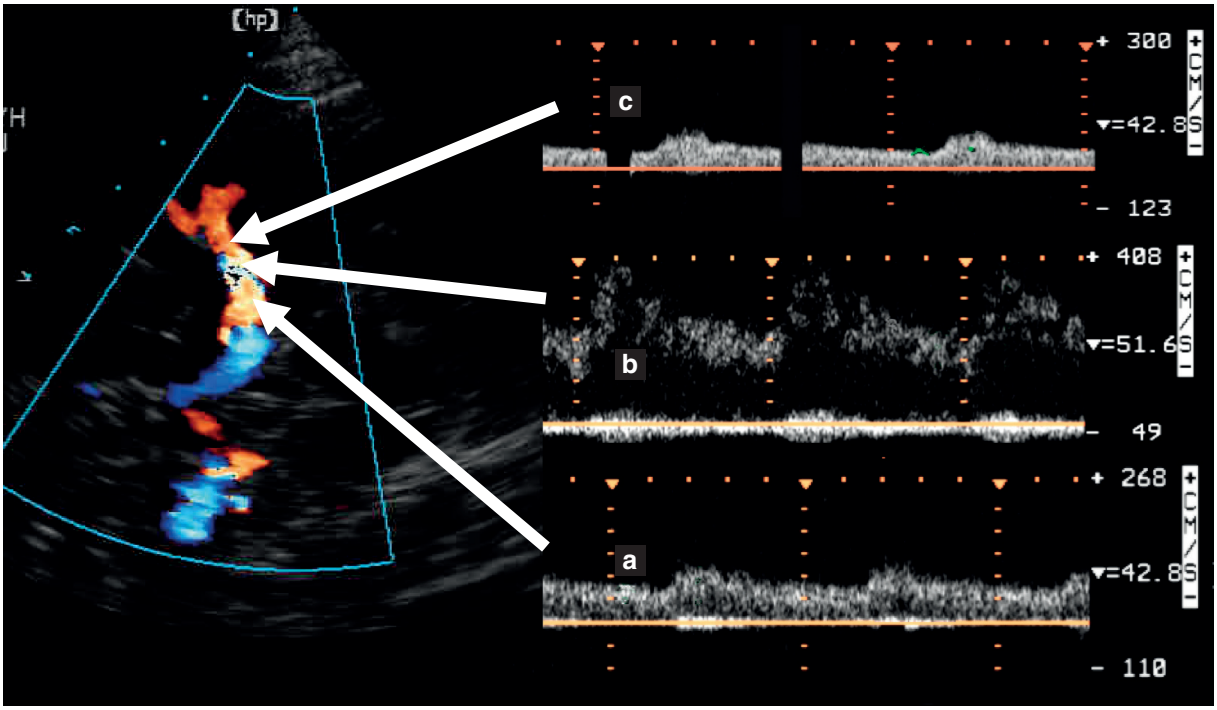

Fig. 52.14. Middle cerebral artery stenosis. (A) Color coded sonography. (B) Doppler frequency spectrum. a = prestenotic; b = intrastenotic; c = post-stenotic.

blood flow pattern can be disturbed with increased pulsatility, while post-stenotic flow frequently shows reduced pulsatility (Fig. 52.14).

Similar to extracranial internal carotid artery stenosis, the degree of luminal narrowing can be estimated by measuring peak systolic blood flow velocity. By comparing ultrasound findings with conventional angiography (the gold standard), Baumgartner et al. (1999) suggested cut-off levels for systolic peak flow velocities for intracranial stenoses greater and less than 50% (Table 52.3). It should, however, be mentioned that the quantification of luminal narrowing on conventional angiographies has some limitations, since biplanar assessment of the stenosis is often not obtainable. Nevertheless, the agreement between both methods was excellent.

52.2.5. Reliability of transcranial ultrasound

Several studies compared transcranial duplex sonography findings with magnetic resonance angiography and reported excellent agreement between both

Table 52.3

Criteria for the quantification of intracranial stenoses (Baumgartner et al., 1999)

	Cutoff-value for stenosis <50%	Pos. predictive value	Neg. predictive value
MCA	≥155 cm/s	95%	100%
ACA	≥120 cm/s	73%	100%
PCA	≥100 cm/s	100%	100%
BA	≥100 cm/s	100%	100%
VA	≥90 cm/s	100%	100%
MCA	≥220 cm/s	100%	100%
	Cutoff-value for stenosis ≥**50%**	Pos. predictive value	Neg. predictive value
ACA	≥155 cm/s	100%	100%
PCA	≥145 cm/s	100%	91%
BA	≥140 cm/s	100%	100%
VA	≥120 cm/s	100%	100%

methods (Kenton et al., 1997; Lien et al., 2001; Tang et al., 2005). Kenton et al. (1997) reported an exact agreement between MRA and TCCS for diagnosing MCA mainstem occlusion. Detection of MCA stenoses, however, was less concordant but still acceptable with a sensitivity between 82% and 83% and a specificity between 91% and 92% (Tang et al., 2005). Discrepancies in these studies, however, can be in part attributed to the limited reliability of MRA for the detection of intracranial stenoses.

The high reliability of transcranial ultrasound, however, is restricted to patients with sufficient acoustic bone windows (approximately 80% in typical stroke patient collectives). Application of ultrasound contrast agents allows sufficient examination in approximately four out of five of these patients (Gerriets et al., 1999; Postert et al., 1999; Gerriets et al., 2002).

52.2.6. Microemboli detection

Embolization of solid and gaseous materials to the cerebral circulation occurs frequently and usually asymptomatically. Emboli causing focal neurological deficits (TIA or stroke) are rare and thus represent the tip of the iceberg of subclinical embolization.

TCD allows the detection of microemboli within the cerebral arteries non-invasively. Microemboli appear within the Doppler spectrum as unidirectional, high-intensity signals of short-duration and are accompanied by a characteristic chirping sound (Fig. 52.15). These microembolic signals are caused by the passage of solid or gaseous material through the ultrasound beam. International standards for the identification of microembolic signals have been established (Markus et al., 1997; Ringelstein et al., 1998).

Since the passage of microemboli can occur infrequently, monitoring time should be sufficiently long to provide acceptable sensitivity (usually between 30 and 120 minutes). Bilateral examination can help to reduce monitoring time. Special head frames have been developed to attach the TCD probe to the temporal bone window for continuous Doppler recording. After adjusting the probe and verification of sufficient Doppler signal quality, digital data storage can be started. Evaluation should be performed off-line according to the established criteria (Ringelstein et al., 1998).

During 1 hour of emboli monitoring, microembolic signals can be detected in 4–20% of patients with asymptomatic carotid artery stenoses. This percentage increases up to 40% in patients with recently symptomatic stenoses (“smoking gun”). There is increasing evidence that the presence of microembolic signals can be regarded as a surrogate marker for symptomatic brain embolism (Molloy and Markus, 1999). Therapeutic measures that are known to reduce the risk of stroke, such as the application of acetylsalicylic acid, also drastically reduce the incidence of microembolic signals (Goertler et al., 1999). Microemboli detection has therefore been used to evaluate the efficiency of antithrombotic drugs. The combination of aspirin with clopidogrel has been shown to be more effective than aspirin alone in reducing microembolization in patients with recently symptomatic carotid stenoses (Markus et al., 2005). Furthermore, microemboli detection has been used to monitor patients during cardiac or carotid surgery. During carotid surgery, microemboli detection can reduce the complication rate and can help to evaluate the efficiency of new filter devices. Microembolic signal counts have been demonstrated to be predictive for the risk of post-operative focal cerebral ischemia (Levi et al., 1997; Ackerstaff et al., 2000; Vos et al., 2005). Microemboli detection can be regarded as a useful tool in the context of clinical trials. Applicability in the clinical routine, however, is still limited due to the lack of valid and reliable automatic microembolic signal detection devices.

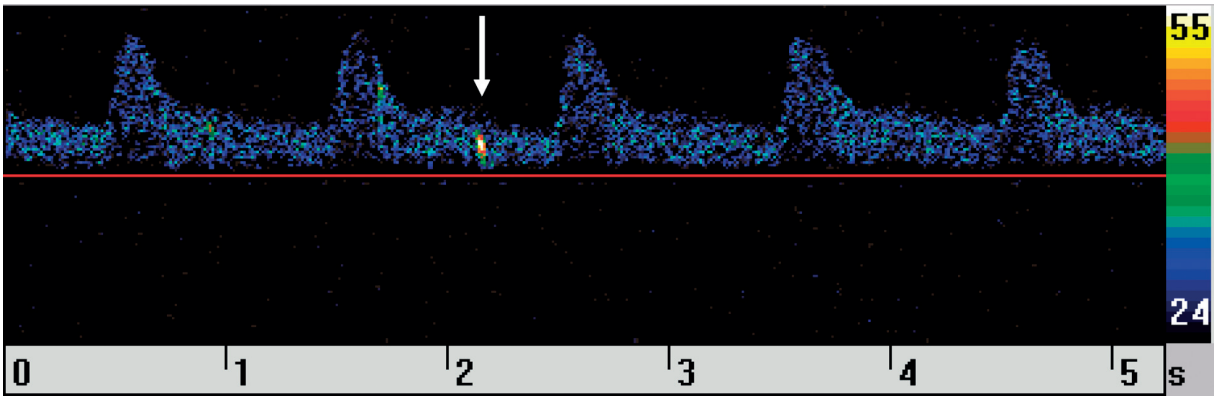

Fig. 52.15. Middle cerebral artery Doppler frequency spectrum of a patient with an 80% internal carotid artery stenosis. The microembolic signal was accompanied by a characteristic chirping sound.

52.2.7. Patent foramen ovale

Patent foramen ovale (PFO) is a frequent finding among healthy individuals with an incidence of 25–30%. Nevertheless, it represents a risk factor for embolic stroke, since it provides a pathway from the right to the left circulation. Formerly, transesophageal echocardiography (TEE) with contrast agents was the only reliable method to detect a PFO. TEE still represents the gold standard in this context, but has been replaced in many centers by TCD techniques because of its semi-invasive character.

TEE as well as TCD techniques use the same basic principle for the detection of a PFO. Gas bubbles are injected intravenously. Under physiological conditions they are trapped in the pulmonary circulation and expired. In presence of a PFO, gas bubbles can pass from the right into the systemic circulation and can thus be detected in the left ventricle (TEE) or in cerebral or other arteries (TCD).

Different procedures of PFO detection with the use of TCD and contrast agents have been evaluated and compared and international standards for the examination procedure have been fixed on a consensus meeting in 2000 (Jauss and Zanette, 2000). Two contrast agents are in use routinely:

1. Agitated saline. Nine milliliters of physiologic solution and 1 ml of air were mixed in two syringes that were connected with a stopcock. Injection has to be performed immediately after the mixing procedure. This contrast agent is cost-effective. The number and size of the gas bubbles, however, is not well controlled.
2. Echovist. This commercially available contrast agent consists of a suspension of galactose microparticles in an aqueous 20% galactose solution with adherent air bubbles with a diameter of 3 µm.

The test should be conducted with the patient in supine position. For contrast application, an 18 G intravenous line should be inserted into the right cubital vein. At least one (better both) middle cerebral artery is traced by TCD. Five seconds after bolus injection of the contrast agent the patient is ask to start Valsalva's maneuver for 10 seconds, followed by an abrupt pressure release. In this phase, a pressure gradient between the left and the right atrium is induced that permits right-to-left shunting through the PFO. Valsalva's maneuver can be regarded efficient if systolic blood flow velocity is diminished at least by one-third. The number of microembolic signals that are detected in the middle cerebral artery and the time of appearance of the first microembolic signals should be documented (Fig. 52.16). Shunting can be quantified as follows:

I: no microembolic signals; no right-to-left shunt
II: 1–10 microembolic signals detected
III: 10 microembolic signals detected (individual signals can be differentiated)
IV: curtain of microembolic signals; individual signals can not be differentiated.

If numerous microembolic signals were detected (grade III or IV), the test should be repeated without performing Valsalva's maneuver to quantify "spontaneous" right-to-left shunting.

Pulmonary shunts can also lead to right-to-left shunting and thus to a positive PFO test. Some authors suggest that the time between bolus injection and the appearance of the first microembolic signals can be used as a marker to differentiate between cardiac and pulmonary shunting, since it takes about 11 seconds for the microbubbles to reach the cerebral arteries through intracardiac shunts and about 14 seconds through intrapulmonary shunts. However, the time window between both conditions appears to be too narrow to differentiate reliably between both types of shunting. Furthermore, residual contrast agent, which can be trapped within venous valves, can be released with some delay and thus obscure the diagnostic value of appearance time.

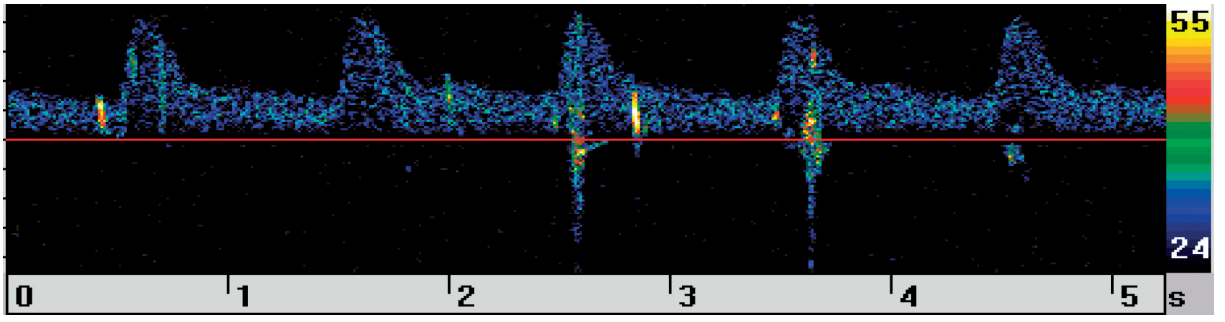

Fig. 52.16. PFO test: Multiple microembolic signals following intravenous injection of agitated saline and Valsalva's maneuver. This finding indicates a right-to-left shunt.

Ischemic stroke workup represents the most important indication for contrast TCD. In particular, juvenile stroke and so-called "cryptogenetic" stroke are major indications, although accurate workup frequently reveals conflicting potential sources of embolism (Serena et al., 1998; Anzola, 2002).

Furthermore, the presence of a PFO appears to play a role in the pathophysiology of migraine with aura, although the exact mechanism has not yet been determined (Anzola et al., 1999; Wilmshurst et al., 2000). Right-to-left shunts moreover represent risk factors for divers since they increase the risk for type II decompression sickness (Gerriets et al., 2000; Saary and Gray, 2001; Torti et al., 2004).

52.2.8. Investigation of brain parenchyma

Transcranial duplex sonography does not only provide information regarding the intracranial hemodynamics, it can also be used for imaging of the brain parenchyma. Compared to computed tomography or magnetic resonance tomography, axial and spatial resolution of ultrasound images is limited due to the low frequency that is required to penetrate the skull. Ultrasound images of the brain are also difficult to interpret and the number of anatomical structures that can clearly be identified is limited. Nevertheless, ultrasound of the brain parenchyma has a number of advantages compared to conventional imaging:

1. Ultrasound is a bedside method and thus can be applied very quickly (i.e., in the emergency room). This advantage is of particular importance for patients that are too unstable for transportation to CT scanners and thus can only be investigated bedside. It is furthermore non-invasive and inexpensive and can therefore be used for repeat examination (i.e., for monitoring of parenchymal findings).
2. Transcranial sonography can be used for the evaluation of the ventricular system. Ventricular enlargement, for instance as a result of space-occupying cerebellar stroke, can be monitored on the intensive care unit. Lateral displacement of the third ventricle, caused by "malignant" middle cerebral artery territory stroke, can be measured with high accuracy and allows the prediction of patient outcome in this life-threatening condition (Gerriets et al., 2001).
3. Transcranial ultrasound, furthermore, can be used to detect intracerebral hemorrhage (i.e., following thrombolysis) (Fig. 52.17). Positive and negative predictive value of this method has been calculated to be 0.88 and 0.96, respectively, indicating that ultrasound cannot replace computed tomography but might be useful as a screening and monitoring method (e.g., in intensive care patients) (Seidel et al., 1995). Further applications of brain parenchyma diagnostics are emerging in the field of movement disorders. Increased echogenicity of the substantia nigra has been identified as an early marker for Parkinson's disease even before onset of clinical symptoms (Sommer et al., 2004; Behnke et al., 2005).

52.3. Present status and future directions of neurosonology

After more than three decades of clinical use, ultrasound is an established method in the diagnostic

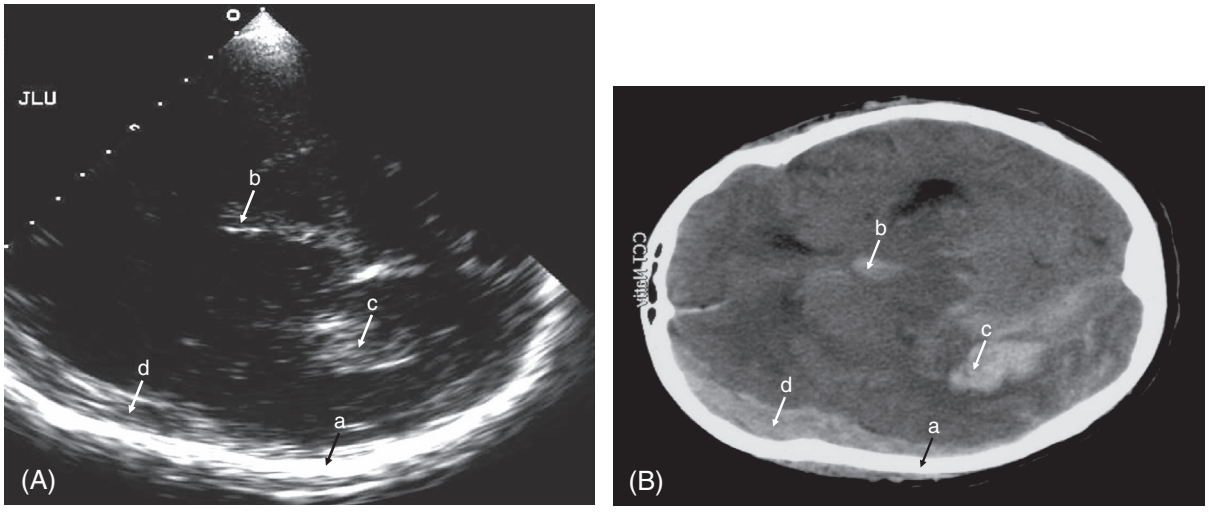

Fig. 52.17. Transcranial sonography (A) and computed tomography (B) of a comatose patient. a = contralateral skull; b = third ventricle (tamponaded with blood); c = lateral ventricle (tamponaded with blood); d = subdural hematoma.

Table 52.4

Comparison of the different imaging techniques for the evaluation of the brain supplying arteries

	MRA	CTA	DSA	Ultrasound
Reliability for the detection of arterial stenoses	+++	+++	+++	+++
Reliability for the quantification of arterial stenoses	+	++	+++	++
Reliability for the detection of arterial occlusions	+++	+++	+++	+++
Observer independency	+	++	++	−
Interpretation of images	+	++	++	+
Non-invasiveness	+++	++	−	+++
Time-efficiency	+	++	−	+++
Avoidance of ionizing radiation	+++	−	−	+++
Cost-effectiveness	+	+	−	++

workup of the intra- and extracranial arteries. It stands on an equal footing beside other non-invasive imaging techniques such as CTA or MRA, although all methods have their specific advantages and disadvantages (Table 52.4).

The invention of transcranial Doppler ultrasound in 1982, the development of transcranial duplex sonography in the early 1990s, and the introduction of ultrasound contrast agents in the mid-1990s represent important milestones in the history of neurosonology. At present, two new applications of ultrasound emerge on the horizon, which will probably lead neurosonology to new directions.

52.3.1. Perfusion imaging

Doppler imaging techniques allow quantification of blood flow within large arteries but fail to detect perfusion at the microcirculation level. Low flow velocities that are associated with parenchymal perfusion, however, can be detected with perfusion imaging using ultrasound contrast enhancers. Perfusion imaging is useful for predicting stroke recovery, for differentiating stroke pathogenesis and for monitoring therapy. Several methods, such as contrast agent imaging, contrast burst imaging, or time variance imaging are currently under evaluation. Clinical studies indicate that ultrasound perfusion imaging, as it stands now, is already sufficient to discriminate between normal and severely pathological perfusion conditions. Although applicability in a routine clinical setting cannot be recommended presently, further progress in the development of contrast agents, data processing and ultrasound emitting techniques are predictable. Thus, migration of this technique to the clinical setting is possible (Kern et al., 2004; Della Martina et al., 2005; Eyding et al., 2005).

52.3.2. Ultrasound-mediated thrombolysis

Systemic application of recombinant tissue plasmin activator (rtPA) has been approved for the treatment of acute stroke within the first 3 hours. Although there is a statistically significant improvement in functional outcome (as compared to placebo), efficiency of systemic thrombolysis is limited. In addition to hemorrhagic complications, the poor recanalization rate of approximately 50% might be accountable for the moderate efficiency. In vitro and in vivo experiments indicated that ultrasound can augment rtPA-mediated thrombolysis and improve vessel recanalization.

The first clinical trials have been conducted to enhance systemic thrombolysis. In these studies, frequency and power output were comparable to conventional "diagnostic" ultrasound applications. Alexandrov et al. (2004) demonstrated improved recanalization frequency in acute stroke patients treated with rtPA and ultrasound compared to patients that received rtPA alone. Eggers et al. (2005) likewise revealed an improved recanalization rate and even a statistically significant better functional outcome, although the small sample size ($n = 25$) limits the power of this study.

In order to improve the thrombolytic potential and the permeability of ultrasound through the skull, application of "low-frequency" ultrasound has been suggested. In the TRUMBI-study the characteristics of low-frequency ultrasound were utilized. Unfortunately this clinical trial had to be stopped prematurely because of frequent hemorrhagic complications. This important drawback necessitates further preclinical research to characterize potential side-effects of ultrasound application to the acutely ischemic brain. Nevertheless, ultrasound mediated thrombolysis appears to be a promising feature to improve acute stroke treatment in the near future and can potentially open a window for new

therapeutic ultrasound applications (Alexandrov, 2004; Alexandrov et al., 2004; Daffertshofer et al., 2005; Eggers et al., 2005).

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Chapter 53

Laboratory studies in the investigation of stroke

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53.1. Introduction

The relationship between hematological abnormalities and stroke has been extensively reported in the literature and so laboratory studies are usually performed as part of the regular etiological workup study carried out in stroke patients. Basic standard hematological and biochemical tests are routinely made as part of the guideline recommendations for the management of stroke patients (Adams et al., 2003; European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003). The prevalence of hematological disorders in patients with stroke is difficult to assess accurately. The major precipitant of brain ischemia has been found to be a hematological disorder or coagulopathy that predisposes to thrombosis in approximately 1% of all patients with ischemic stroke and up to 8% of young adults with stroke (Adams et al., 1986; Bogousslavsky et al., 1988; Hart et al., 1990; Tatlisumak and Fisher, 1996; Markus and Hambley, 1998; Castillo and Dávalos, 2001).

However, in spite of the recognition of hypercoagulable states as an ischemic stroke risk factor it is often difficult to establish a direct causal relationship as other stroke etiological factors can coexist. The percentage cited is even lower in patients with hemorrhagic stroke in whom coagulopathies have been reported to cause cerebral bleeding mainly in children (Quinones-Hinojosa et al., 2003; Chalmers, 2004; Lietz et al., 2005). Moreover, stroke itself, especially in the acute phase, as well as some of the therapies usually administered for stroke prevention (e.g., warfarin) may be responsible for abnormalities in the levels of the proteins that are analyzed in order to rule out hematological abnormalities. These factors must therefore be taken into account when considering hematological diseases as a possible cause of stroke.

Although still in the research phase, the use of serum markers released into the cerebrospinal fluid (CSF) and the peripheral blood as a result of cerebral damage secondary to stroke is becoming increasingly important for the diagnosis and prognosis of stroke. In fact, excitotoxicity markers including glutamate and GABA (Castillo et al., 1996, 1997; Serena et al., 2001) as well as inflammatory markers such as interleukins (IL), tumor necrosis factor (TNF)-α and adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cellular adhesion molecule (VCAM)-1 (Fassbender et al., 1994; Vila et al., 1999) among others have been shown to be related to ischemic lesion growth as well as to poor outcome in patients with acute ischemic stroke. Markers of endothelial basal lamina disruption such as matrix metalloproteinases (MMP) and cellular-fibronectin (c-Fn) have been shown to predict hemorrhagic transformation in patients with acute ischemic stroke both in those who receive and do not receive thrombolytic therapy (Castellanos et al., 2003, 2004a; Montaner et al., 2003). A panel of serum markers has recently been found to be useful for the diagnosis of stroke in the acute phase (Reynolds et al., 2003; Lynch et al., 2004).

The examination of the cerebrospinal fluid (CSF) is also a useful tool for the study of patients with acute stroke. CSF examination is indicated to establish the presence of subarachnoid hemorrhage and to exclude the presence of infection, immunologic disorders, and meningeal malignancies as possible causes of stroke (Fishman, 1992).

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The present chapter outlines those laboratory tests that have proved to be useful in the diagnosis of diseases associated with ischemic and hemorrhagic strokes. The utility of serum markers for the diagnosis and the prognosis of stroke as well as the usefulness of CSF analysis in stroke patients are also discussed. A detailed revision of the hematological diseases related to stroke is made in Chapter 45 and is beyond the scope of the present chapter.

53.2. Laboratory tests in stroke patients

Table 53.1 shows the basic laboratory workup that is recommended for patients with stroke (Adams et al., 2003; European Stroke Initiative Executive Committee and the EUSI writing committee, 2003). These tests provide useful information for revealing the cause of stroke (e.g., polycythemia, thrombocytosis, thrombocytopenia, leukemia, coagulopathies), ruling out stroke mimic (e.g., hypoglycemia, hyponatremia) and providing evidence of concurrent illnesses (e.g., anemia, diabetes).

When specific hematological disorders are suspected as being the cause of stroke more specific laboratory tests need to be performed in order to complete the etiological study. Table 53.2 shows a list of hematological disorders that have been related to stroke. Some of these diseases can be suspected due to abnormalities revealed in the basic laboratory workup (Table 53.3). More specific tests aimed at determining the activity of platelets as well as the levels and activity of the coagulation and fibrinolytic factors should be performed when a thrombophilic or hemophilic syndrome is suspected. Immunologic and genetic tests are necessary to rule out the presence of lupus anticoagulant and anticardiolipin antibodies as well as specific mutations related to hypercoagulability.

As most well-controlled studies suggest that the contribution of hypercoagulable states to the overall stroke risk is low, considerable controversy exists as to which patients should be tested to rule out these disorders and when. Moreover, it is not possible to interpret some of the screening tests for coagulopathies in the acute stroke phase, so the test should be performed when the patient is not in an active thrombotic state and the coagulation and fibrinolytic factors have stabilized, usually 6–8 weeks after the thrombotic event (Tohgi et al., 1990; Macik and Ortel, 1995; Tatlisumak and Fisher, 1996; Bridgen, 1997; Bushnell and Goldstein, 2000). In general, it is accepted that young patients without obvious causes of stroke and patients with a previous personal or family history of venous thrombosis should be tested for hypercoagulable states. The existence of abnormalities in routine screening laboratory tests (hemoglobin, hematocrit, platelet count or coagulation tests) should also make the clinician suspect a prothrombotic state (Hart and Kanter, 1990; Markus and Hambley, 1998; Bushnell and Goldstein, 2000; Van Cott et al., 2002).

Table 53.1

Basic laboratory tests for patients with stroke

Erythrocyte sedimentation rate	
C-reactive protein	
Hematological tests	
Cellular blood count (erythrocytes, platelets, leukocytes)	
Hemoglobin concentration	
Hematocrit levels	
Biochemistry	
	Glucose levels
	Electrolytes
	Renal and hepatic chemistry
Coagulation tests	
	Prothrombin time
	Partial thromboplastin time
	Activated partial thromboplastin time
	Fibrinogen levels

53.3. Serum markers of stroke

In the last few years, research into the pathophysiology of stroke has demonstrated that molecular mechanisms participate as mediators of cerebral injury after stroke (Kogure and Kato, 1998). The study of molecular markers has proved to be of considerable utility as the blood and CSF levels of these molecules released as a result of cerebral damage have been found to be useful in diagnosing ischemic stroke (Reynolds et al., 2003; Lynch et al., 2004) and especially in predicting the evolution of the cerebral lesion (e.g., lesion growth, and spontaneous and secondary hemorrhagic transformation) and the clinical evolution (e.g., progressing stroke and outcome) (Castillo and Rodríguez, 2004).

53.3.1. The ischemic cascade

Cerebral ischemia results in a cascade of molecular events that are triggered as a consequence of the decrease in the cerebral blood flow and the subsequent energetic failure (Fig. 53.1). This marked ATP reduction leads to the depolarization of the cellular membranes and secondary permeability abnormalities with an intracellular increase of $[Na^+]$, $[Ca^{2+}]$ and $[Cl^-]$, and an extracellular increase of $[K^+]$, which in turn results in the extracellular release of glutamate and other excitatory and inhibitory amino acids such

Table 53.2

Hematological disorders associated with stroke

I. ISCHEMIC STROKE			
1. Cellular disorders:			
	a) Myeloproliferative diseases		
		Polycythemia rubra vera	
		Essential thrombocythemia*	
	b) Sickle-cell disease		
	c) Paroxysmal nocturnal hemoglobinuria		
	d) Thrombotic thrombocytopenic purpura		
	e) Malignancy (leukemia*/ intravascular lymphoma)		
2. Disorders of coagulation/fibrin:			
	a) Congenital		
		Natural anticoagulation disorders:	
			Antithrombin III deficiency
			Protein C deficiency
			Protein S deficiency
			Factor V Leiden (activated protein C resistance)
			Prothrombin gene mutation (G20210A)
		Fibrinolytic system disorders:	
			Plasminogen deficiency
			Dysfibrinogenemia
			tPA deficiency
			PAI-1 excess
		Uncertain mechanism	
			Homocysteinemia
	(b) Acquired		
		Disseminated intravascular coagulation	
		Lupus anticoagulant/ anticardiolipin syndrome	
		Pregnancy and puerperium	
		Oral contraceptive pill	
		Paraproteinemias	
II. HEMORRHAGIC STROKE			
Disorders of coagulation			
	(a) Congenital		
		Hemophilia (A and B)	
		Von Willebrand's disease	
		Factor X deficiency	
		Prothrombin deficiency	
		Factor VII deficiency	
	(b) Acquired		
		Thrombopenia	
		Vitamin K deficiency	
		Chronic hepatopathy	
		Intravascular disseminated coagulopathy	
		Anticoagulant treatment (heparin/warfarin)	

tPA = tissue plasminogen activator; PAI = inhibitor of plasminogen activator.
*Intracerebral bleeding has also been reported.

Table 53.3

Laboratory abnormalities in diseases associated with stroke

	Erythrocytes	Platelets	Leukocytes	PT	APTT
Polycythemia rubra vera	↑↑	N/↑	N/↑	N	N
Essential thrombocythemia	N	↑↑	N	N	N
Sickle cell disease	↓	N	N	N	N
Paroxysmal nocturnal hemoglobinuria	↓	N/↓	N/↓*	N	N
Thrombotic thrombocytopenic purpura	↓	↓↓	N	N	N
Hemophilia	N	N	N	**N**	↑
Von Willebrand's disease	N	N	N	N	N/↑
Factor X deficiency	N	N	N	↑	↑
Prothrombin deficiency	N	N	N	↑	↑
Factor VII deficiency	N	N	N	↑	N
Vitamin K deficiency	N	N	N	↑	N/↑
Chronic hepatopathy	N	N	N	↑	↑
Disseminated intravascular coagulation	N	↓	N	↑	↑
Heparin treatment	N	N	N	N/↑	↑
Warfarin treatment	N	N	N	↑	N/↑

N = normal value; PT = prothrombin time; APTT = activated partial thromboplastin time.
*When the leukocyte count is decreased it is due to mild lymphopenia.

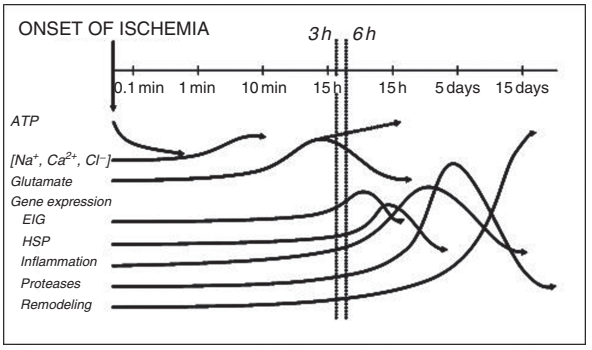

Fig. 53.1. Summary of molecular events triggered by cerebral ischemia. HSP = heat shock protein; IEG = immediate early genes.

as glycine and GABA respectively. Glutamate activates glutamate-mediated channels (NMDA and AMPA) and originates an intracellular increase of calcium. Intracellular calcium participates in the formation of free radicals through the activation of nitric oxide synthase that promotes nitric oxide formation and the subsequent synthesis of the highly toxic peroxynitrite radical and mediates apoptosis or delayed cellular death (Schmidley, 1990; Linink et al., 1993; Fisher and García, 1996; Kogure and Kogure, 1997). The intracellular increase of calcium triggers the inflammatory cascade which starts with the local expression of inflammatory cytokines including the TNF-α and the IL-1β (Liu et al., 1994; Wang et al., 1994), which in turn stimulates the release of other cytokines including IL-6 and IL-8, and chemotactic factors such as leukocyte adhesion molecules (selectines), the ICAM-1, the VCAM-1, and the platelet endothelial cellular adhesion molecule (PECAM) (Feuerstein et al., 1998). The leukocytes reaching the ischemic zone as a result of the release of chemotactic factors interact with the endothelial cells of the capillary walls resulting in the occlusion of the arteries and leading to the "no-reflow" phenomenon that does not allow the complete recovery of the CFB within the ischemic zone (Ames et al., 1968; Schmid-Schönbein et al., 1980). Moreover, leukocytes also stimulate the release of vasoconstrictor substances with secondary damage of the vascular reactivity (Härtl et al., 1996) and of proteolytic enzymes that break down the endothelial wall and permit the leakage of water and erythrocytes, which may result in brain edema and hemorrhagic transformation of the ischemic lesion, respectively (Hamann et al., 1995; Hamann et al., 1996).

Inflammatory molecules also stimulate the release of proteolytic enzymes such as matrix metalloproteinases, a group of proteolytic enzymes contributing to the rupture of the endothelial basal lamina (Romanic, 1994) and that have been related to brain edema and hemorrhagic transformation development both in experimental models of cerebral ischemia (Rosenberg et al., 1990; Hoe Heo et al., 1999) and in humans (Montaner et al., 2001; Castellanos et al., 2003).

53.3.2. Serum markers and stroke diagnosis

A rapid diagnosis of stroke is important in the clinical setting in order to increase the number of patients who

can receive an effective therapy in the appropriate time window. Thrombolytic therapy with recombinant tissue-plasminogen activator (rtPA) has proved to be the only effective treatment of ischemic stroke when administered in the first 3 hours after symptom onset (National Institutes of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995; Adams et al., 1996) and the administration of activated recombinant factor VII (rFVIIa) in the first 3 hours after onset has been found to be the only effective drug to avoid the expansion of bleeding in patients with intracerebral hemorrhage (Mayer et al., 2005a,b). Moreover, the earlier the treatment is administered, the greater the efficacy of the drug. Neuroimaging techniques are the only tools capable of differentiating between ischemic and hemorrhagic stroke and the fact that these techniques are not available in many smaller hospitals frequently results in a delay in treatment administration. New tools are therefore necessary to reduce the time between symptom onset and the administration of an effective therapy. The determination of blood markers may prove useful to diagnose stroke and to differentiate between ischemic and hemorrhagic stroke. The feasibility of developing a panel of biomarkers for the diagnosis of ischemic stroke has recently been tested. After analyzing 26 biomarkers involved in the pathogenesis of stroke including markers of glial activation and inflammation, apoptosis, myelin breakdown and peroxidation, thrombosis, and cellular injury, a model including MMP-9, vWF and VCAM provided a sensitivity and specificity of 90% for predicting stroke (defined clinically by the presence of focal neurological symptoms lasting >24 hours) (Lynch et al., 2004). In a later work including more than 50 biomarkers, the same group reported a high correlation between 5 biomarkers including protein S-100β, B-type neurotrophic growth factor (BNGF), von Willebrand factor, MMP-9 and monocyte chemotactic protein-1 (MCP-1) and the diagnosis of both ischemic and hemorrhagic stroke. In a panel algorithm in which three or more marker values above their respective cut-offs were scored as positive, these five markers provided a sensitivity of 93% and specificity of 93% for the diagnosis of ischemic stroke within the first 9 hours of symptom onset. The algorithm also allowed the diagnosis of hemorrhagic stroke within the first 6 hours of evolution with a sensitivity of 80–89% and specificity of 93% (Reynolds et al., 2003).

53.3.3. Serum markers of early neurological deterioration

Early neurological deterioration, which is considered to occur between stroke onset and the first 72 hours of evolution (Röden-Jülig, 1997), occurs in approximately one-third of patients with ischemic stroke and increases mortality and functional disability (Dávalos et al., 1990; Castillo, 1999). Several clinical and radiological factors including a previous history of diabetes mellitus and ischemic heart disease (Jorgensen et al., 1994; Dávalos et al., 1999), high and low systolic blood pressure levels (Dávalos et al., 1990; Jorgensen et al., 1994), hyperthermia (Castillo et al., 1994; Dávalos et al., 1997a), hyperglycemia (Dávalos et al., 1990; Toni et al., 1995), elevated fibrinogen levels (Dávalos et al., 1997a) and early signs of cerebral ischemia on cranial computed tomography (CT) (Toni et al, 1995; Dávalos et al., 1997a) have been found to be associated with early neurological deterioration. However, it is only partially predictable based on these data, so the participation of other factors on progressing stroke needs to be investigated.

Recent clinical and experimental research has shown that biochemical mechanisms participate as mediators of early neurological deterioration (Dávalos and Castillo, 1999). Of these, plasma glutamate levels have been found to be the strongest biochemical predictor of progressing stroke. Plasma and CSF glutamate levels have been reported to be significantly higher in patients with early neurological deterioration than in those who do not deteriorate (Castillo et al., 1997; Dávalos et al., 1997b). Glutamate concentrations >200 μmol/l in plasma (OR, 26.1; 95% CI 6.9–98.6) and >8.2 μmol/l in CSF (OR, 40.9; 95% CI 7.6–220) have been shown to be independent predictors of early neurological deterioration in the acute phase of hemispheric cerebral infarct and to classify correctly a progressing evolution with a probability of 92% and 93%, respectively (Castillo et al., 1997). A later study also confirmed the association between excitotoxicity and early neurological deterioration in patients with lacunar infarctions. In this particular group of patients, plasma glutamate concentrations >200 μmol/l and plasma GABA concentrations <240 nmol/l were reported to have a positive predictive value for neurological deterioration of 67% and 84%, respectively, and an excitotoxic index (plasma glutamate concentrations/plasma GABA concentrations) >106 correctly predicted neurological deterioration in 85% of patients with lacunar infarctions (Serena et al., 2001).

The association of glutamate levels with progressing stroke may be related to the participation of excitotoxicity in the recruitment of the penumbral zone (the tissue at risk of infarction surrounding the ischemic core) towards infarcted tissue. Different neuroimaging techniques, including positron emission tomography, diffusion/perfusion magnetic resonance imaging (MRI) and cranial CT perfusion, allow the identification of penumbral tissue in the earliest stages of cerebral ischemia and

to follow the dynamic evolution of the ischemic lesion (Schlaug et al., 1997; Heiss et al., 2004). The spread of glutamate from the ischemic core to the periphery of the ischemic lesion may induce irreversible injury in the penumbra. Glutamate has in fact been shown to be a mediator in the occurrence of peri-infarct depolarizations originating at the infarcted core and propagating towards the periphery of the lesion with the result of an increase in the infarcted volume (Hossman, 1996). In experimental studies, a correlation between the number of peri-infarct depolarizations and infarct volume has been found (Mies et al., 1993, 1994) and the pharmacological suppression of peri-infarct depolarizations by glutamate and glycine antagonists has been shown to reduce infarct volume (Gill et al., 1992; Tatlisumak et al., 1998). Moreover, in a clinical setting, a high correlation between glutamate levels and infarction volume has been found in patients with acute ischemic stroke (Castillo et al., 1996) as well as a strong association between glutamate levels on admission and diffusion-weighted imaging lesion growth in patients with acute hemispheric infarction (Castellanos et al., 2004b). These peri-infarct depolarizations probably result in ischemic enlargement by increasing the energetic demands within an already energetically compromised tissue due to the low cerebral blood flow in the penumbral zone.

Iron-mediated free radical generation also plays an important role as a mediator of progressing stroke. Plasma and CSF ferritin concentrations have been shown to be significantly higher within the first 24 hours of evolution in patients with subsequent early neurological deterioration, larger infarct volumes and poor outcome at 1 month (Dávalos et al., 1994, 2000). Plasma ferritin concentrations >275 ng/ml and CSF ferritin concentrations >11 ng/ml have been found to be independently associated with early neurological deterioration in patients with acute hemispheric infarction (Dávalos et al., 2000). A positive correlation has been reported between ferritin concentrations and glutamate and inflammatory molecule levels in both experimental (Castellanos et al., 2002a) and clinical studies (Dávalos et al., 2000) so enhanced iron-mediated excitotoxic and inflammatory mechanisms might explain the association between ferritin concentrations and progressing stroke. Nitric oxide, which also participates in free radical generation, has also been reported to mediate early neurological deterioration. The levels of nitric oxide metabolites (NO-m) in CSF are significantly higher in patients with progressing stroke. CSF NO-m concentrations >5 μmol/ml independently predicted early neurological deterioration (OR 5.7; 95% CI 1.2–27.4) in patients with acute ischemic stroke even after adjustment for CSF glutamate levels (Castillo et al., 2000).

Inflammatory mechanisms also play an important role in the progression of cerebral ischemia. High IL-6 concentrations in plasma and CSF have been associated with larger infarct volume, neurological deterioration, and poor outcome in patients with acute ischemic stroke (Fassbender et al., 1994; Tarkowski et al., 1995; Elneihoum et al., 1996; Vila et al., 1999, 2000; Castillo and Dávalos, 2001). Plasma IL-6 concentrations >21.5 pg/ml and CSF IL-6 concentrations >6.3 pg/ml have been found to be independent predictors of early neurological deterioration (Vila et al., 2000). In patients with lacunar infarctions in particular, plasma TNF-α concentrations >14 pg/ml and ICAM-1 >208 pg/ml have been shown to be associated with early neurological deterioration and poor outcome at 3 months even after adjustment for plasma glutamate and GABA concentrations (Castellanos et al., 2002b). Significantly lower plasma concentrations of IL-10, an anti-inflammatory cytokine, has also been reported to be independently associated with early neurological deterioration in patients with acute ischemic stroke (Vila et al., 2003). As mentioned above, cytokines and adhesion molecules facilitate leukocyte adherence and their migration from capillaries into the brain (Pozzilli et al., 1985; Akopov et al., 1996) resulting in subsequent microvessel occlusion and the progressive reduction in blood flow that might result in cell death and an increase in infarct volume (Feuerstein et al., 1998). The administration of anti-adhesion molecules has been shown to reduce infarct volume (Chen et al., 1994) and the administration of IL-1β and TNF-α antagonists results in neuroprotection in experimental models of cerebral ischemia (Relton and Rothwell, 1992; Carlson et al., 1999) (Fig. 53.2).

53.3.4. Serum markers of final infarct volume

Several biochemical markers have been shown to be related to the final infarct volume. A significant correlation has been reported between plasma levels of glutamate and IL-6 at admission and the final infarct volume in patients with acute hemispheric infarction (Castillo et al., 1996; Vila et al., 2000; Castellanos et al., 2004b). In a clinical study including 122 patients with acute hemispheric infarction, glutamate levels were found to be the only independent predictor of diffusion-weighted image ischemic lesion growth between admission and 72 hours of evolution, after adjusting for other inflammatory markers including IL-6 levels and other neurotransmitter amino acids including GABA and L-arginine levels (Castellanos et al., 2004b).

Biomarkers of endothelial damage have also been found to be predictors of infarct lesion growth and final infarct volume. There is a high association

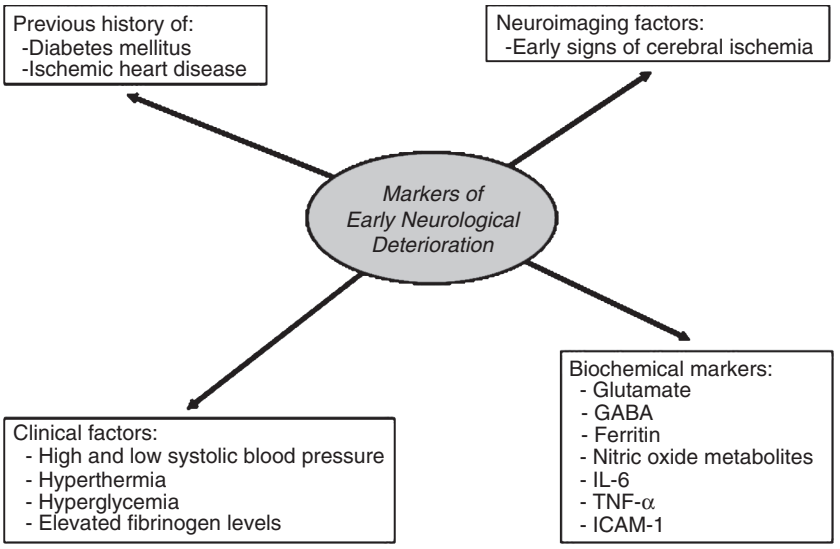

Fig. 53.2. Neuroimaging, clinical, biochemical and vascular risk factors associated with early neurological deterioration. IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; ICAM-1: intercellular adhesion molecule-1.

between plasma MMP-9 levels and final infarct volume (Castellanos et al., 2004c; Rosell et al., 2005) and the levels of MMP-9 and MMP-13 have also been reported to be independent predictors of DWI lesion volume increase in human ischemic stroke (Rosell et al., 2005). Plasma concentrations of the astroglial protein S100β correlate with the final extent of tissue damage and neurological outcome in patients with acute ischemic stroke (Missier et al., 1997; Foerch et al., 2005).

53.3.5. Serum markers of malignant middle cerebral artery infarction

Malignant middle cerebral artery infarction is a life-threatening complication mainly related to the development of massive brain edema. As only aggressive treatment including early hemicraniectomy and hypothermia has been reported to be effective (Schwab et al., 1998), it is important to find predictors that might indicate to the clinician which patients are at risk of developing this complication and therefore likely to benefit from the appropriate treatment within the effective therapeutic window. As brain edema after cerebral ischemia seems to be due to the lack of integrity of the endothelial basal membrane, which is secondary to the release of proteolytic enzymes, biochemical markers of endothelial damage may provide useful information for the prediction of malignant middle cerebral artery infarction. In fact, baseline MMP-9 and c-Fn levels have been found to be significantly higher in patients who develop malignant middle cerebral artery infarction. Plasma MMP-9 concentrations $\geq$140 ng/ml predicted the development of malignant middle cerebral artery with a sensitivity of 64%, specificity of 88%, PPV of 85%, and NPV of 69% whereas the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of plasma c-Fn $\geq$16.6 μg/ml for the prediction of malignant middle cerebral artery infarction were 90%, 100%, 100%, and 90%, respectively (Serena et al., 2005).

53.3.6. Serum markers of hemorrhagic transformation of the ischemic lesion

Although hemorrhagic transformation after ischemic stroke may occur as part of the natural evolution of the ischemic lesion, the use of anticoagulants and especially the use of thrombolytic therapy increases the risk of this complication and often precludes the use of thrombolytic treatment in clinical practice (NINDS rtPA Stroke Study Group, 1997). As thrombolytic therapy with rtPA has been proved to be the only effective therapy in patients with acute ischemic stroke, the search for biomarkers that might be useful to predict the development of hemorrhagic transformation, especially in patients who are candidates for thrombolytic treatment, is becoming of critical importance.

The loss of the integrity of the endothelial basal lamina seems to be the primary cause of hemorrhage after cerebral ischemia (Hamann et al., 1996). The activation of MMP after cerebral ischemia appears to play a major role in basal lamina degradation and secondary hemorrhagic transformation of the ischemic area (Rosenberg et al., 1996; Clark et al., 1997; Rosenberg et al., 1998; Gasche et al., 1999; Hoe Heo et al., 1999). It has been shown that the antigens of the basal lamina components

such as laminin, collagen IV, and fibronectin disappear during experimental focal cerebral ischemia (Hamann et al., 1995) and this effect has been associated with cerebral bleeding after middle cerebral artery occlusion in primates (Hamann et al., 1996).

Clinical studies have demonstrated the association between high levels of MMP-9 and the risk of developing hemorrhagic transformation in patients with acute ischemic stroke who have (Montaner et al., 2003) and have not (Castellanos et al., 2003) received rtPA. Plasma MMP-9 levels $\geq$140 ng/ml were found to independently predict the development of any type of hemorrhagic transformation in a large and non-selected group of patients with ischemic stroke (OR 12; 95% CI 3–51) with a sensitivity of 87%, specificity of 90%, positive predictive value of 61%, and negative predictive value of 97% (Castellanos et al., 2003). In a selected group of patients with cardio-embolic stroke who received thrombolytic treatment, plasma MMP-9 levels were also found to independently predict hemorrhagic transformation development (OR 9.62; 95% CI 1–70.26). In this group of patients, plasma MMP-9 levels $\geq$191.3 ng/ml predicted the development of parenchymal hemorrhage with a sensitivity of 100%, specificity of 78%, positive predictive value of 67%, and negative predictive value of 100% (Montaner et al., 2003).

Plasma levels of c-Fn have also been found to predict hemorrhagic transformation in patients who receive rtPA treatment. As c-Fn is mainly located at the vascular endothelium it is likely that the levels of this protein provide a more accurate reflection of the endothelial disruption responsible for the hemorrhagic transformation of the ischemic lesions. Plasma c-Fn and MMP-9 levels at admission were independent predictors of hemorrhagic transformation development in patients who received rtPA treatment (OR 2.1, 95% CI 1.3–3.3; and OR 1.1, 95% CI 0.9–1.3, respectively). Plasma c-Fn levels $\geq$3.6 μg/ml were found to predict the development of hemorrhagic transformation type-2 and parenchymal hemorrhage with a sensitivity of 100%, specificity of 96%, positive predictive value of 44%, and negative predictive value of 100% whereas the sensitivity, specificity, positive predictive value and negative predictive value of plasma MMP-9 levels $\geq$140 ng/ml for the same types of hemorrhagic transformation were 81%, 88%, 41% and 98% (Castellanos et al., 2004a).

The levels of endogenous fibrinolytic inhibitors have also been reported to be associated with the development of hemorrhagic transformation in patients who have received thrombolytic treatment. Plasma PAI-1 levels were shown to be significantly lower and thrombin-activated fibrinolysis inhibitor (TAFI) levels significantly higher in patients with symptomatic hemorrhage after rtPA treatment. PAI-1 levels >180% and TAFI levels <21.4 ng/ml were independent predictors of symptomatic hemorrhagic transformation (OR 12.9, 95% CI 1.41–118.8; and OR 12.75, 95% CI 1.17–139.2, respectively). The combination of plasma PAI-1 levels >180% and TAFI levels <21.4 ng/ml predicted the development of symptomatic hemorrhagic transformation after rtPA administration with a sensitivity of 75%, specificity of 97.6%, positive predictive value of 75%, and negative predictive value of 97.6% (Ribo et al., 2004b).

53.3.7. Serum markers of arterial recanalization

It is accepted that the benefit of thrombolytic therapy depends on whether the recanalization of the occluded artery is achieved so allowing for the early reperfusion of the ischemic brain. However, recanalization is observed in less than half of the treated patients (Katzan and Furlan, 2001) and so other factors must come into play in the dissolution of the clot. The activity of the fibrinolytic and coagulation systems at the time the arterial occlusion occurs may at least in part be responsible for the high or low rate of arterial recanalization when the thrombolytic drug is administered.

In a clinical study which included 44 patients with middle cerebral artery occlusion who received thrombolytic treatment with rtPA, the levels of the antigenic PAI-1 were significantly lower in patients who had recanalization after rtPA administration. PAI-1 levels >34 ng/ml were found to be the only independent predictor of resistance to thrombolysis. There were no differences in the levels of other markers of endogenous fibrinolytic activity including the functional thrombin activatable fibrinolysis inhibitor (fTAFI) and homocysteine (Ribo et al., 2004a).

With the hypothesis that high fibrinolytic activity and/or low procoagulant activity at the time of arterial occlusion could improve arterial recanalization after rtPA administration, plasma markers of coagulation (fibrinogen, prothrombin fragments 1 and 2, factor XIII, and factor VII) and fibrinolysis (α_2-antiplasmin, functional PAI-1, and fTAFI) were analyzed in 63 patients with middle cerebral artery occlusion who received rtPA. Patients who showed middle cerebral artery recanalization had significantly lower plasma levels of α_2-antiplasmin and fTAFI at admission, although the levels of α_2-antiplasmin was the only predictive variable of recanalization after adjusting for potential confounders (OR 0.95, 95% CI 0.91–0.99). Levels of α_2-antiplasmin of 85% predicted recanalization with a sensitivity of 25% and a specificity of 85% (Martí-Fábregas et al., 2005).

53.3.8. Serum markers of progression of intracranial atherosclerosis

C-reactive protein is an indicator of systemic inflammation and a marker of the inflammatory activity underlying atherothrombotic disease. Plasma C-reactive protein levels have been found to increase in patients after acute ischemic stroke (Canova et al., 1999; Muir et al., 1999; Di Napoli and Papa, 2002) and high levels significantly predict the risk of future ischemic stroke independently of other vascular risk factors. Data from the Framingham study that included a total of 1,462 patients who were followed for up to 14 years demonstrated that the risk of having a first ischemic stroke or transient ischemic attack (TIA) significantly increased with each increasing quartile of baseline C-reactive protein concentrations. The relative risk of having a first ischemic stroke/TIA increased by almost two times in those patients with plasma C-reactive protein levels in the third quartile ($\geq$3 μg/ml) compared to those whose C-reactive protein levels were in the first quartile (Rost et al., 2001). Moreover, plasma C-reactive protein levels have also been shown to predict future ischemic events after a first TIA or ischemic stroke in patients with intracranial large-artery occlusive disease. In a clinical study including 71 patients with intracranial large-artery occlusive disease, 13 patients (18.3%) had a new ischemic event in the follow-up period. Plasma C-reactive protein concentrations >1.41 mg/dl independently predicted further intracranial large-artery occlusive disease-related ischemic events (hazard ratio 30.67; 95% CI 3.6–255.5) with a sensitivity of 85.7% and a specificity of 87.5%, which suggests that inflammation plays an important role in the progression and destabilization of intracranial large-artery atherosclerotic plaques (Arenillas et al., 2003). In fact, C-reactive protein induces various inflammatory changes in endothelial and smooth muscle cells that have been associated with atherosclerosis (Verma and Yeh, 2003). C-reactive protein binds to oxidized low-density lipoproteins (LDL) forming a complex that is opsonized by macrophages and results in the generation of foam cells. It also induces the expression of inflammatory mediators such as E-selectin, VCAM-1, and ICAM-1 by endothelial cells, and is associated with endothelial cell dysfunction and the progression of atherosclerosis, possibly by decreasing nitric oxide synthesis. Moreover, C-reactive protein is able to sensitize endothelial cells to being destroyed by cytotoxic $CD4^+$ T cells and to facilitate thrombogenesis through stimulation of the procoagulant tissue factor biosynthesis by macrophages (Di Napoli et al., 2005).

Soluble CD40L, a potent immunomodulator that is expressed on endothelial cells, smooth muscle cells, mononuclear phagocytes and platelets, also seems to participate in the initiation and progression of atherosclerotic lesions. By binding to its receptor CD40, sCD40L triggers the expression of several inflammatory mediators including TNF-α, IL-1, IL-6, IL-12, ICAM-1, VCAM-1, MMPs and tissue factor. The inhibition of the CD40/CD40L binding results in a decrease in the progression of the atheroma and an increase in plaque stabilization (Lutgens et al., 2000; Schönbeck et al., 2000). In a group of 130 healthy women who were followed for 4 years, high levels of sCD40L were found to be predictive of the development of cardiovascular events, including myocardial infarction, stroke, or cardiovascular death. Women with sCD40L levels >3.71 ng/ml had a significantly increased relative risk of developing future cardiovascular events (RR 3.3; 95% CI 1.2–8.6) (Schönbeck et al., 2001).

53.3.9. Serum markers of prognosis of intracerebral hemorrhage

Research into the pathophysiological mechanisms accompanying intracerebral hemorrhage has mainly focused on the association between serum markers and early hematoma growth and the neuronal injury surrounding the bleeding lesion, commonly referred to as the perihematoma hypodensity rim. Early hematoma growth due to continuous bleeding occurring especially within the first few hours of intracerebral hemorrhage onset has been shown to cause early neurological deterioration due to an increase in the hemorrhage volume with secondary brain herniation (Brott et al., 1997); perihematoma hypodensity rim has also been reported to be related to early neurological deterioration and may be responsible for delayed damage and late deterioration (Mayer et al., 1994a).

53.3.9.1. Serum markers of the perihematomal hypodensity rim

Several mechanisms seem to be involved in edema formation after spontaneous intracerebral hemorrhage. These include an early phase occurring in the first hours of evolution of bleeding and involves hydrostatic pressure and clot retraction with secondary expulsion of serum from the clot that contributes to the creation of a low cerebral blood flow zone around the bleeding; a second phase which occurs in the first 2 days of evolution and involves the activation of the coagulation cascade and thrombin production, which stimulates excitotoxicity, inflammation and blood–brain barrier breakdown; and a third phase after 3 days of evolution which is mainly mediated by red blood cell lysis and hemoglobin-induced neuronal toxicity. The activation of the cascade complement also participates in the

second and third phase of perihematoma hypodensity rim development (Xi et al., 2002).

Pro-inflammatory molecules released as a result of the activation of thrombin (Lee et al., 1997; Xi et al., 1998, 2001) and endothelial damage markers related to blood–brain barrier disruption (Rosenberg and Navratil, 1997) have already been reported as being associated with perihematoma hypodensity rim development. There is a significant correlation between high plasma levels of IL-6, TNF-α, and ICAM-1 and the volume of perihematoma hypodensity developed in the third to fourth days of evolution in intracerebral hemorrhage patients (Castillo et al., 2002). The volume of the perihematoma hypodensity rim also correlated with glutamate levels. High glutamate levels are associated with poor neurological outcome and increased volume of the residual cavity after intracerebral hemorrhage (Castillo et al., 2002). MMP-9 levels positively correlate with the volume of the perihematoma hypodensity rim as well as with its enlargement within the first 48 hours of evolution (Abilleira et al., 2003; Álvarez-Sabín et al., 2004). Significantly higher MMP-9 levels were found in patients with neurological worsening (Abilleira et al., 2003) whereas MMP-3 levels were associated with mortality at 3 months in patients with intracerebral hemorrhage (Álvarez-Sabín et al., 2004). In experimental models of cerebral ischemia, the inhibition of MMP has been reported as decreasing the perihematoma hypodensity rim (Rosenberg and Navratil, 1997).

53.3.9.2. Serum markers of early hematoma growth

Early hematoma growth has been related to the occurrence of multifocal bleeding in the periphery of the clot formed after intracerebral hemorrhage development (Mayer et al., 1994b). As mentioned above, in the periphery of the bleeding the activation of the coagulation cascade with the release of thrombin leads to an increase in the inflammatory response and MMP, which contributes to blood–brain barrier rupture with the subsequent leakage of erythrocytes and a secondary increase in the volume of the hematoma. Higher levels of inflammatory molecules including IL-6 and TNF-α as well as markers of endothelial damage including MMP-9 and c-Fn have been found in patients with early hematoma growth (Silva et al., 2005). IL-6 levels >24 pg/ml and c-Fn levels >6 μg/ml were independent predictors of early hematoma growth (OR 16; 95% CI 2.3–119 and OR 92; 95% CI 22–381, respectively). The levels of c-Fn were found to be the only predictive factor of relevant early hematoma growth, considered as an increase of >33% of the volume of the hematoma compared with the volume at admission (Silva et al., 2005) (Fig. 53.3).

53.4. CSF and stroke

Lumbar puncture has been relegated to a minor role in the diagnosis of stroke mainly due to the availability of high-quality brain imaging. However, as mentioned in

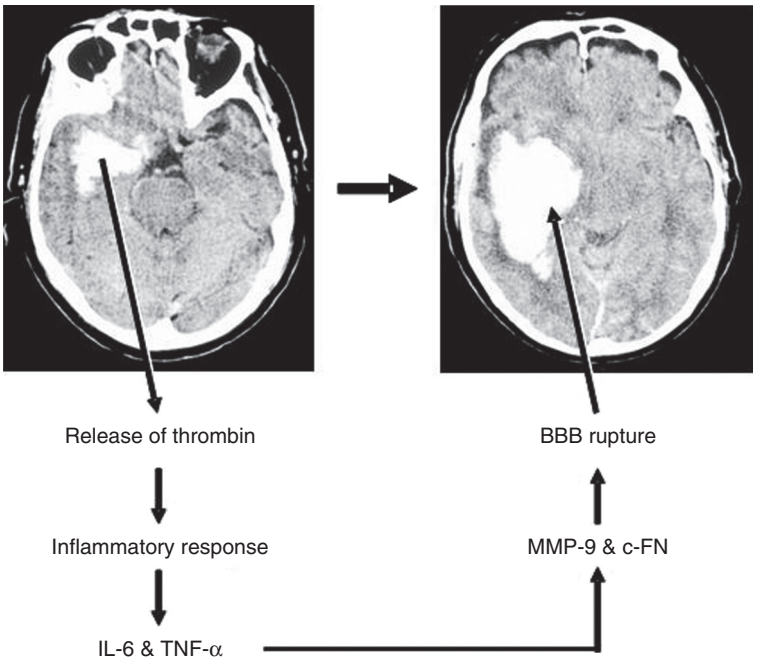

Fig. 53.3. The activation of the coagulation cascade with the release of thrombin in the periphery of the bleeding increases the inflammatory response and the release of matrix metalloproteinases (MMP) and cellular fibronectin (c-Fn) contributing to blood–brain barrier rupture. The erythrocytes then leak and the volume of the hematoma increases.

the introduction of this chapter, the study of CSF is distinctive for the identification of subarachnoid hemorrhage and lumbar puncture must be performed when neuroimaging tests do not demonstrate the existence of blood in the subarachnoid space but subarachnoid hemorrhage is suspected from the clinical point of view. In this case, CSF usually detects blood, high protein levels, and positive xantocromia provided that it is obtained at least 6 hours after the onset of bleeding (Lee et al., 1975).

CSF examination is also crucial to ruling out infectious diseases that may cause cerebral vasculitis and secondary cerebrovascular diseases. Infectious causes of vasculitis include meningovascular syphilis, tuberculous meningitis, and other bacterial and fungeal meningitis, including human immunodeficiency virus infection. Besides the clinical suspicion of these disorders, CSF examination is very useful in the diagnosis of these diseases. Hyperleukocytosis and low levels of glucose are frequently found. The culture of the CSF may demonstrate the presence of the pathogen especially in bacterial infections (Weststrate et al., 1996; Zalduondo et al., 1996; Qureshi et al., 1997; Ries et al., 1997; Hsu and Kim, 1998).

Lumbar puncture may also be useful for the diagnosis of immunologic/inflammatory diseases such as Behçet's disease, isolated angiitis of the central nervous system, and Susac's syndrome among others. In Behçet's disease, an inflammatory condition of unknown etiology that may present as stroke-like episodes (Iraguli and Maravi, 1986), CSF examination usually demonstrates a predominantly lymphocytic moderate pleocytosis as well as increased proteins, usually less than 100 mg/dl. In the isolated angiitis of the central nervous system the most consistent CSF abnormality is an increase in the protein concentration (usually $>$100 mg/dl) although CSF may occasionally be normal. In Susac's syndrome or retinocochleocerebral vasculopathy, CSF examination may demonstrate a mild pleocytosis (predominantly lymphocytic) and increased protein concentration (Elkind and Mohr, 2004). CSF is also useful in the diagnosis of cerebral venous thrombosis as the CSF is rarely (10%) entirely normal in this pathology. An elevated protein content, the presence of red blood cells (in two-thirds of cases), and pleocytosis (in one-third) is frequently observed (Bousser and Barnett, 2004).

Finally, CSF abnormalities can be found in patients with cancer-related stroke. Approximately 15% of patients with cancer have cerebrovascular disease, with the frequency of cerebral infarctions being similar to that of cerebral hemorrhage. Mechanisms related to cerebral ischemia in patients with cancer include atherosclerosis, non-bacterial thrombotic endocarditis, disseminated intravascular coagulation, infection, tumor embolism, and cerebral venous thrombosis. The most usual mechanism for cerebral hemorrhage is intratumoral hemorrhage (Arboix, 2000). An increase in the cerebral arterial or venous thrombosis can complicate cancer due to the higher activation of the coagulation system related to the cancer. The metastatic infiltration of the leptomeninges causes CSF abnormalities, which mainly include hyperleukocytosis. The existence of malignant meningeal infiltration is confirmed through cytological studies revealing the presence of malignant cells in the CSF (Rogers, 2003).

53.5. Conclusions

Although still in the research phase, the usefulness of biomarkers as predictors of stroke lesion evolution is becoming increasingly important as it may be valuable in guiding patient management decisions as well as in designing future clinical trials to test new therapeutic interventions. Based on the more consistent available data it seems that the progression of ischemic lesions can be prevented by the blocking of excitotoxic and inflammatory mechanisms in particular. Biomarkers of endothelial basal membrane disruption, especially c-Fn and MMP-9, have been shown to accurately predict the development of malignant middle cerebral artery infarction as well as the hemorrhagic transformation of ischemic lesions both in patients who have and have not received thrombolytic treatment. The data about the predictive capacity of antigenic PAI-1 and α_2-antiplasmin on arterial recanalization after thrombolytic treatment support the hypothesis that the efficacy of rtPA in achieving the recanalization of the occluded artery seems to be related to the balance between endogenous fibrinolytic and coagulation systems. Finally, the progression of atherosclerosis and the possibility of ischemic stroke recurrence may be predicted by analyzing CPR and sCD40L levels. Further studies are still necessary to validate the use of biomarkers in the diagnosis of stroke as well as their utility in the management of stroke patients.

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Chapter 54

Imaging functional recovery from stroke

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Stroke remains a major source of human morbidity and mortality. Stroke is the third leading cause of death in the Western countries, with approximately 1 in 15 deaths attributable to stroke, and the second leading cause worldwide. Approximately 85% of patients survive an acute stroke, living an average of 7 years thereafter. Most are left with significant disability (Gresham et al., 1995; Rathore et al., 2002; Kugler et al., 2003), reducing activities and participation.

Stroke is most frequently caused by an ischemic infarct due to thrombo-embolic cerebral artery occlusion and can therefore affect all aspects of brain function. The nature and severity of post-stroke deficits vary widely. Over the weeks and months following a brain infarction, most patients do show some spontaneous improvement in those behaviors affected by stroke (Kertesz and McCabe, 1977; Hier et al., 1983; Duncan et al., 1992). However, this recovery is highly variable and generally incomplete. As a result, stroke is the leading cause of adult disability in the USA and many other countries.

Increasing investigation has explored the neurobiology of spontaneous post-stroke recovery in part because of the hope to use this information to develop strategies to improve patient outcomes. More recently studies have examined the brain events underlying experimentally derived post-stroke gains. Most studies of stroke recovery have focused on recovery of motor or language function, two domains commonly affected by stroke (Gresham et al., 1995). A number of brain mapping techniques has been used to investigate stroke recovery, each with its relative strengths. Functional magnetic resonance imaging (fMRI) has been the tool for many of these given relative safety and accessibility of MRI machines, as well as its good temporal and excellent spatial resolution. Positron emission tomography (PET) scanning was the first method employed for the study of recovery from stroke. It capitalizes on tracer technology and can measure many aspects of brain physiology. However, PET uses radioactive tracers, has poor temporal resolution, and is generally less accessible. The activation studies using PET or MRI can reveal the brain areas participating in a certain function. They fail, however, to demonstrate the specificity and functional relevance of the cerebral activation areas. Thus, other physiological methods have been applied to address these questions. They include transcranial magnetic stimulation (TMS), which allows non-invasive stimulation of the cerebral cortex for a number of different purposes. It has been used to investigate the functionality of the corticospinal motor output system, to study changes in cortical excitability following brain lesions including stroke, and to interfere with brain function by introducing so-called virtual brain lesions (Jahanshahi and Rothwell, 2000). The current chapter is focused on recovery of motor function, one of the major sources of disability in stroke patients. However, findings in motor recovery overlap substantially with investigations of recovery in other brain systems such as language (Baron et al., 2004).

The long-term goal of many studies, to better understand post-stroke reorganization of brain function in order to improve patient outcomes, might be realized by better prediction of outcomes, patient triage to incipient restorative therapies, defining duration and intensity of restorative therapy, and measuring treatment effects. A number of restorative interventions are under study, including cell-based approaches, selective serotonin reuptake inhibitors, catecholaminergics, brain stimulation,

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robotic and other device-based interventions, mental imagery-based protocols, and constraint-induced and other intensive physical therapy regimens—though currently none is approved for enhancing outcome after CNS injury such as stroke. The maximum value of functional neuroimaging methods such as fMRI will be appreciated in the current context when applied in association with an established restorative intervention.

54.1. The biological consequences of stroke

A number of changes arise in the brain over the weeks following a stroke. These have been described at multiple levels in experimental models of stroke in laboratory animals. Cellular and molecular studies in animals undergoing an experimental unilateral infarct have characterized ion and neurotransmitter changes, changes in cortical excitability, inflammation, angiogenesis, neurogenesis, synaptogenesis, and cellular growth, many of which evolve bilaterally, during the days to weeks that follow a unilateral insult (Dirnagl et al., 1999). A body of evidence suggests that many of these events contribute to spontaneous recovery of function after a stroke (Cramer and Chopp, 2000).

Furthermore, exogenous interventions have been found that amplify these molecular events and simultaneously improve behavioral outcome. Examples include amphetamine (Stroemer et al., 1998), growth factors (Kawamata et al., 1997; Ren et al., 2000), cellular therapies (Chen et al., 2003; Mahmood et al., 2004), brain stimulation (Adkins-Muir and Jones, 2003; Kleim et al., 2003; Plautz et al., 2003), increased environmental complexity (Johansson and Ohlsson, 1996; Johansson and Belichenko, 2002), and increased physical activity level (Jones et al., 1999). There are therefore discrete molecular brain events that arise days to weeks after an infarct. These events likely underlie or substantially contribute to spontaneous recovery and can be therapeutically augmented in association with improved behavioral outcome in animals.

However, translating preclinical restorative findings into improved therapeutics for human stroke patients is hampered by difficulty in measuring these cellular-molecular events in human patients, among whom brain tissue is uncommonly available for examination. In some cases, functional neuroimaging can provide insights into these measures (Table 54.1).

Furthermore, human brain imaging studies are important because of the limitations of animal models in this context (Cramer, 2003). For example, rodent studies are of limited value because these creatures are quadrupeds with vastly different brain organization from humans, such as relatively large size of basal ganglia compared to white matter. Primate studies have been instructive; however, size and pathogenesis of brain injury has limited overlap with spontaneous human cerebrovascular disease. Animal models often lack the heterogeneity of injury found in the human condition; animals generally have a more uniform pre-infarct behavioral status and are generally at a much younger point in their lifespan. Most if not all human stroke risk factors are absent in animal models, cognitive/affective features important to all aspects of recovery usually have limited correspondence with the human condition, and medical complications that, when combined, affect a majority of human stroke patients are generally absent in animal studies. Given some of these concerns related to animal models, it remains true that there is no human like humans to understand humans, and neuroimaging methods remain among the most useful tools for measuring neurobiological events of interest.

Table 54.1

Some human brain properties measured with neuroimaging

Stroke topography		
	acute	PWI, DWI
	subacute to chronic	CT, MRI
Stroke lesion load		
	acute ischemia	rCBF-PET, DWI, PWI
	chronic damage	CT, MRI, FDG-PET, FLZ-PET, MRS
Brain tissue salvageable from ischemia		OEF-PET, PWI
Brain artery occlusion and re-opening		CTA, MRA
Activation of residual brain functions		rCBF-PET, fMRI
Activation of reorganized brain functions		rCBF-PET, fMRI

Legend: PWI = perfusion weighted imaging, DWI = diffusion weighted imaging, FDG = fluorodeoxy-glucose, FLZ = flumazenil, OEF = oxygen extraction fraction, CTA = computer assisted angiography, MRA = magnetic resonance angiography, MRS = magnetic resonance spectroscopy, rCBF = regional cerebral blood flow.

First, human brain imaging techniques can provide insights into the pathophysiology of stroke-related brain injury, data that are of direct relevance to understanding recovery from stroke. Acute focal interruption of the brain perfusion is the cause of acute neurological deficits such as hemiparesis or aphasia. Importantly, reversal of this hypoperfusion can be a major contributor to very early functional recovery after stroke (Labiche et al., 2003; Seitz et al., 2005). The perfusion abnormalities measured with PET or MRI provide information both about the severity and the spatial extent of blood flow depression (Heiss et al., 1992; Rordorf et al., 1998). Figure 54.1 shows examples of five patients who presented with a severe contralateral hemiparesis and extensive middle cerebral artery territory hypoperfusion on perfusion-weighted imaging (PWI). In addition, note that the resulting structural brain lesions, as demonstrated with diffusion-weighted imaging (DWI), were far smaller than the initial perfusion deficit in these five patients. In parallel with this, the patients recovered dramatically from the acute ischemic event.

These patients demonstrate an important concept regarding the influence of acute stroke events on the process of stroke recovery: that the nature of the injury and of the surviving tissue impacts the nature of recovery events. Note that in these five patients the locations of the resulting brain lesion was associated with a variable (though mild) pattern of stable sensorimotor deficits, as demonstrated using equipment useful for measuring sensorimotor control of hand function (Binkofski et al., 2001). Use of PWI and DWI, as well as PET scanning of GABA-benzodiazepine-receptors with flumazenil (Sette et al., 1993; Heiss et al., 1998), provides important insight as to how large the area of salvageable brain tissue is, which helps to predict the final infarct volume, the degree of behavioral recovery from injury, and specifies the substrate available for recovery-related events (Fig. 54.2) (Kleiser et al., 2005).

Further, functional neuroimaging in human subjects is important because these data at times provide insights not apparent with structural imaging or behavioral assessment. Behavioral changes do not consistently correspond tightly with the molecular/physiologic events that comprise therapeutic targets. For example, there are many ways a brain can produce a given behavioral phenotype, but only some of these brain states might be appropriate targets for therapeutic intervention. Also, behavioral assessments at times do not provide mechanistic insights or distinguish patient subgroups. Functional imaging, spanning molecular and behavioral levels, can be useful in these regards because the data provide insights into brain changes at the systems level.

As an example, functional imaging can provide improved insight beyond those obtained via anatomical measures. Human (Brott et al., 1989; Saver et al., 1999) and experimental animal (Lyden et al., 1997; Rogers et al., 1997) studies of brain infarction have consistently found that behavioral deficits correlate significantly with acute or with chronic measurement of infarct volume. However, these correlations are sometimes limited, especially chronically, as this approach to understanding brain injury assumes an equivalency of cortical function akin to theories of cerebral mass action (Lashley, 1950). Introduction of functional MRI measures into analysis of injury can improve the correlation between injury and behavioral effects (Crafton et al., 2003), and thus this approach may have improved value for predicting stroke outcome compared with anatomical scans to measure total stroke volume (Fig. 54.3). In Fig. 54.3, infarct volume was shown to have a significant inverse relationship with pegboard performance by the affected hand, but this relationship was stronger when expression of injury incorporated a functional MRI measure of hand territory; injury to more than 37% of the hand motor map was associated with total loss of hand motor function. There are many other neurological settings whereby functional imaging can provide insights when behavioral exam or anatomical brain imaging provide limited insight. For example, when neurological exam is normal, expression of genetic risk for

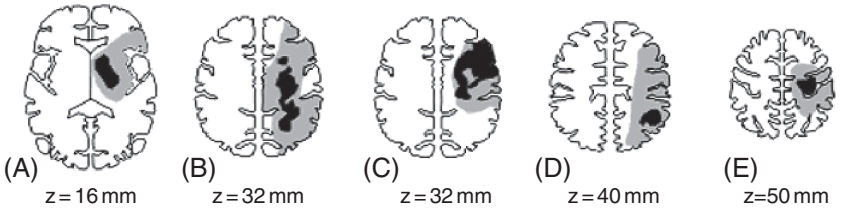

Fig. 54.1. Infarct lesions of five patients with initial severe hemiparesis and excellent recovery. The shaded area shows the perfusion lesion as assessed for a delay of 4s in time-to-peak maps, the black area shows the definite infarct lesion in DWI. The MR images were obtained within 24 hours after stroke onset. A = capsular infarction; B = hemispheric white matter infarction; C = infarction of the premotor cortex; D = infarction of the parietal cortex; E = infarction of the precentral cortex.

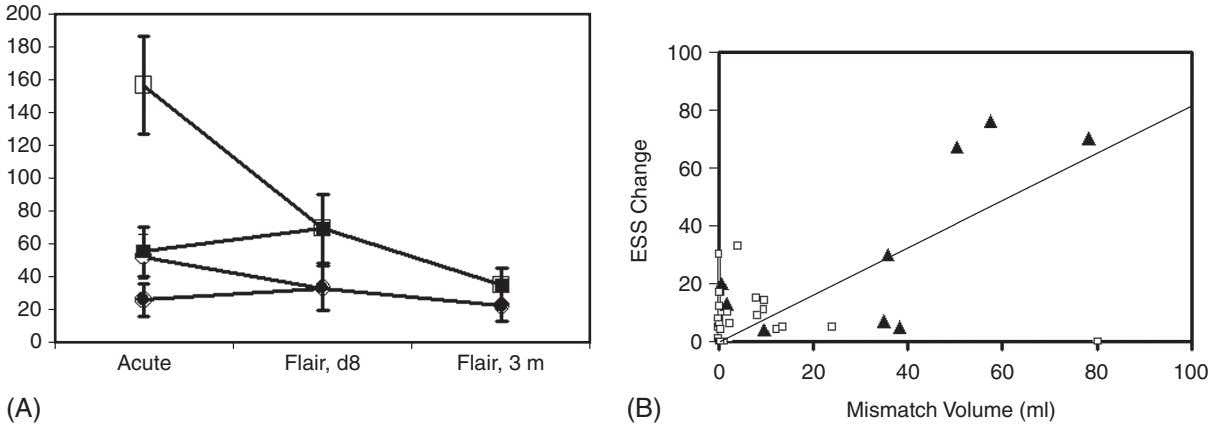

Fig. 54.2. (A) Salvage of ischemic brain tissue at risk of infarction by systemic thrombolysis with rtPA (squares) and stable lesion presentation in patients not eligible for thrombolysis (dots). The structural stroke lesions as visualized on day 8 in FLAIR images are smaller than the PWI-lesions with a delay of 4 s in time-to-peak maps (open square, circle, $p < 0.02$) but virtually identical to the DWI lesions in the acute MRI scans obtained within 3 hours after stroke onset before treatment. At 3 months the stroke lesions had regressed in volume, particularly in the treated patients (data from Ritzl et al., 2004). (B) Relation of the neurological improvement assessed with the European Stroke Scale (ESS) and the volume of impaired perfusion. The correlation was significant for the patients subjected to thrombolysis (triangles, $r = 0.763$, $p < 0.02$) but not for those not eligible for thrombolysis (Weller et al., 2006).

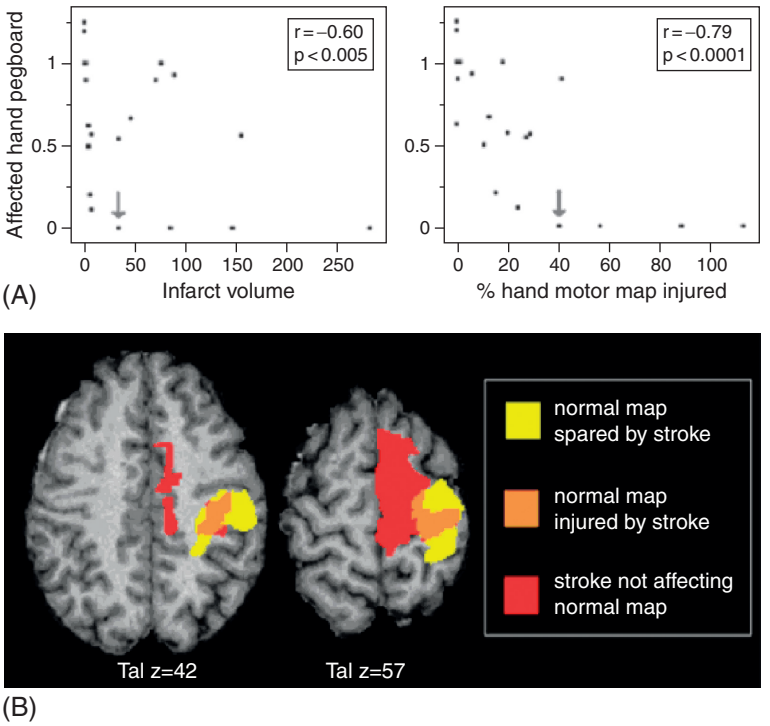

Fig. 54.3. (A) Infarct volume (top left) and fraction of hand motor map injured by stroke (top right) each show a significant inverse relationship with pegboard performance by the affected hand (normalized to pegboard results for the unaffected hand). However, correlation is stronger and more significant in the latter case. Note that injury to > 37% of the hand motor map was associated with total loss of hand motor function. The arrow indicates the patient whose images are displayed below. (B) Images from a patient whose stroke was mild–moderate in size (33 cm^3), but injured 35% of the hand motor area and was associated with total loss of hand motor function. Reproduced from Crafton et al. (2003) with permission from Oxford University Press.

Alzheimer's disease (Bookheimer et al., 2000) can nevertheless be measured when a memory task is performed during functional magnetic resonance imaging. When neuropsychological testing is normal, fMRI can be used to measure effects of HIV on the brain during a memory task performance (Ernst et al., 2002). When anatomical MRI is unrevealing, PET scanning can be used to measure the relationship between cognitive deficits and decreased cortical metabolism after traumatic brain injury (Fontaine et al., 1999). When stroke renders a patient hemiplegic, and exam is thus silent, fMRI permits measurement of activity across brain motor networks (Cramer et al., 2002a). Even in patients without a neurological diagnosis, functional brain imaging studies suggest that the same behavioral phenotype can arise from varying patterns of brain activity; for example, some elderly patients might activate a greater fraction of their cognitive reserve to maintain normal function (Scarmeas et al., 2003).

It is possible that such human brain mapping data might be used to derive neurophysiological data for improved clinical decision-making at the level of the individual patient. This goal has precedence in medical practice. For example, when a patient presents with a ventricular tachyarrhythmia or a refractory epileptic disorder, current practice often incorporates electrophysiological data to guide specific decisions in treatment (Sheth, 2002; Wetzel et al., 2003). One recent study serves as an example of using the information in brain maps for decision making in the context of a clinical trial (Cramer et al., 2005). Motor maps via fMRI were used to localize the stroke hemisphere's hand motor area in patients with chronic stroke. This information was then used to guide targeted subthreshold cortical stimulation.

When considering clinical measures for clinical and brain mapping studies of stroke recovery, it is important to remember that restorative therapeutics emphasizes specific brain systems. This is true at the behavioral level, where therapeutically reinforcing a specific behavior, for example after exposure to a restorative drug, is critical to successfully improving the behavior of interest (Feeney et al., 1982). This is also true for functional imaging, where specific behavior is required to activate the brain. Thus, the global clinical measures used in acute stroke trials by themselves are likely to be insufficient in many cases to capture system-directed therapies, or to interpret many studies of functional activation after stroke.

54.2. Limitations of neuroimaging studies on stroke recovery

Many patterns of altered brain function have been described during the study of patients with stroke. These have been exhaustively compiled elsewhere (Cramer and Bastings, 2000; Chen et al., 2002; Rijntjes and Weiller, 2002; Calautti and Baron, 2003; Baron et al., 2004; Seitz et al., 2004).

Initial functional imaging studies were cross-sectional and designed as small-sample, proof of principle studies. Subsequent studies have examined stroke patient subpopulations, increased sample size, correlated features of brain activation with clinical measures, and performed serial studies during the period of behavioral gains post-stroke. However, the understanding of changes in brain function after stroke, and the relationship between these changes and clinical measures, remains limited. There are at least three groups of issues that limit the current understanding of brain events underlying spontaneous return of function following a stroke. The first is the heterogeneity of stroke. There are a great number of variables that likely modify brain function after stroke (Table 54.2). Some are related to the injury, such as pathogenesis, features of infarction, behavioral sequelae, and therapies. Some variables overlap with issues relevant to the study of brain function in health, such as age, hemispheric dominance, and medical comorbidity. Others are also important to the study of brain function in the setting of acute stroke, such as concomitant depression and prestroke disability. Each is a source of variance that can reduce power in functional imaging studies of stroke recovery.

As a subset of this issue, the behavioral experience during the process of brain mapping can be a source of variance in elderly or impaired subjects. Instructions sufficient for young control subjects might result in divergent behaviors or strategies among patients. In elderly and impaired subjects undergoing

Table 54.2

Clinical variables influencing stroke recovery and its functional imaging

Stroke topography	Medical co-morbidities
Time post-stroke	Pre-stroke disability
Age	Pre-stroke experience and education
Hemispheric dominance	Type of post-stroke therapy
Side of brain affected	Amount post-stroke therapy
Depression	Acute stroke interventions
Injury to other brain network nodes	Medications during stroke recovery period
Infarct volume	Medications at time of brain mapping
Initial stroke deficits	Final clinical status
Arterial patency	Stroke mechanism

From Cramer (2004).

fMRI scanning, brain activity can be influenced by a number of common comorbidities such as cervical arthritis, bladder dysfunction, muscle spasms, reduced visual or auditory acuity, pain, anxiety, inattention, and cognitive dysfunction in domains other than those being evaluated. These points also emphasize the need for particular care in screening for MRI-incompatible objects in body and clothing when dealing with elderly or infirm subjects. Endurance can be reduced, making a protocol that is appropriate for young subjects a challenge for those with neurological disease or advanced age. Polypharmacy might have a significant effect on subject status as well as possibly neuronal–vascular coupling. A good bedside manner in the scanner room, a concept of reduced importance in most studies of healthy subjects, likely has a substantial effect on results of fMRI studies of patients with stroke.

A second group of issues pertains to the divergence of investigative approaches to study impairment and recovery of brain function in neurological patient populations. For example, in the motor system, squeezing versus finger tapping activates different motor circuits (Ehrsson et al., 2000; Cramer et al., 2001c). Differences in force (Dettmers et al., 1995; Cramer et al., 2002c; Ward and Frackowiak, 2003), frequency (VanMeter et al., 1995; Blinkenberg et al., 1996; Rao et al., 1996; Schlaug et al., 1996), amplitude (Waldvogel et al., 1999), or complexity (Rao et al., 1993; Sadato et al., 1996; Gerloff et al., 1998) of finger movements can substantially impact activation in multiple brain sensorimotor areas. A similar degree of variability exists in clinical assessments used to measure stroke recovery (Duncan et al., 2000; Uchino et al., 2001). This situation in stroke recovery contrasts with that found in multiple sclerosis, where the Multiple Sclerosis Functional Composite (Cutter et al., 1999) is routinely included across studies; and in spinal cord injury, where the American Spinal Injury Association (ASIA) motor score, sensory scores, and Impairment Scale (Ditunno et al., 1994) are routinely reported. Adoption of a standardized approach to be included in studies of stroke recovery might reduce the impact of this latter issue.

A third group of issues pertains to brain and vascular changes common in patients with stroke. Vascular disease can modify neuronal–vascular coupling as well as vasoreactivity. Available data suggest this is most important with highly advanced stenosis or occlusion of cerebral arteries (Bilecen et al., 2002; Carusone et al., 2002; Cramer et al., 2002b; Hamzei et al., 2003; Hund-Georgiadis et al., 2003; Rossini et al., 2004; Ziyeh et al., 2005). Moreover, advanced large cerebral artery narrowing itself, in the absence of an MRI-resolvable infarct, can be associated with reorganization of brain function (Krakauer et al., 2004). Further studies are needed in this area. Also, brain injury such as stroke can affect the intrinsic T2* property of brain tissue, the underlying measurement in blood-oxygen-level-dependent fMRI. Recent data from our lab (below) raise the possibility that this might be important.

Furthermore, interpretation of functional imaging data can be improved with a multimodal approach, such as addition of electrophysiological measures. Methods such as electroencephalography and magnetoencephalography have reduced spatial resolution compared with fMRI, but offer a high temporal resolution, in the range of milliseconds. Moreover, these techniques assess brain electric activity directly, in contrast to rCBF-PET and fMRI whose measurements are profoundly influenced by vascular abnormalities found in stroke patients. Furthermore, TMS has been used to probe post-stroke brain physiology, including conduction rates and excitability, as reviewed in detail elsewhere (Cramer and Bastings, 2000; Seitz et al., 2004).

54.3. Spontaneous changes in brain function after stroke

Despite current limitations, functional imaging studies examining spontaneous events related to stroke recovery converge on a number of findings.

54.3.1. Changes in networks

The earliest studies emphasized altered function within multiple nodes of relevant distributed networks (Brion et al., 1989; Azari et al., 1996). This finding has been replicated repeatedly. Clearly, altered function within one area changes function within interconnected areas within a distributed brain network after stroke, similar to multifocal, distant changes in brain function reported after a focal brain perturbation in the motor system of healthy subjects (Ilmoniemi et al., 1997; Siebner et al., 2000; Lee et al., 2003). A number of animal studies have been concordant with results in humans (see for example Jones and Schallert, 1992; Kolb, 1995; Jones et al., 1996; Nudo et al., 1996; Xerri et al., 1998; Liu and Rouiller, 1999; Biernaskie and Corbett, 2001; and Dijkhuizen et al., 2003). Figure 54.4 presents a model that compiles these findings. This model assumes a three-step temporal evolution of restorative changes following stroke, affording a sequence of functional and ultimately structural plasticity and suggesting unique epochs for therapeutic intervention.

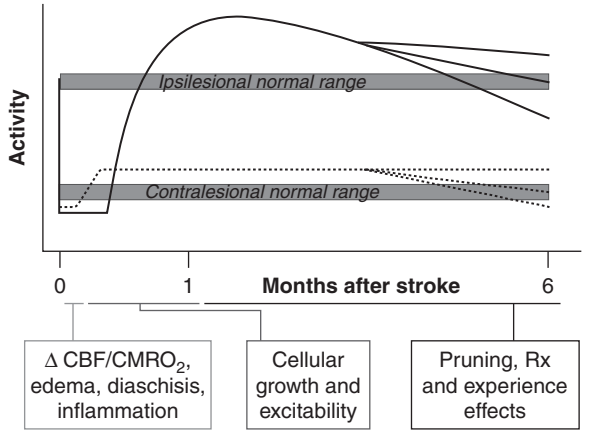

Fig. 54.4. Changes in bilateral brain areas after unilateral stroke have been grouped into three time periods. (1) In the initial hours–days after a stroke, brain function and behavior can be globally deranged (Grotta and Bratina, 1995), and few restorative structural changes have started. (2) A period of growth then begins lasting several weeks. Structural and functional changes in the contralesional hemisphere precede those of the ipsilesional hemisphere, and at such times activity in relevant contralesional areas can even exceed activity in the lesioned hemisphere. This growth-related period may be a key target for certain restorative therapies. (3) Subsequently, there is pruning, reduction in functional overactivations, and establishment of a static pattern of brain activity and behavior. The final pattern may nevertheless remain accessible to plasticity-inducing, clinically meaningful, interventions (Liepert et al., 2000; Pariente et al., 2001; Carey et al., 2002a). An excess of growth followed by pruning has precedence in human neurobiology, being a recapitulation of normal developmental events (Chugani et al., 1987). Supra- and sub-normal activity levels in the ipsilesional and contralesional hemispheres correlate with features of behavioral outcome in specific patient populations, as described above. Reproduced from Cramer (2004) with permission from Lippincott, Williams & Wilkins.

54.3.2. Changes in laterality

One commonly reported effect of stroke on brain function in humans is a reduction in the laterality of activity related to many behaviors, such as motor and language tasks (Chollet et al., 1991; Weiller et al., 1993; Cramer et al., 1997; Cao et al., 1998; Hamdy et al., 1998; Seitz et al., 1998; Thulborn et al., 1999). This issue has also received considerable attention in the study of normal aging (Cabeza, 2002) and has furthermore been described in a number of other neurological contexts including epilepsy (Detre, 2004), traumatic brain injury (Christodoulou et al., 2001), and multiple sclerosis (Lee et al., 2000). Early reports emphasized a less lateralized pattern of activation after stroke than normal; that is, the effect of stroke on motor system function is to increase the extent to which both hemispheres are recruited rather than just the hemisphere contralateral to movement. For example, a language task or a right-hand motor task that activates the left hemisphere in healthy controls will activate relevant regions within both the right and the left hemispheres in patients with a left hemisphere stroke.

A number of factors have been found to modify the extent to which stroke is associated with reduced laterality. Examples include time after stroke (laterality often increases towards normal as patients recover (Heiss et al., 1999; Marshall et al., 2000; Calautti et al., 2001; Feydy et al., 2002; Fujii and Nakada, 2003; Nhan et al., 2004), hemispheric dominance (motor task performance with the dominant hand is more lateralized than with the non-dominant hand in both health and after stroke (Kim et al., 1993; Cramer et al., 1997; Zemke et al., 2003), and topography of injury (higher laterality may be more common with a subcortical [compared with a cortical infarct] (Feydy et al., 2002; Luft et al., 2004b). Also, several studies suggest that the spontaneous increase in activity within the non-stroke hemisphere after stroke; that is, reduced laterality, reflects greater injury and/or deficits. This is particularly emphasized in the serial fMRI study by Fujii and Nakada (2003), an fMRI study that examined the question using multiple motor tasks to activate the brain (Cramer and Crafton, 2005), and by TMS studies (Turton et al., 1996; Netz et al., 1997). TMS studies have further suggested possible mechanisms for this finding. In primary motor cortex, stroke hemisphere inhibition upon the non-stroke hemisphere is reduced (Shimizu et al., 2002), and non-stroke hemisphere inhibition upon the stroke hemisphere is increased (Murase et al., 2004), though these inhibitory patterns might vary with level of deficits (Butefisch et al., 2003).

Other factors relevant to laterality in normal subjects are also likely important to the experience of stroke recovery, such as task complexity (higher laterality with less complex tasks) (Shibasaki et al., 1993; Just et al., 1996; Wexler et al., 1997), subject age (higher laterality with lower age) (Cabeza, 2002), task familiarity (higher laterality with novel behaviors) (Lohmann et al., 2004), proximal versus distal (higher laterality with distal motor tasks) (Colebatch et al., 1991; Cramer et al., 2001c; Cramer and Crafton, 2004), and perhaps gender (Vikingstad et al., 2000). Note that the motor cortex activation site ipsilateral to movement that is recruited with reduced laterality is different from the site activated during movement of the contralateral hand and is on the anterior precentral gyrus, possibly representing the premotor cortex (Cramer et al., 1999).

Some studies suggest that changes in laterality of brain function might be important to whatever behavioral recovery is achieved after stroke (Cappa et al., 1997; Heiss et al., 1999; Thulborn et al., 1999; Johansen-Berg et al., 2002b; Cardebat et al., 2003), even if the final behavior is less than normal. A number of cases have been published where brain activation is mostly or completely restricted to the non-stroke hemisphere, contralateral to results in controls (Buckner et al., 1996; Cramer et al., 1997, 1999; Gold and Kertesz, 2000). In fact, laterality of cerebral activation is dynamically modulated after stroke (Fig. 54.5). For example, while activity related to exploratory finger movements of the affected hand showed a bilateral activation pattern initially, in the first days after stroke onset, activation adjacent to the infarct was absent subsequently, after approximately two weeks—this was in spite of partially recovered hand function as well as the presence of motor evoked potentials in the affected hand (Binkofski and Seitz, 2004). Interestingly, this lack of activity in the affected sensorimotor cortex also held for the non-affected hand indicating a general hemodynamic–electrical decoupling in the affected cortex. After complete recovery at 2 months following stroke, the fMRI signal related to finger movements of the formerly affected hand was again lateralized as normal. These data suggest that, in some patients with a cortical infarct, lateralization of activity to the contralesional hemisphere is a transient phenomenon that vanishes after complete recovery. Nevertheless, some degree of contralesional activation in the motor cortex may persist in patients with excellent recovery even if they do not show abnormal activity in the non-affected hand as evident from simultaneous electromyographic recordings at the time of fMRI scanning (Nhan et al., 2004; Butefisch et al., 2005; Cramer and Crafton, 2005). This accords with the observation that a patient who has recovered from post-stroke motor deficits and suffers a second infarct affecting the side contralateral to the first infarct can be afflicted by the initial weakness again (Fisher, 1992; Song et al., 2005).

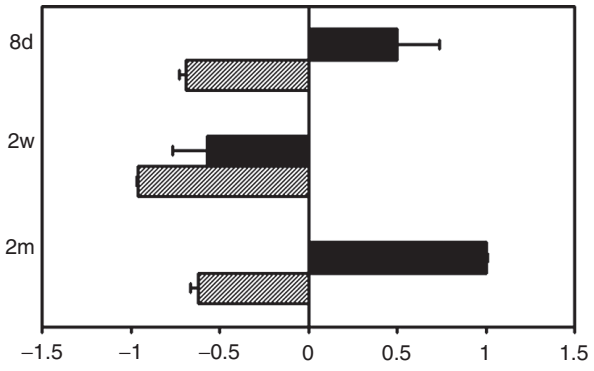

Fig. 54.5. Lateralization of the blood-oxygen-level-dependent response at 2 days, 2 weeks, and 2 months after focal infarct in the motor cortex. A value of +1 indicates lateralization entirely to the stroke-affected hemisphere, while a value of −1 indicates lateralization entirely to the non-stroke hemisphere. At the acute stage, affected hand (black bars) movement is associated with a blood-oxygen-level-dependent response that is weakly lateralized towards the stroke-affected hemisphere, contralateral to movement. At the subacute stage, the blood-oxygen-level-dependent response to affected hand movement is lateralized to the non-affected hemisphere, ipsilateral to movement, while in the chronic stage when the patient had fully recovered, lateralization had returned to the affected hemisphere. Non-affected hand movement (shaded bars) was associated with activation that was lateralized to the non-affected hemisphere, contralateral to movement, at all time points. In this regard, note lateralization of the blood-oxygen-level-dependent response to the non-affected hemisphere is complete in the subacute stage. Data from Binkofski and Seitz (2004).

54.3.3. Changes in activation site

A spontaneous shift in the site of activation has also been reported after stroke, in all manner of direction, by fMRI, PET, and TMS. The most common changes described in the motor system have been a ventral or a posterior shift in the contralateral (stroke hemisphere) activation site during unilateral motor task performance by the stroke-affected hand. Weiller et al., in a PET study of patients with subcortical stroke, described a ventral shift in the center of activation during motor task performance in recovered patients whose stroke affected the posterior aspect of the internal capsule, as compared with more anterior sites, suggesting that topographic shifts in cortical activation site might reflect survival of selected corticospinal tract fibers (Weiller et al., 1993). An fMRI study whose enrollees had a range of stroke topographies also reported the same finding: patients with complete motor recovery had more ventral motor cortex activation as compared with patients with partial recovery (Zemke et al., 2003) (Fig. 54.6). Similar results were reported in a serial fMRI study (Tombari et al., 2004). This suggests that, at least for hand motor recovery, a ventral shift might be associated with better recovery of function. Corresponding with these observations is a report that larger infarcts within primary sensorimotor cortex are associated with a more dorsal site of activation (Cramer and Crafton, 2005). Such ventral or dorsal shifts of activation related to finger movement activity seem to reflect a more general principle of post-lesional reorganization in the human cortex as was found similarly in human gliomas (Wunderlich et al., 1998).

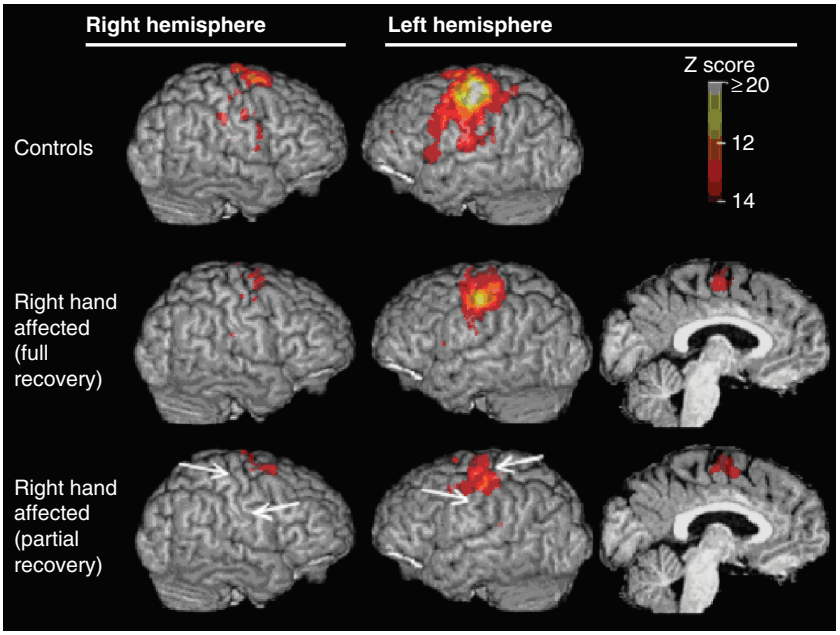

Fig. 54.6. Group maps from healthy controls, from patients with stroke affecting the right arm (left brain) and complete recovery, and from patients with stroke affecting the right arm and good but incomplete recovery show a difference in activation site and size. Among patients, differences varied with level of recovery. All subjects tapped right index finger. The Talairach coordinates for center of activation for the activation cluster in left primary sensorimotor cortex in those with complete recovery was (31, −21, 50), which was ventral as compared with those with partial recovery, among whom the center of activation was located at (30, −19, 54). In addition, patients with full recovery, as compared with partial recovery, showed a 2.7-fold larger contralateral sensorimotor activation, with negligible differences in the supplementary motor area, despite no differences in finger tapping force or in surface electromyogram (EMG) recordings. Reproduced from Zemke et al. (2003) with permission from Lippincott, Williams & Wilkins.

A posterior shift in activation site has been described in motor studies of stroke recovery across multiple imaging modalities (Rossini et al., 1998; Cramer et al., 2000; Pineiro et al., 2001; Calautti et al., 2003), and has also been described in the motor system of patients with multiple sclerosis (Lee et al., 2000) or spinal cord injury (Green et al., 1998; Turner et al., 2003). In most studies of stroke patients, a posterior shift did not correlate with clinical status; however, a recent study suggests that degree of posterior shift is linearly related to degree of recovery, at least for proximal movements (Cramer and Crafton, 2005).

54.3.4. Changes in activation size

Studies have described changes in activation size in many brain areas in the setting of stroke recovery. Functional neuroimaging studies have emphasized that recovery of function is associated with increased activation over time in several areas within the stroke-affected hemisphere, accompanied by decreased activation over time in several areas, particularly within the non-stroke hemisphere (Heiss et al., 1999; Nelles et al., 1999; Marshall et al., 2000; Nhan et al., 2004; Tombari et al., 2004). This is consistent with TMS studies (Traversa et al., 1997, 2000). TMS studies suggest that the primary motor cortex becomes more excitable than normal, and that enlargement of the excitable cortex within the stroke hemisphere during the period of stroke recovery is a feature of patients with superior motor outcomes (Cicinelli et al., 1997; Traversa et al., 1997). Importantly, while clinical status reaches a plateau in 3 months or less for many functions such as motor function (Duncan et al., 1992; Nakayama et al., 1994), brain reorganization might continue to evolve for months beyond this (Traversa et al., 2000; Tombari et al., 2004).

The task used to probe activation can significantly influence the volume of activation. For example, contralateral activation volume during right hand squeezing is significantly larger than the volume during right index finger tapping (Cramer et al., 2001c). This illustrates one of the important principles of brain mapping of stroke recovery, that the results are highly influenced by the nature of the fMRI task used to address the questions.

Both the volume of tissue activated and the height (or magnitude) of activation might be useful measures

of regional activation. These do not always change in parallel, but instead can be independent measures. Further attention to both of these measures, as has been done in some optical topography studies (Prakash et al., 2004), might be useful for best characterizing changes in activation size after stroke.

54.3.5. Correlations between behavior and changes in brain activation

In some serial functional imaging studies, the correlate of better clinical outcome has been increased activation in key stroke-hemisphere areas (Heiss et al., 1999; Marshall et al., 2000; Fujii and Nakada, 2003; Zemke et al., 2003; Nhan et al., 2004), but in other studies, the correlate has been a reduction (Calautti et al., 2001; Ward et al., 2003a). These differences across fMRI studies might arise from several sources. Several methodological issues might contribute, such as divergence in time after stroke at which investigations are performed, the task used to activate the brain, the patient populations enrolled, the nature of therapy given to patients after stroke, or in other variables. Indeed, when applying the same fMRI probe, tapping affected index finger at 2 Hz (driven by auditory metronome) across a 25° range of motion with eyes closed, shoulder adducted, and elbow extended, at 1.5 Tesla field strength, it was found that, as compared to age-matched controls, activation volume is *decreased* after stroke (Zemke et al., 2003) and *increased* after spinal cord injury (Cramer et al., 2001b). Together, these observations suggest that a particular brain mapping method will have the best clinical validity when applied to a specific patient population and clinical context.

Across studies, results converge on certain likely relationships between behavior and brain function. First, for behaviors arising from a lateralized, *primary* cortex-driven brain area, increased activation in the primary cortex correlates with *better* outcome (Traversa et al., 1997; Heiss et al., 1999; Zemke et al., 2003) (Fig. 54.6), indicating preservation of key substrate with optimal connections for supporting the behavior of interest. Second, in other brain areas such as the association cortex, for example, greater activation of *secondary* motor areas correlates with *poorer* outcome, as in this case greater activation represents a compensatory event that is generally not able to support full return of behavior due to the nature of anatomical connections in these areas (Ward et al., 2003b). Best outcomes are associated with the greatest return to the normal state of brain function (Ward et al., 2003b).

54.3.6. Changes along infarct rim

Increased activity along the rim of a cortical infarct has been described in fMRI and PET studies (Cramer et al., 1997; Rosen et al., 2000; Luft et al., 2004b). These changes appear to be modulated in magnitude most probably due to hemodynamic abnormalities in the affected cortex (Powers et al., 1988; Binkofski and Seitz, 2004). Butz et al. (2004) found peri-infarct low-frequency activity in the majority of patients after cortical stroke showing that the electrical state of the peri-lesional brain tissue is also abnormal. It should be emphasized that the residual brain lesion represents only the core of the far larger ischemic damage in the acute stage after stroke (Seitz et al., 2005). Thus, the rim along the infarct may appear intact on standard MRI but most likely severely abnormal on a microscopical level, a suggestion supported by studies of patients with a TIA and a normal MRI but reorganized brain function (Krakauer et al., 2004).

Changes in peri-infarct activation might correspond to the increased levels of growth-related proteins found along the rim of an experimental infarct introduced into animals (Li et al., 1998; Stroemer et al., 1998). Nevertheless, this tissue along the infarct rim has been shown to accommodate the cortical representations allowing for post-stroke recovery (Binkofski and Seitz, 2004; Kleiser et al., 2005). An important consideration in the interpretation of fMRI studies of this zone is that the intrinsic T2* property of brain tissue, changes which underlie activation in blood-oxygen-level-dependent fMRI, can be altered by stroke (Goodyear et al., 2004). Recent data from our lab suggest that the area surrounding an infarct might have increased T2* signal compared with normal brain tissue, the impact of which upon blood-oxygen-level-dependent fMRI might be important. However, further studies on this topic are needed.

54.3.7. Diaschisis

Diaschisis may also be an important process related to behavioral recovery after stroke. Brain areas connected to, but spatially distant from, the region of infarction show numerous changes post-stroke (Baron et al., 1986; Witte and Stoll, 1997; Seitz et al., 1999; Nhan et al., 2004). For example, several patients with a behavioral deficit early after stroke were observed among whom areas that normally showed activation were near silent. These areas with reduced brain activation had no injury from stroke and showed normal resting cerebral blood flow. Behavioral recovery was associated with restitution of brain activity in these areas (Nhan et al., 2004). Indeed, in several cases an

area of the brain had normal perfusion, was inactive early after stroke, and highly active months later, and was sufficiently distant from the infarct so as to be in a separate vascular territory. While numerous methods have been used to describe diaschisis, this process may be most directly measured using fluoro-deoxy-glucose-PET (Heiss et al., 1993; Cappa et al., 1997) and resting rCBF-PET (Seitz et al., 1999). Further studies in humans are needed to understand this spontaneous distant suppression of function, its impact on behavioral status, and the extent to which it might be a therapeutic target.

54.4. Recovery resulting from therapeutic intervention

Functional MRI and other brain mapping methods have provided insights into the brain events underlying spontaneous return of function after stroke. These methods are also useful for understanding the brain events underlying behavioral gains arising from exogenous interventions. Furthermore, the promise of these methods extends beyond gaining neurobiological insight, as measures of brain function might provide useful information on prognosis, triage, and as a surrogate marker (Dobkin, 2003), as described above. In some therapeutic contexts, information derived from functional neuroimaging can guide certain treatment decisions (Cramer et al., 2005).

Several examples of treatment effects on stroke recovery have been published. Animal studies provide useful lessons in this regard (Nudo et al., 1996; Jones et al., 1999; Biernaskie and Corbett, 2001; Johansson and Belichenko, 2002; Kleim et al., 2003). Many human studies to date have focused on effects of increased physical activity (Liepert et al., 1998; Carey et al., 2002; Johansen-Berg et al., 2002a; Schaechter et al., 2002; Wittenberg et al., 2003; Luft et al., 2004a). Effects of pharmacologic (Pariente et al., 2001) and other (Meinzer et al., 2004; Cramer et al., 2005) interventions have also been studied.

A number of adjuvant factors are important to reorganization of brain function after stroke, both in the spontaneous and treatment-induced settings, including repetitiveness of intervention, learning, sensorimotor integration, complexity, imagery, and attention. Restorative therapy will likely need to be graded to patient status with regard to such issues, such as by altering dose, context, demand level, and complexity of intervention. Such dosing adjustments might be based on features of behavior or perhaps of functional brain organization. These adjuvant aspects of restorative therapeutic interventions thus warrant consideration. Defining recovery can be complex. Clinically, a wide number of scales are used to measure neurological and disability status (Duncan et al., 2000; Uchino et al., 2001; Duncan et al., 2005).

The goals of restorative therapy concerning the recovery of hand function can be considered from at least three perspectives. First, performance of very similar hand movements is highly correlated, but these are in some cases controlled by separate cerebral structures and thus have different recovery patterns and responses to therapy (Azari et al., 1996; Binkofski et al., 1996; Cramer et al., 2001c; Kuhtz-Buschbeck et al., 2001). Second, recuperation of finger movements in the affected hand might not be independent from evolution of motor behavior in the contralateral (non-stroke) hand. In fact, associated finger movements in the ipsilesional hand can be observed regularly after a focal brain lesion, such as stroke, that impairs a patient's ability to perform activities of daily life that are normally performed in a bimanual manner (Kazennikov et al., 1994; Nelles et al., 1998; Seitz et al., 2004). Third, recovery of the affected limb involves control in both the spatial and temporal domain. In fact, even patients with excellent recovery of sensorimotor functions due to physiotherapy may retain deficits in skilled finger movement capacity that can be appreciated in the experimental context of functional neuroimaging. For example, somatosensory discrimination of cubic objects is a routine procedure easily performed by healthy subjects as well as patients with excellent recovery from striatocapsular or cortical stroke (Weder et al., 1994; Seitz et al., 1998; Binkofski et al., 1999; Stoeckel et al., 2003). Nevertheless, a patient might retain severe difficulties to perform this forced choice alternative paradigm showing continued difficulties related to the cognitive control of action. Several scales used to measure recovery might have a ceiling effect, being insensitive to mild deficits (Cramer et al., 2001a). Such an effect can influence interpretation of recovery and its functional imaging. Thus, analyzing fMRI data in a performance-related manner, such that the image frames are grouped with respect to electromyographic activity recorded during scanning, can vastly improve identification of activation in some paradigms (Fig. 54.7).

54.4.1. Active, intense, repetitive content of therapy

Active repetitive movement practice (Woldag and Hummelsheim, 2002) can enhance the strength and functional use of the affected limb in patients with chronic stroke. For instance, repetitive practice of hand and finger flexion and extension movements resulted

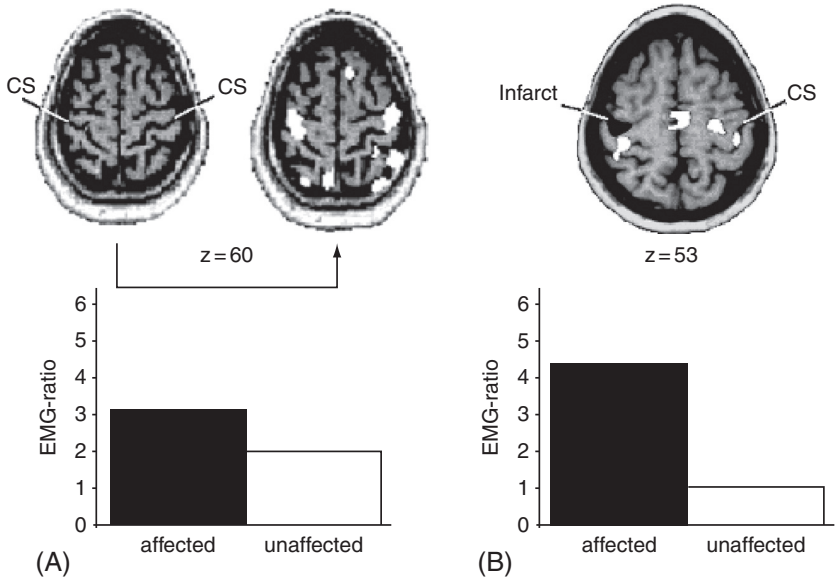

Fig. 54.7. Activation maps related to visually triggered finger movements of the affected hand in two patients after marked recovery from hemiparetic stroke. The activation maps were generated in a performance-related manner with respect to simultaneous recordings of the surface EMG from the first dorsal interosseus muscle on either side. (A) The patient presented with abnormal activity in the non-affected hand paralleled by a bilateral activation pattern in motor and parietal cortical areas. Analysis of his imaging data with regard to the stimulation protocol failed to show any cerebral activity due to his failure to comply with the go and stop signals. (B) The patient had strictly unilateral electromyographic activity in his moving affected arm. An EMG ratio of 1 indicated no increase as compared to rest. Nevertheless, there was brain activation in the contralesional premotor cortex and even a small activation area in the contralesional motor cortex. Note the greater amount of EMG activity in the recovered hand in this patient as compared with the other patient. Data from Bütefisch et al. (2005).

in significant motor performance improvements during the therapy period (Butefisch et al., 1995). Intensity of therapy might be an important factor in the level of functional improvement (Kwakkel et al., 1999), and in this regard repetitive therapy may in part be based on events related to normal learning (Karni et al., 1996; Nudo et al., 2001; Kleim et al., 2002). Active participation has been found to be more effective in improving motor performance improvement compared to passive training (Lotze et al., 2003). Constraint-induced movement therapy (CIMT) includes intense, active training of the affected hand while the non-affected hand is in a cast or glove to prevent movements. Changes in brain function have been described after CIMT, with the divergent functional neuroimaging results possibly reflecting differences in patients and study methods (Liepert et al., 1998; Kopp et al., 1999; Schaechter et al., 2002; Wittenberg et al., 2003; Park et al., 2004).

54.4.2. Sensorimotor integration

Motor gains can be demonstrated when impaired voluntary movements are supplemented with some form of assistance, either through neuromuscular stimulation (Cauraugh et al., 2000; Cauraugh and Kim, 2002; Muellbacher et al., 2002) or by mechanical assistance (Volpe et al., 2000; Lum et al., 2002). Studies that utilize techniques to enhance somatosensory input have shown effectiveness at improving motor function in healthy (Muellbacher et al., 2002) and paretic limbs (Floel et al., 2004). Sensorimotor integration theory might provide insight into the basis for these motor gains: motor output is inextricably linked to sensory input, and those unable to voluntarily complete movements cannot produce appropriate sensory patterns associated with motor effort (Bornschlegl and Asanuma, 1987; Pavlides et al., 1993). This theory provides a rationale for active assistive therapy (Reinkensmeyer et al., 2004). Implementation of sensorimotor integration theory might be improved with measurement of function in key brain functional areas for integration (Huttunen et al., 1996; Thickbroom et al., 2001).

54.4.3. Environmental complexity and context

Environmental complexity or enrichment has been found to alter brain function and structure in normal (Diamond et al., 1977; Kempermann et al., 1997; Van Praag et al., 2000) and neurologically impaired (Kolb et al., 1987; Kolb and Gibb, 1991; Biernaskie

and Corbett, 2001) animals. Animals with experimental stroke have improved functional outcomes when exposed to enriched environments that allow social interaction and a broad range of activities (Will et al., 1977; Johansson, 2003). Post-stroke experience likely similarly influences functional outcome in humans. For example, specialized multidisciplinary stroke units show improved patient outcomes compared to that of general wards (Langhorne et al., 1993; Ottenbacher and Jannell, 1993).

Computer, robotics, and motion tracking technology have recently been used to produce rich virtual reality environments (Holden et al., 2001; Jack et al., 2001; Ku et al., 2003). This technology can be utilized in a variety of settings and can influence environment in numerous ways such as by augmenting sensory feedback (Sisto et al., 2002). Deriving maximum clinical gains from implementing environmental complexity into restorative therapies might be achieved by incorporating findings from brain mapping studies on the neurobiology of complexity (Just et al., 1996; Gerloff et al., 1998; Stowe et al., 1998; Dhamala et al., 2003; Verstynen et al., 2005). In addition, virtual reality approaches lend themselves readily to incorporation into most brain mapping protocols.

The context in which restorative therapy is administered influences clinical gains. Task-specific training (Nelson et al., 1996; Trombly and Wu, 1999; Carey et al., 2002; Muellbacher et al., 2002; Alon et al., 2003; Schaechter, 2004), use of a functionally rich task ecology (Wu et al., 1998; Ma et al., 1999; Wu et al., 2000), and increased purpose of practiced exercise (Hsieh et al., 1996) each can improve clinical gains. Functional imaging can contribute to implementation of these observations by providing insight into mechanism of effect on the injured brain.

54.4.4. Imagery

Imagery and observation represent the planning and preparation stages of movement (Grezes and Decety, 2001; Jeannerod, 2001). Various forms of covert rehearsal, such as motor imagery or action observation, might be effective in producing increased recovery. This might be particularly true in patients among whom stroke-induced behavioral loss is complete, such as those with hemiplegia who are unable to perform the repetitive goal-directed movements important to recovery (Page et al., 2001; Pomeroy et al., 2005).

Brain mapping studies in human subjects have found that motor imagery and action observation are each associated with widespread activation of a distributed motor control network (Van Mier, 2000). A range of movement-related areas such as contralateral primary motor cortex, supplementary motor area, premotor cortex, and parietal cortex are also active during motor imagery and during movements observation (Porro et al., 1996; Lotze et al., 1999; Gerardin et al., 2000; Grezes and Decety, 2001; Jeannerod, 2001; Lacourse et al., 2005). Mere observation of a movement can activate complex motor output circuits in healthy (Gangitano et al., 2004) or in hemiplegic (Cramer et al., 2002a) human subjects.

Primate studies by Rizzolatti et al. have identified a cortical action-observation matching system with ties to physical movement, in which cells termed mirror neurons fire during both action observation and action execution (Di Pellegrino et al., 1992; Rizzolatti et al., 1996). Brain mapping studies suggest that a similar system exists in humans (Fadiga et al., 1995; Decety et al., 1997; Hari et al., 1998; Buccino et al., 2001) with preservation of substantial somatotopic specificity (Maeda et al., 2002). These observations add strength to the suggestion that action observation can give rise to a covert experience of that same action, including pre-movement planning and preparation stages. In fact, preliminary data showed the surprisingly strong effect of cognitive-imaginative training in patients after stroke (Müller et al., 2007).

54.4.5. Attention

Practice conditions that make performance more difficult have the potential to enhance the cognitive and motor processes involved with improving long-term performance (Lee et al., 1991). For instance, contextual interference, which incorporates random practice conditions, is known to stimulate attention and cognition. This pattern of practice conditions has been shown to enhance retention and transfer of motor skill learning (Wulf and Schmidt, 1988; Lee et al., 1991; Hall and Magill, 1995; Immink and Wright, 2001; Shea et al., 2001; Ste-Marie et al., 2004). Associative plasticity also depends on attention (Stefan et al., 2004). Indeed, simply looking at one's tapping finger, versus looking away, increases by 50% the volume of motor cortex activated (Baker et al., 1999). Studies examining the effect of attention on brain function in healthy subjects (Li and Wright, 2000; Immink and Wright, 2001; Stefan et al., 2004) may be of guiding value in understanding how to manipulate attention in order to maximize therapeutic gains in patients with stroke. This may be reflected in a different degree of activation in the parietal cortex in patients who had recovered and were studied in the chronic stage as compared with the acute situation when the patients were maximally impaired (Ward et al., 2004).

54.5. Summary

Functional imaging of stroke recovery is a unique source of information that provides insights into recovery of function after stroke and might lay the groundwork for development of restorative treatments. A number of features of brain function change spontaneously after stroke. Current studies have defined many of the most common events. Key challenges for the future are to develop standardized approaches to help address more refined questions in more natural tasks, determine the psychometric qualities of these measures, and define the clinical utility of these methods.

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Chapter 55

Practical and comprehensive approaches to evaluating stroke patients: today and tomorrow

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55.1. Initial stroke workup

The last decade was characterized by refining stroke as a widespread disease. Accompanied by a worldwide campaign led by the American and European stroke societies, neurologists brought stroke and its symptoms into the awareness of clinicians and the public. Alongside heart disease, stroke became one of the most recognized emergencies, and certainly one of the most important neurological diseases. Significant improvements in patient care, diagnostics, and treatment were made driven by results from experimental and clinical cerebrovascular research. Direct transfer into clinical practice consequently resulted in landmark innovations in stroke therapy such as the approval of tissue plasminogen activator (tPA), and the implementation of stroke units for patient care.

Such approaches require the workup of stroke patients ruled by the "time is brain" domain. Standardized workups are now available in all main stroke centers (Fig. 55.1). After admission of stroke patient into hospital, the initial clinical evaluation includes (in addition to the patient's history and examination) the survey of standardized scales such as the Glasgow Coma Scale (GCS) and National Institute of Health Stroke Scale (NIHSS). Accompanied by an assessment of the patient's medical status, including an electrocardiogram (ECG) and an emergency laboratory screening (see Fig. 55.1), this evaluation typically takes about 10–15 minutes, and builds the basis for subsequent treatment decisions. The typical stroke workup represents a stepwise approach in an escalating fashion due to occurrence and clinical symptoms of the disease. After the initial workup (Figs. 55.1 and 55.2), which precedes the therapeutic intervention, diagnostic testing is escalated based on the suspected origin and the course of the stroke in the individual patient, as outlined in Fig. 55.2 (levels II and III).

Allocation of treatment is at present dominated by the 3-hour time window according to the initial criteria for approval of tPA (NINDS Study Group, 1995). A pathophysiological approach for positive detection of vessel occlusion or the evolution of stroke in the individual situation is based on this original study. The function of stroke imaging in this context (computed tomography) is to exclude potential contraindications such as cerebral hemorrhage or marked early infarct signs. The wide availability of dynamic stroke imaging with computed tomography (CT) and magnetic resonance imaging (MRI) may refine the indication for thrombolysis when a vessel occlusion or a stroke within the 3 hour time window cannot be detected, and may extend the therapeutic time window beyond 3 hours. Stroke imaging alone could therefore alter the patient's workup including allocation of potential future treatments.

55.2. Imaging stroke

MRI has evolved over the last decade to become the preferred brain imaging modality over CT. MRI-based diffusion-weighted imaging (DWI) can demonstrate, in contrast to CT, the onset of ischemia within minutes, while perfusion-weighted imaging (PWI) precisely defines the areas of hypoperfusion (Warach

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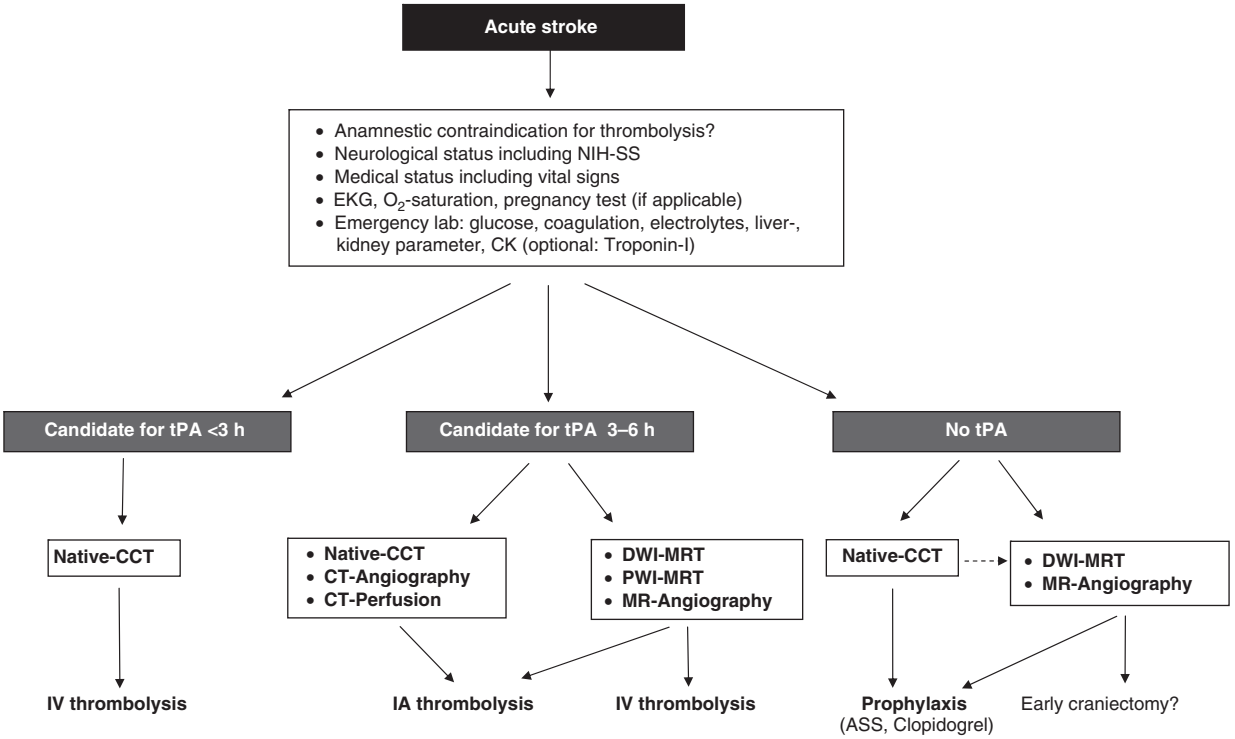

Fig. 55.1. Initial workup of the acute stroke patient. Allocation to treatment is currently based on the 3 hour time window. Between 3 and 6 hours an IA or IV thrombolysis should be considered. Large hemispheric infarction may be treated with early craniectomy.

et al., 1995). A PWI–DWI mismatch, which indicates tissue with decreased perfusion extending beyond that of diffusion abnormalities, is thought to represent tissue at risk of further infarction, which could potentially be salvaged (Warach et al., 1996). A PWI–DWI mismatch can be seen in about 80% of stroke patients examined in the acute phase and is thought to predict infarct growth (Barber et al., 1998). MR angiography (MRA) sensitively localizes vessel stenosis or occlusion, and correlates with patterns of infarction that can be further improved by contrast enhancement (Fujita et al., 1994). MRI was also shown to be sensitive for imaging acute or chronic intracerebral hemorrhage by susceptibility-weighted T_2* imaging (Fiebach et al., 2004). Intracerebral hemorrhage causes a characteristic imaging pattern on stroke MRI that is accurately detectable even in less experienced practitioners. Such susceptibility-weighted T_2* imaging is even able to show small chronic hemorrhages as focal areas of signal loss, indicating hemosiderin deposits caused by minor bleeding from small fibrohyalinized arterioles (Lee et al., 2004).

The mismatch phenomenon awaits further specification regarding quantification and correlation to structural morphology. Recently published direct comparisons of MRI and PET data of the ischemic penumbra represent the first step in this direction. Indeed, it appears that a matching DWI/PWI lesion may still represent salvageable tissue (Guadagno et al., 2004). On the other hand, the simple DWI–PWI mismatch concept may overestimate the penumbra (Sobesky et al., 2004). More detailed analysis on the MRI side, probably by implementing quantitative PWI and time-to-peak delay maps, may refine the penumbra definition by DWI–PWI mismatch. MRI appears nevertheless as the ideal sole imaging modality in hyperacute stroke without requiring additional CT. MRI alone may refine within the next decade patients for any kind of therapy by individually identifying salvageable tissue. This could replace the current standard (see Fig. 55.1) of allocation to treatment according to a rigid time window, with an individually assessed dynamic brain tissue window (Fig. 55.3). Practicing precursor studies such as Desmoteplase in acute stroke (DIAS) may justify a new wave of hope of extending the therapeutic time window for stroke patients (Hacke et al., 2005).

In clinical practice there are always situations where an MRI cannot be obtained; for example, in agitated or

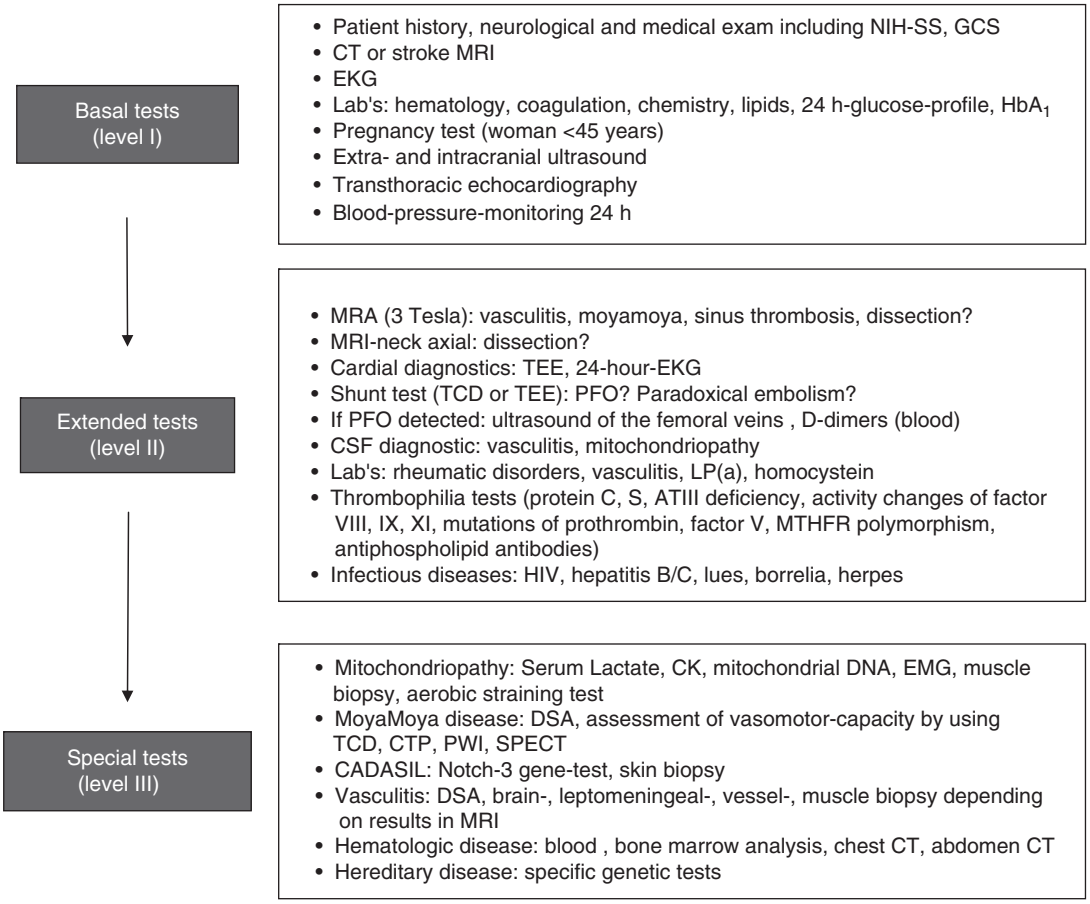

Fig. 55.2. Complete workup of stroke patients in an escalating fashion. After basal tests (level I), the workup should be escalated to levels II and III according to the patient's individual situation to detect typical (cardiac embolism, vasculitis, dissection) and rare (moyamoya disease, Cadasil, mitochondriopathies) causes of an ischemic stroke.

pacemaker-carrying patients. In addition, the infrastructural capacity in smaller hospitals often lack expensive hardware and software so that the latest MRI technology may not be available. Under such circumstances CT might be the method of choice. CT has a general weaker sensitivity for detection of infratentorial processes, and advantages and drawbacks in determining tissue at risk for infarction without reperfusion. Because signal intensity is more directly related to contrast dye concentration, CT has advantages over MRI in quantifying perfusion. CT provides quantitative mean transit time (MTT), cerebral blood flow, and cerebral blood volume, allowing characterization of absolute thresholds in the penumbra (thresholded cerebral blood flow lesion minus thresholded cerebral blood volume lesion) (Wintermark et al., 2002a). The cerebral blood volume abnormality itself was shown to correlate well with the DWI lesion size (Wintermark et al., 2002b). A "mismatch" can then be defined as the difference between the abnormality on cerebral blood flow CT perfusion study and the expected core infarct based on cerebral blood volume abnormality. Recent data suggest that after vascular occlusion, it is only the amount of "core" that is important in making treatment decisions (Jovin et al., 2003). From the current perspective, however, it remains questionable if CT technology can be developed to compete equally with MRI in precisely imaging the brain tissue window of the individual stroke patient.

55.3. Ultrasound in stroke

Neurological ultrasound is an inexpensive, noninvasive, real-time monitoring tool that has become routine for the diagnostic workup of stroke patients. Color-coded duplex sonography then evolved to become the gold standard. This technique sensitively enables the detection of extra- and intracranial vessel

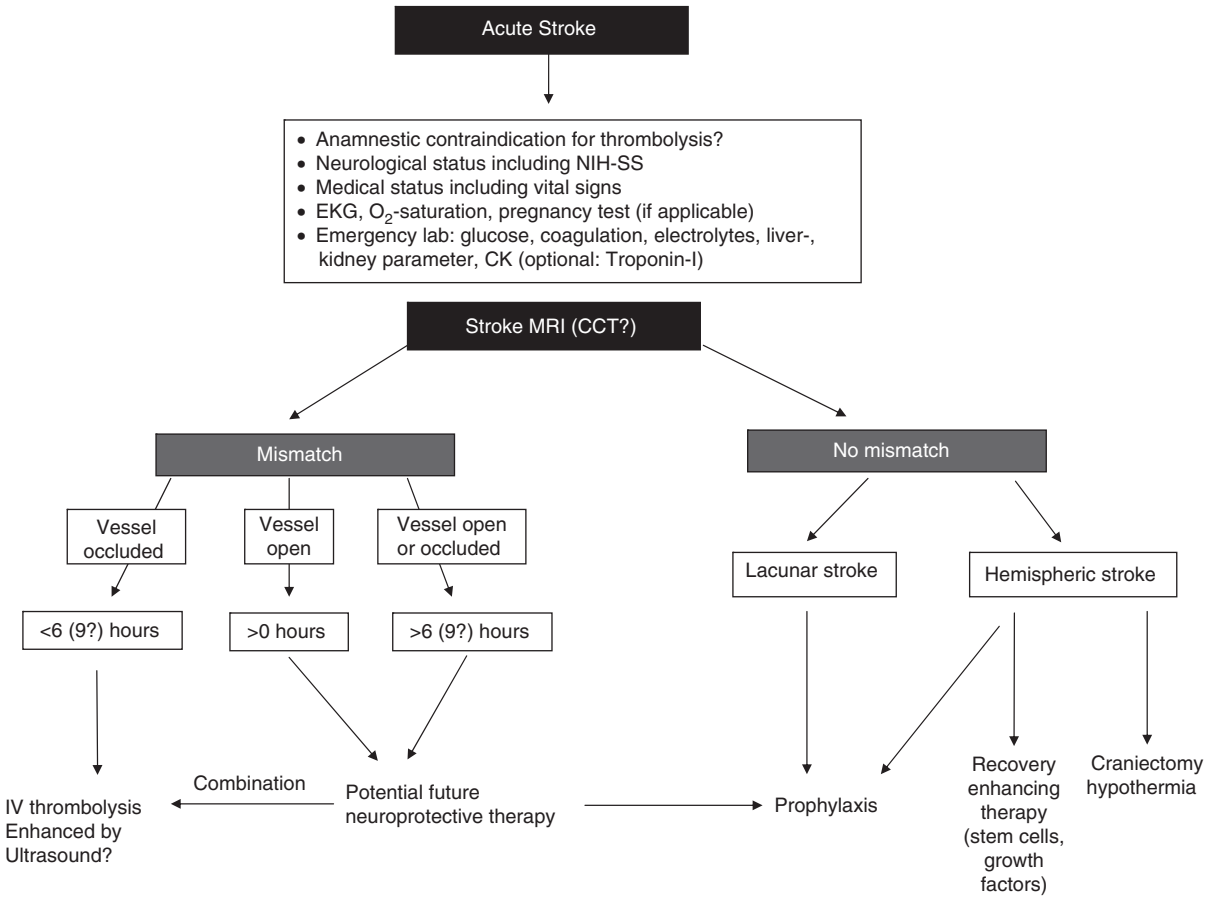

Fig. 55.3. Suggestion of a future evaluation paradigm in stroke patients. Note that the rigid time window concept is shifted towards a dynamic pathophysiologically oriented approach to treat salvageable tissue in the individual patient.

occlusions or stenosis, can in experienced hands replace vessel imaging with CT or MRI, and is therefore (in the present authors' department) typically part of the basal stroke workup (Fig. 55.2, level I). A good temporal window and an experienced operator can accomplish a focused stroke workup in 10 minutes, which may be delayed in patients with suboptimal windows to 20 minutes. Ultrasound testing can be performed at bedside simultaneously with neurological examination, monitoring of vital signs, and drawing blood, making it the ideal real-time monitoring tool at stroke units for the detection of vasospasms in subarachnoid hemorrhage patients, midline shifts in patients with hemispheric infarctions, or the documentation of lesion evolution in patients with intracerebral hemorrhage. In addition to these applications the use of ultrasound is established for the detection of cardiopulmonary shunts and circulating microemboli as well as for the verification of brain death.

Innovations in ultrasound will carry this technique into the future with several interesting applications that could improve the diagnostic capacity, and may even enhance therapy. One of these innovations includes the use of gas-filled microbubbles that have a much stronger echo-enhancing effect than conventional echocontrast agents. The result is a much better delineation of cerebral blood flow, vessel occlusion, pseudo-occlusion, or stenoses in the extracranial (but also in the intracranial) vasculature. Microbubble-based methods such as bolus injection kinetics, refill kinetics, and diminution kinetics are at present used to qualitatively describe or relatively quantify brain tissue perfusion under ischemic conditions (Martina et al., 2005). It is, however, not yet clear which of the models or parameters will be best for clinical brain perfusion assessment in humans.

Doppler ultrasound may be also used in the future to monitor treatment or even to improve treatment. Non-image-guided Doppler sonography identifies

thrombus location with an accuracy greater than 90% for the middle cerebral artery and internal carotid artery. Once this thrombus/residual flow interface is found, a narrow 3–10 mm pulsed-wave ultrasound beam can be steadily aimed at the thrombus location to monitor the effect of a thrombolytic drug. By exposing thrombus surface and structures to tPA, thrombolytic activity can be enhanced with a 2 MHz transcranial Doppler. A randomized, multicenter, clinical trial called CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA) showed a 49% rate of complete recanalization or dramatic clinical recovery from stroke within 2 hours after tPA bolus when tPA infusion was continuously monitored with TCD, compared with 30% among patients who received tPA without ultrasound monitoring (Alexandrov et al., 2004). Early complete recanalization was sustained at 2 hours by 38% of monitored patients compared with 12.7% controls. Ultrasound may therefore substitute thrombolysis in the future as depicted in Fig. 55.3. Therapeutic ultrasound may further be developed towards targeting microbubbles with ligands such as antibodies or synthetic peptides (e.g. intracellular adhesion molecule 1) that can interact with endothelial or intracerebral function (Villanueva et al., 2002, 2004). Potential future therapeutic use of the microbubble technique incorporates drugs (e.g. tPA) into ultrasound-sensitive microcapsules. Such microcapsules can be monitored using low mechanical indices owing to their acoustic properties. Once the thrombus is localized, the microcapsules can be destroyed and placed by higher mechanical index pulses inducing the burst release of the encapsulated therapeutic agent (Martina et al., 2005). This technique could principally also be used for gene therapy by tagging genes to cationic microbubbles (Christiansen et al., 2003).

Ultrasound imaging also includes the evaluation of vascular ageing as a degenerative process; the demonstration of plaque development, motion, and vulnerability in atherosclerosis; and multi-dimensional as well as innovative imaging techniques (e.g., compound imaging) to depict early and small vascular lesions (Hennerici et al., 2004).

55.4. Cardiac investigations

In clinical studies, cardiogenic embolism accounts for up to one-sixth of ischemic strokes (Cerebral Embolism Task Force, 1986, 1989). Echocardiography and 24-hour ECG serve as cornerstones in the evaluation and diagnosis of stroke patients (Cerebral Embolism Task Force, 1986, 1989). While a non-invasive, inexpensive, and simple 24-hour ECG study can easily be assessed in all suspected patients, referral to transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE) usually requires a more defined clinical indication. The difficulty here is that there are no sensitive or specific clinical diagnostic criteria for cardio-embolic stroke. In less than 2% of patients found to have a cardiac source of stroke without clinical evidence of heart disease, the identification of the embolic source by echocardiography reaches nearly 10% (Lerakis and Nicholson, 2005).

Cardio-embolic sources for stroke can be separated into three distinct categories. The first subset includes cardiac lesions that have a propensity for thrombus formation. This includes specific characteristics of the left atrial appendage and the presence of mitral annular calcification in patients with nonrheumatic atrial fibrillation. A second group of causes is the presence of cardiovascular masses, which may include intracardiac tumors, thrombi, or atherosclerotic plaques of the aorta. The third subset includes passageways within the heart serving as conduits for paradoxical embolization from the venous system. The most commonly identified passageways implicated in cardiogenic strokes are atrial septal defects and patent foramen ovale (Lerakis and Nicholson, 2005). TEE is superior to TTE in detecting embolic sources in all structures related to or neighboring the left atrium which are usually at high risk for embolization. TTE can be used to detect mitral- and aortic-valve insufficiencies, dilation, hypo- or hypertrophy, and ejection fraction of the left ventricle—conditions associated with a moderate embolic risk. The differential indication for a TEE or a TTE should therefore be balanced as outlined in the algorithm in Fig. 55.4. The search for thrombophilic diseases which could cause or promote the formation of such emboli should always be considered when a cardiac embolic source is detected (see Fig. 55.5).

55.5. Conclusion

The future of diagnostic testing in stroke patients will further move towards a specific analysis of the disease in the individual patient. Significant innovations are awaited from stroke imaging with CT and MRI, and from ultrasound technology. As outlined, such innovations improve or establish not only diagnostic methods, but are also particularly suited to pioneering the way for therapeutic approaches, and could build the future basis for a tailored therapy which moves away from fixed time window frames towards a pathophysiologically targeted treatment of salvageable tissue in the individual patient.

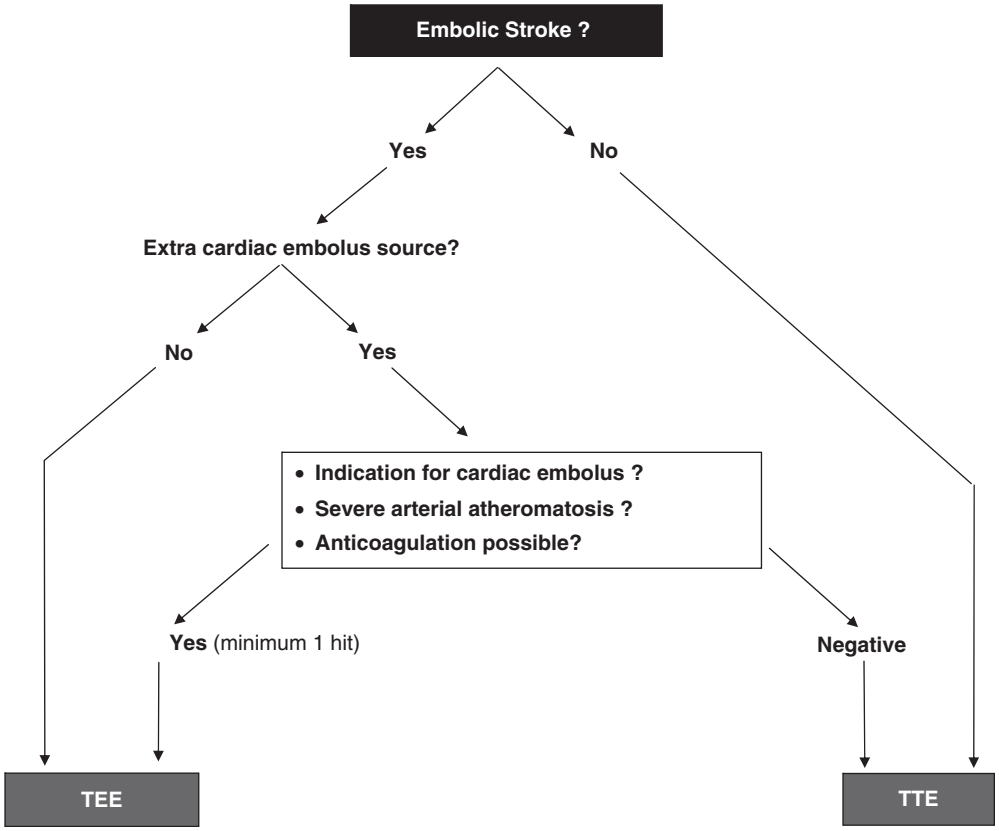

Fig. 55.4. Outline for diagnostic allocation of patients to TEE or TTE.

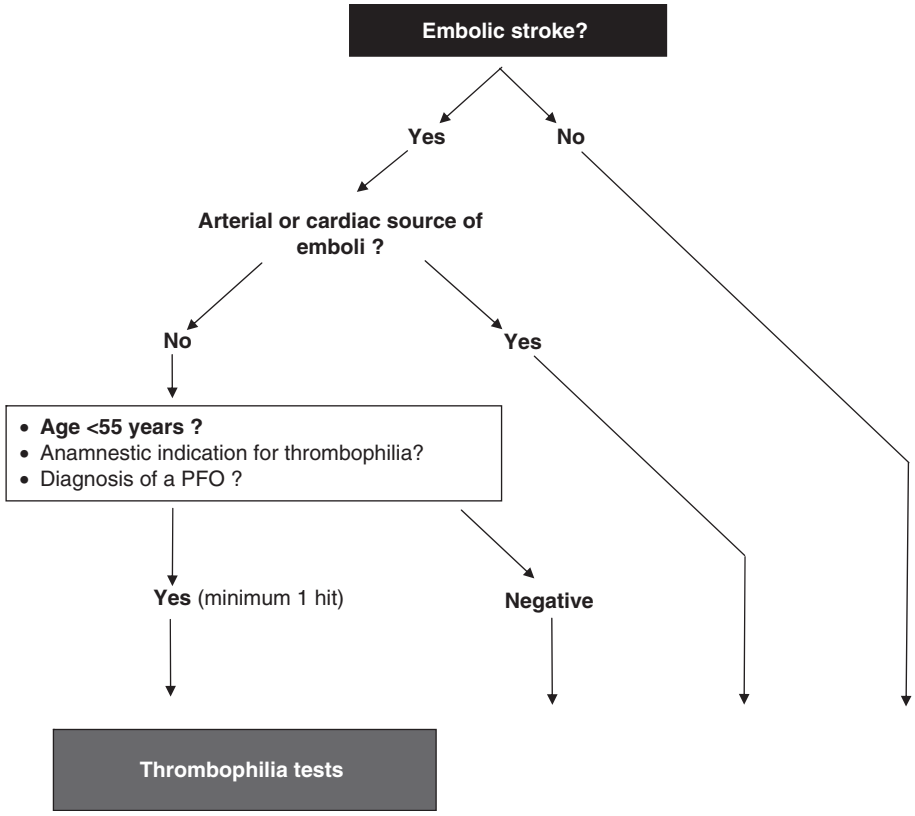

Fig. 55.5. Outline for diagnostic allocation of patients to thrombophilia tests. We recommend thrombophilia tests in all patients under 55 years, and/or anamnestic indication for thrombophilia, and/or existence of a PFO.

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Chapter 56

General principles of acute stroke management

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56.1. Introduction

The goals of a comprehensive acute stroke treatment management are (1) to minimize the amount of brain damage by reversing penumbra and by preventing further bleeding in acute hemorrhages, (2) to prevent early neurological and medical complications, and (3) to promote early recovery. If the multiple small steps to achieve excellence in stroke management succeed, the patient will likely have a better chance of survival, and ultimately have a better outcome.

An organized system of care in the prehospital and emergency room phase is a prerequisite for effective treatment. Immediate diagnosis of stroke subtype is now possible in most patients arriving at the hospital thanks to acute neurological expertise (in the form of a stroke consultant) and advanced neuroimaging. Although acute recanalization treatment is the most effective intervention, general care, prevention of complications, and early and late rehabilitation remain the cornerstones of stroke therapy.

56.2. Prehospital management, chain of rescue, and referral

56.2.1. Recognition of stroke by the patient and bystanders

Ignorance or minimization of symptoms of acute stroke and transient ischemic attacks (TIAs) remains a major problem in the rapid activation of the emergency medical system (EMS) after stroke onset. Public awareness campaigns focusing on the general public or high-risk populations may have some impact on this problem. Other reasons for late information of the EMS are acute cognitive and behavioral problems that make patients unable to recognize or communicate their symptoms. Examples of such problems induced by acute stroke include the inability to move, anosognosia, anosodiaphoria, aphasia, disturbances of consciousness, memory deficits, and confusional states.

56.2.2. Activation of the EMS system chain of rescue

Patients or witnesses of an acute stroke should call the regional or national medical emergency number. Personnel responding should have proper training and algorithms to recognize stroke symptoms. They should give these patients a high priority for ambulance dispatch (Porteous et al., 1999; Camerlingo et al., 2001), especially if symptom onset is recent.

The presence of a physician at the site of stroke is only required if the patient is considered hemodynamically unstable or has a severely depressed consciousness potentially requiring intubation. If a general practitioner receives a call about or consults a patient with suspected stroke, he should recommend/arrange/organize emergency transportation, preferably through the EMS system, to the nearest emergency room of a hospital providing acute stroke care. Time is the most important factor for the success of acute stroke treatment. Therefore transport by paramedics should be the quickest available according to distances, transport capacities, and weather. Helicopter transport plays an increasingly important role in the rapid transfer of patients with stroke (Thomas et al., 2002). Whenever symptoms and signs suggestive of TIAs or stroke are recognized—within minutes, hours or days—they should prompt immediate referral to the next casualty or stroke center. If several days or weeks have passed before the symptoms come to the attention of the

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physician, semi-urgent referral to a neurologist or stroke center is appropriate.

56.2.3. Prehospital assessment and scales

Paramedical personnel need specific training and algorithms for patients with suspected stroke. Their assessment includes the evaluation of the patient's airway, breathing, and circulation (i.e., the "ABC" of resuscitation) (Hachimi-Idrissi and Huyghens, 2002; Adams Jr et al., 2003). A measure of blood sugar is recommended. They should obtain thorough information from the patient and the witnesses about the usual state of health, time of symptom onset, and usual medications. The EMS ambulance dispatchers and the ambulance drivers should notify the emergency and stroke team that they will be arriving with a stroke patient and describe his/her clinical status. If possible, the ambulance driver should indicate a prehospital stroke scale and should advise a next of kin to come to the hospital immediately. Scales such as the Los Angeles Pre-hospital Stroke Scale (Kidwell et al., 1998), the Cincinnati Pre-hospital Stroke Scale (Kothari et al., 1999), or the "Face, Arm, and Speech Test" (FAST) (Harbison et al., 2003) are easy to use.

56.2.4. Referral

Admission to a stroke unit has been shown to reduce handicap and mortality, presumably due to a combination of better acute treatment, prevention and treatment of complications, and early rehabilitative interventions. Therefore, it should be a health policy goal of each community to provide enough stroke unit beds and watch over the quality of such units. Different network models of medical centers providing organized acute stroke care are possible, and have to be set up and publicized for in each community. Referral algorithms, education, and technology-facilitated communication by telemedicine can improve the performance of such networks.

If thrombolysis or other acute recanalization treatments are considered, referral to a stroke center should not be delayed by neuroimaging in a non-specialized hospital. This will usually be done in the stroke center where neuroimaging may be analyzed with more expertise. Furthermore, patients with intracerebral hemorrhages may benefit similarly from acute stroke treatment (Mayer et al., 2005; Steiner et al., 2006) and stroke unit care as ischemic stroke patients.

If the number of stroke unit beds are limited in a community, a triage checklist for referral to a stroke center should be established. Such criteria for referral could be, other than thrombolysis, recurrent or progressive neurological deficits, an anticipated high risk of complications, and need for specialized diagnostic tests or neurosurgical evaluation.

56.2.5. Prehospital treatment

Airways patency and protection, oxygenation, and circulatory function have to be assured by the paramedical personnel, or a physician in the field, if needed. Antithrombotics or anticoagulation must not be given until brain imaging has excluded intracranial hemorrhage. Blood pressure may only be lowered if above 220/120 mmHg, especially in patients with signs of cardiac failure or myocardial ischemia (Adams Jr et al., 2003; Toni et al., 2004). Neuroprotection with drugs and external cooling devices is now being investigated in the prehospital phase.

56.3. Emergency room assessment and hospital admission

56.3.1. Triage, stabilization, and acute evaluation of stroke

Acute evaluation should be performed simultaneously by a vascular neurologist and an emergency room physician. Acute assessment of neurological and vital functions parallels treatment of acutely life-threatening conditions. Emergency management of acute stroke includes three parallel processes: (1) management of life-threatening comorbid conditions and complication of stroke, (2) medical and neurological evaluation with advanced neuroimaging, and (3) treatment of the stroke itself.

The initial examination includes observation of breathing function, assessment of blood pressure and heart rate and determination of arterial oxygen saturation using infrared pulse oxymetry if available. Simultaneously, blood samples for clinical chemistry, coagulation and hematology studies are drawn and a venous line is inserted. Standard electrolyte solutions are given until clinical chemistry results are available. Twelve-lead electrocardiography and chest radiography support the clinical evaluation of cardiothoracic pathologies. The possibility of initiating thrombolytic treatment without knowledge of platelet counts and coagulation parameters has recently been suggested. For patients on oral anticoagulation, portable bedside international normalized ratio (INR) measurements tools may be more rapid than an usual blood test.

56.3.2. Telemedicine

Systems linking the ambulance or a secondary hospital emergency room with a stroke center and their specialists are emerging (Fisher, 2005). They can increase

adherence to evaluation and treatment protocols, and decrease mortality (Audebert et al., 2006). Their downsides are technical issues, costs and energy for installation and maintenance.

56.3.3. Stroke team

A stroke team should consist of a neurologist, a neuroradiologist, a nurse coordinator and a neurosurgeon. They work closely with the medical personnel in the emergency department, the radiology department, and the (neuro-) intensive care units. Not all hospitals will have the resources to provide a complete stroke team at all times. The more components of the team are involved in acute stroke care, the more rapidly treatment can be initiated. The stroke team is usually responsible for confirming the onset time, evaluating the neuroimaging, establishing the diagnosis and reviewing the inclusion/exclusion criteria for thrombolytic therapy, then making the final decision to initiate the treatment.

56.3.4. Standard protocols and clinical pathways

Written protocols and checklists for stroke should be produced for each stage of the management, from prehospital to long-term follow-up care. They are likely to improve resource utilization and clinical outcome, although this has not been firmly established by randomized trials (Kwan and Sandercock, 2004).

Management algorithms may differ depending on whether the patient arrives at the hospital within the first few hours after stroke onset or much later. Conditions and complications such as hypertensive crisis, elevated blood glucose, aspiration, increased intracranial pressure, seizures, or cardiac arrhythmias should enter into a predefined management framework.

56.3.5. Hospital admission and monitoring

Stroke patients should be admitted to the hospital, which should be equipped with a monitored integrated stroke unit and neurointensive care (Indredavik et al., 1998; Stroke Unit Trialists' Collaboration, 2000). This permits frequent neurological and general assessments during the first 24–48 hours. A minimal monitoring during this period includes neurological surveillance by trained nurses, online electrocardiogram (ECG) monitoring, respiratory monitoring by ECG leads or pulse oxymetry, and blood pressure measurements with automatic inflatable sphygmomanometry. More intensive monitoring may be justified according to stroke severity, and could include a central venous catheter with central venous pressure monitoring and intra-arterial blood pressure measurements.

Approximately 25% of patients may deteriorate during the initial period, although it is difficult to predict which patients will do so (Yamamoto et al., 1998; Castillo, 1999). Continuous observation will allow:

1. observation of cardiovascular and neurological events;
2. measurement of prevent complications;
3. improvement of the diagnosis rate of stroke etiology;
4. detection of changes in the patient's condition that might prompt initiation of medical or surgical interventions.

56.3.6. General care of the stroke patient

The proven efficacy of stroke units is likely to be due to the adherence to guidelines for general treatment. These are based more on consensus than on placebo-controlled, randomized, blinded studies. General management of stroke patients comprises respiratory and cardiac care, fluid and metabolic management, and blood pressure control. In addition, prophylactic measures concerning deep venous thrombosis (DVT), pulmonary embolism, aspiration pneumonia, other infections, and decubital ulcer, likely decrease morbidity and increase long-term independence. Clinical worsening of the patient may be due to medical (Table 56.1) causes or neurological complications (Table 56.2). Any worsening should prompt a

Table 56.1

Medical causes of clinical worsening in stroke patients

Infections	
Pneumonia	
	Urinary tract
	Endocarditis
	Sinusitis
	Others
Respiratory	
	Bronchoaspiration/pneumonia
	Pulmonary emboli
	Atelectasis
	Respiratory failure
Cardiac	
	Output failure
	Arrhythmias, myocardial infarction
Metabolic	
	Hyper-/hypoglycemia
	Hyper-/hyponatremia
	Other electrolyte disturbances

Table 56.2

Neurological causes of worsening in stroke patients

Ischemic stroke:	
Worsening of ischemia	
	Persistent occlusion/insufficient collaterals
	Progression of stenosis, reocclusion
	Hypotension (often nocturnal or iatrogenic)
	Recurrence of embolic stroke
	Hemorrhagic transformation
Mass effect with intracranial hypertension*	
Epileptic seizures*	
Withdrawal of alcohol, nicotine, drugs, hypnotic*	
Iatrogenic worsening with psychotropic drugs*	
Confusional states*	
Psychological/psychiatric reasons*	
Hemorrhagic stroke:	
Above*, and	
Early rebleed or continuing bleeding	
Hydrocephalus, especially with intraventricular or cerebellar hemorrhage	

Table 56.3

What to do if the patient is getting worse

Ask the patient and ask the nurse
Check vital signs
Do a thorough neurological and medical exam
Consider brain imaging and vascular imaging
Consider labs (electrolytes, blood count, CRP, etc.), chest x-ray, urinary sediment, blood cultures, etc.
Consider blood gases, CT for pulmonary embolus, EEG, cardiac echo, etc.

new clinical evaluation (Table 56.3), often accompanied by laboratory exams.

Although there is a general rule to maintain the patient in a "normal physiological condition," there is increasing evidence that this may not be true for certain parameters:

1. overzealous lowering of elevated blood pressure is likely to do more harm than good;
2. hypothermia may be preferable to normothermia;
3. early feeding (by mouth or by tube) in patients with dysphagia may increase the rate of aspiration.

56.3.7. Neurological complications

Detecting and treating promptly neurological complications of ischemic and hemorrhagic stroke is one of the main reasons for improved survival of patients with acute phase of stroke. It requires a well-equipped, staffed, and trained neurological monitoring unit which may have a neurointensive care or an intermediate care status.

The main neurological complications of ischemic and hemorrhagic stroke are listed in Table 56.2 and are discussed below.

56.4. Clinical diagnosis of stroke in the acute setting

56.4.1. Accuracy of stroke diagnosis, ischemic versus hemorrhagic stroke versus TIA

The presence of a focal neurologic deficit and a history of abrupt onset of symptoms in the absence of trauma suggest the occurrence of a stroke. Paramedics correctly diagnose stroke in about two-thirds of cases and emergency room physicians in about 90% (Ferro et al., 1998).

Patients with intracerebral hemorrhage often have progressive symptom onset over 5–20 minutes, rather than maximal onset at the beginning (as in embolic stroke) or a stuttering onset (as in large- or small-artery thrombosis). Symptoms are more frequently severe. Signs of increased intracranial pressure (such as decreased level of consciousness, vomiting, and headaches) may be present early, and blood pressure may be more severely increased (Panzer et al., 1985). Intracerebral hemorrhage very rarely occurs during sleep. Despite these clinical differences, neuroimaging is mandatory to differentiate ischemic from hemorrhagic stroke and from stroke imitators (Poungvarin et al., 1991; Weir et al., 1994).

Given the time-dependent effectiveness of intravenous thrombolysis and advances in neuroimaging, the

historical definition of TIA has become questionable (Albers et al., 2002). In TIAs clinical signs disappear completely within 1 hour in about 60% of the patients. In the remaining patients, signs often persist/linger for more than 24 hours, and neuroimaging studies are more frequently pathological.

56.4.2. History taking

The most valuable tools in diagnosing strokes and TIAs are a precise history taking, which should include questioning of the family or caregivers, and a basic neurological exam (Table 56.4). This information helps to differentiate stroke from stroke-like manifestations of non-vascular disorders. TIAs and strokes are characterized by their rapid onset over seconds to minutes, and by a typical constellation of signs and symptoms that can be attributed to a specific vascular territory. Repeated questioning and precise chronological description of symptom onset by the patient or witnesses may allow the differentiation of ischemic events from migraine with aura, focal epileptic seizures, and psychogenic deficits (Michel and Bogousslavsky, 2004a). Loss of consciousness is rarely caused by TIA or stroke and should lead to a search for epileptic seizures, hypoglycemia, orthostatic hypotension, and cardiac diseases. Precise history taking is also extremely helpful in identifying previous TIAs or other undiagnosed risk factors, triggers of stroke (medications, drugs, recent infection, head and neck trauma), and associated diseases.

Table 56.4

Rapid neurological assessment in the suspected acute patient

General:
Vital signs, including cardiac rhythm
Cardiac bruits, meningismus
Cognitive:
Level of consciousness, behavior
Orientation, attention (digit span), hemineglect of space
Language (fluency, comprehension, repetition)
Primitive reflexes (grasping, lack of initiative, perseveration)
Short-term memory (3 words after 5 min)
Cranial nerves:
Ptosis, pupillary reaction to light, visual fields to confrontation
Ocular pursuit, nystagmus
Facial paralysis and sensation to pinprick
Tongue and palate deviation, dysarthria
Extremities:
Bilateral arm and leg raising and strength
Ataxia (finger-to-nose and heel-to-shin)
Sensation (asymmetry of pinprick and vibration)
Reflexes (asymmetry of tendon reflexes, cutaneous plantar reflexes)

56.4.3. Physical examination

The patient should be seen as soon as possible by a stroke neurologist, as a delay in clinical evaluation may obscure the localization of the stroke or TIA (Bamford et al., 1991; Toni et al., 2000). The clinical examination begins with the assessment and treatment of the airway, breathing, circulation, and temperature. A brief standard neurological exam (Table 56.4) should be performed. To facilitate acute treatment decisions, it may contain the items that are part of a stroke scale such as the National Institutes of Health Stroke Scale (NIHSS). It usually helps to make a rapid distinction between territorial and lacunar syndromes and stroke imitators. One needs to remember that a "non-focal" exam rules out neither TIAs nor stroke. The most frequently missed "non-focal" signs of stroke are hemi- and quadranopsias (because they are not tested), mild aphasias (missed or mistaken as confusional states), mild confusional states due to right hemispheric or thalamic strokes, for example, somnolence and upward gaze paresis due to midbrain strokes (not recognized), and bilateral ptosis in right hemispheric or midbrain strokes (often not recognized or mistaken as somnolence). As mentioned above, rapid disappearance of symptoms and a normal exam is characteristic of TIAs and should in no way undermine the urgency and thoroughness of a cerebrovascular workup.

Clinical examination helps to localize the lesion in anterior versus posterior circulation. Stroke severity and its course can be quantified by scales such as the NIHSS. Training in applying such scales increases their reproducibility.

56.4.4. Determination of time of onset, wake-up, and unknown onset stroke

Stroke occurrence can frequently be determined by asking the patient and witnesses, and by looking for circumstantial evidence. Onset during sleep occurs in about 25% of patients (Chaturvedi et al., 1999; Fink et al., 2002; Serena et al., 2003; Spengos et al., 2005). Clinical, neuroimaging and etiopathogenic characteristics of stroke of unknown onset are not significantly different from strokes with known onset (Fink et al., 2002; Serena et al., 2003), with the possible exception of

sleep-onset stroke being more frequently lacunar (Chaturvedi et al., 1999; Spengos et al., 2005). If the precise onset of stroke is unknown, the last time where the patient was seen in his usual state of health is the presumed onset of stroke. For a patient with symptoms of stroke on awakening, the time of onset is assumed to be when the patient went to bed (or when he was last known to be symptom-free before retiring). If a patient had mild impairments but then had worsening over the subsequent hours, the instant the first symptom began is assumed to be the time of onset. In contrast, if a patient has symptoms that completely resolved (TIA) and then has a second event, the time of onset of the new symptoms is used.

56.5. Selection of diagnostic tests for acute stroke

In addition to the history and clinical exam, acute brain and cardiovascular imaging and some basic laboratory tests (Table 56.5) are essential aids to the diagnosis of acute stroke. Acute brain imaging (CT or MRI) distinguishes immediately and reliably ischemic stroke from intracerebral hemorrhage. After a large ischemic stroke involving the cortex or basal ganglia, early abnormalities on CT appear within 1–3 hours. Small and brainstem strokes may not be visualized for 12–24 hours on CT, and may actually never show up on CT. They are occasionally missed on MRI, too. Clinical information such as suspected stroke localization as well as joint visualization of images by the clinician and radiologist is very helpful in interpreting subtle abnormalities on brain imaging. In acute stroke, the advantages of MRI (higher resolution, faster appearance of abnormalities, better brainstem imaging) are offset by its limited availability and more complicated monitoring of the stroke patient. Furthermore, perfusion-CT has emerged as a practical detection tool for early ischemia (Michel and Bogousslavsky, 2005) and reliably differentiates reversible from irreversible ischemia (Wintermark et al., 2006). If there is a clinical suspicion of subarachnoid hemorrhage but the cranial CT or MRI is negative (as in less than 10% of cases in the first 24 hours), lumbar puncture is necessary to rule out this diagnosis.

Acute imaging of cervical and intracranial arteries is highly recommended for ischemic stroke. The type of imaging used depends mainly on local availability and expertise. CT angiography using spiral CT technique is rapid and practical, but experience is still limited. Acute Doppler and duplex ultrasonography with transportable equipment is practical and easily repeatable. On the other hand, it depends on the availability of a trained examiner and may give limited intracranial information. MR angiography is a reliable and validated method for extra- and intracranial arterial imaging. Cerebral conventional (or digital subtraction) angiography is the preferred method in the acute phase if intra-arterial thrombolysis is considered. Cerebral blood flow measurements (by perfusion CT and perfusion MRI) are becoming more currently used in stroke centers. Basic laboratory tests (Table 56.5) help exclude a number of metabolic causes of neurological signs (for example hypoglycemia) and screen for contraindications to thrombolysis.

Following initial brain imaging, the further workup (Table 56.6) should depend on a stepwise hypothesis testing of stroke pathogenesis, but costs and limited length of hospitalization may force the clinician into making an early choice based on the clinical information and the initial exams. If the patient is not being taken care of in a stroke unit, neurological consultation should be obtained as soon as possible.

Table 56.5

Emergency exams in the patient with suspected stroke

Brain imaging (at least one of the following):
Cranial CT, including perfusion imaging
Brain MRI, including diffusion and perfusion imaging, FLAIR and T2* susceptibility sequences
Imaging of cervical and intracranial arteries (at least one of the following):
CT angiography
MR angiography
Doppler and duplex ultrasonography
Conventional or digital subtraction angiography (if intra-arterial thrombolysis is an option)
Laboratory:
Complete blood count, INR, aPTT, blood glucose, sodium, potassium, creatinine, CK, CK-MB, CRP
Pregnancy test
Others:
Twelve-lead electrocardiogram
Lumbar puncture (if SAH is suspected and CT is normal or if meningo-vascular infection is suspected)

56.6. Early prognosis and decision making

The main factors for prognosis after acute ischemic stroke are age, initial and 24 hours symptom severity as measured by the NIHSS, premorbid conditions, the localization and size of the brain lesion, and the presence and success of early arterial recanalization. Very early statements on prognosis should be avoided, as the natural course may be surprisingly benign in

Table 56.6

Additional exams potentially useful to determine stroke etiology and acute complications of stroke

Twenty-four-hour monitoring of	
	Vital signs (arrhythmia, hypo- and hypertension, fever, oxygen desaturation)
	Neurological signs (neurological complications of stroke)
	Early medical complications (infection, cardiac problems, deep venous thrombosis)
Chest radiography	
Echocardiography	
	Transthoracic
	Transesophageal
	Intravenous injection of microbubbles to detect cardiac shunt
Cervical and transcranial Doppler and duplex	
	Intravenous injection of microbubbles to detect cardiac shunt
	Injection of contrast agents to better evaluate intracranial arteries
	Monitoring for high-intensity transient embolic signals
Brain MRI and angio MRI of cervical and cerebral arteries (if not done on emergency admission)	
	With diffusion and perfusion images
	With T2* susceptibility (gradient echo) and FLAIR images
	Conventional cervical and cerebral angiography (mostly digital subtraction arteriography)
Electroencephalography (to identify epilepsy or encephalopathy)	
Neuropsychological testing	
Laboratory tests in most patients	
	Sedimentation rate, TSH
	Lipid profile, liver function tests
Laboratory tests in selected patients	
	Total proteins, serum or protein immuno-electrophoresis, fibrinogen, blood viscosity, serum osmolality
	Differentiation of leucocytes, erythrocyte morphology (sickle cells)
	Urine or serum toxicology screen
	Blood alcohol concentration
	Syphilis serology (TPHA and/or VDRL), HIV
	Homocysteine, mutations of homocysteine regulating genes
	Antiphospholipid antibodies, antinuclear antibodies, rheumatoid factor and other auto-antibodies
	Proteins C and S, anti-thrombin-III, plasminogen and tPA-deficiency, activated protein C resistance, search for mutations of prothrombin-II and factor V Leiden
	Mutations of the notch-3 gene (CADASIL), mitochondrial, DNA (e.g., MELAS)
Lumbar puncture	
Urinary sediment	
Biopsy of temporal arteries, meninges, cortex (suspicion of vasculitis)	

some (elderly) patients with initially severe deficits. Early neuroimaging using perfusion techniques may improve the accuracy of prognosis, including for mass effect (Thomalla et al., 2003) and hemorrhagic transformation (Tong et al., 2000) after thrombolysis. In intracerebral hemorrhage, several scales such as the intracerebral hemorrhage-score (Hemphill III et al., 2001) help to predict the outcome quite reliably.

Physicians talking to the next of kin in acute settings have to be very cautious and inform them of the potentially severe and sometimes irreversible nature of the disease. The clinical and radiological state at 24–48 hours is currently much more reliable for prognostication than the early assessment. If prognosis seems very poor at this point, a discussion about the patient's wishes, intensity of resuscitation, further diagnostic test, and nutritional support should be initiated with the next of kin. Palliative care consultations may be obtained to help in decision making and to guarantee the patient's comfort.

56.7. Airways, oxygenation, and respiratory function

56.7.1. Overview and pathophysiology

A substantial number of patients experience hypoxemia at some point during the acute phase of stroke (Sulter et al., 2000). The ischemic penumbra with its decreased blood flow and increased oxygen extraction is particularly sensitive to hypoxemia; infarct growth is one likely mechanism worsening the neurological injury in hypoxemic patients.

Causes for hypoxemia are multiple: pre-existing lung and heart disease, decreased ventilatory drive, generalized epileptic seizures, airway obstruction, cardiac failure, and decreased pulmonary gas exchange due to pneumonia, atelectasis, and pulmonary emboli. Patients with large hemispheric or bilateral brainstem strokes are at highest risk for early broncho-aspiration (Smithard, 2002). Sleep apnea and hypopnea is frequent during the first night after cerebral infarction and is associated with early neurological worsening (Iranzo et al., 2002; Bassetti et al., 2006).

Small randomized studies have not yet shown a benefit from routine oxygen supplementation (Ronning and Guldvog, 1999), and trials randomizing patients with hypoxemia would be ethically difficult to perform. The use of high flow (Nighoghossian et al., 1995) or hyperbaric oxygen therapy (Bennett et al., 2005) still lacks evidence of efficacy in acute ischemic stroke patients.

56.7.2. Monitoring

Continuous monitoring with pulse oxymetry in the acute and subacute stage of stroke will detect hypoxemia. Blood gas analysis or an expiratory pCO_2 measurement should be performed in patients with signs of impaired respiratory functions or with severe stroke. In experimental settings, intracerebral oxygen utilization may be measured by PET or estimated by MRI (Geisler et al., 2006).

56.7.3. Management

Maintaining oxygen saturation above 92% is recommended (Adams Jr et al., 2003; Toni et al., 2004) and can often be achieved by administration of 2–4 litres of O_2/min via a nasal tube. In patients with nocturnal oxygen desaturation due to obstructive sleep apnea, non-invasive continuous positive airway pressure via a nasal or face mask might be used (Iranzo et al., 2002). Situations where intubation may be considered are the patient's inability to maintain sufficient tissue oxygenation, the need for sedation during intra-arterial procedures, the risk of broncho-aspiration, the preoperative management of mass effect, and experimental hypothermia treatment. The prognosis of patients who need endotracheal intubation is rather poor (Grotta et al., 1995; Steiner et al., 1997). Therefore, rapid assessment of the chances for recovery from respiratory compromise and stroke, and of the patient's will should be performed before intubation.

56.8. Temperature management, hyperthermia, and hypothermia

56.8.1. Overview and pathophysiology

Body temperature is increased in up to 50% of patients in the acute phase of stroke (Corbett and Thornhill, 2000). The main causes may be the stroke itself, especially if it is severe (Boysen and Christensen, 2001) and infections occurring before (Grau et al., 1995) or after stroke onset (Grau et al., 1999). Stroke is rarely the cause of persistent fever however.

High body temperature may favor stroke progression (Castillo, 1999) and a body temperature above 37.5° decreases the odds for a good outcome (Reith et al., 1996; Hajat et al., 2000). Experiments have shown that fever increases infarct size (Fukuda et al., 1999), presumably due to decreased survival of penumbral parenchyma.

56.8.2. Monitoring

Frequent measures of temperature with external devices is recommended, especially in the acute phase. In cases of fever, a thorough search for frequent causes of infections (pneumonia, urinary tract infections, phlebitis, sinusitis) and rarer causes (endocarditis, sepsis, abdominal or retroperitoneal abscess, bed sores, prostatitis) should be undertaken. If hypothermia is induced experimentally, continuous semi-invasive (esophageal, rectal) measurements should be used.

56.8.3. Management

Although randomized studies with high-dose of antipyretics provide contradictory data (Dippel et al., 2001; Koennecke and Leistner, 2001; Kasner et al., 2002), treating an elevated temperature in stroke patients is highly recommended. One may consider lowering body temperature as soon as it reaches 37.5°C (Adams Jr et al., 2003; Toni et al., 2004). Other than antipyretic drugs, a cooling blanket or other surface cooling may lower core and brain temperature. A large trial giving the antipyretic drug paracetamol to patients independently of their temperature is ongoing (van Breda et al., 2005). It is recommended to use antibiotics for bacterial infections as early as possible, but use of prophylactic antibiotics in all stroke patients had no effect on outcome in a randomized study (Chamorro et al., 2005).

56.8.4. Hypothermia

Several mechanisms such as reduction in metabolic and enzymatic activity, glutamate release and reuptake, inflammation, reactive oxidant production, and the expression of other genes are responsible for the neuroprotective effect of hypothermia in experimental studies of hypoxic brain injury (Krieger and Yenari, 2004). Given these data, spontaneous mild hypothermia should probably not be treated. Actively inducing hypothermia in acute stroke is feasible (Schwab et al., 2001). As therapeutic hypothermia becomes more pronounced, so do its complications: pneumonia, thrombocytopenia, hyponatremia and cardiac arrhythmias are the most frequent. Albeit rapid and effective cooling is achievable with intravenous methods, surface cooling devices may be more applicable in clinical settings. Anti-shivering medication, sedation, and intubation are often necessary.

Comparative clinical studies suggest an effect on lesion seize (De Georgia et al., 2004), but improved clinical outcome has yet to be demonstrated. Effect on edema is pronounced (Schwab et al., 2001; Georgiadis et al., 2002; De Georgia et al., 2004), but rebound edema after may limit its effect. Currently ongoing studies may provide more data on the timing, degree, and application mode of this promising method.

56.9. Inflammation and infections

56.9.1. Overview and pathophysiology

Acute and chronic non-infectious inflammation is implicated in propagating atherosclerosis and acute coronary events (Danesh et al., 2004), but its role in stroke pathogenesis is less certain. Infection may be a trigger, a sign of severity, and a complication of stroke. It worsens functional prognosis (Aslanyan et al., 2004) mainly through fever and probably also by the effect of circulating inflammatory proteins and cytokines on ischemic or recovering tissue. The most frequent infection after stroke is probably pneumonia. It is closely associated with dysphagia (see below), and occurs even if patients are not fed. Urinary tract infections are also frequent in immobilized patients with indwelling catheters. Pressure sores, sinusitis from nasogastric tubes, endocarditis, and sepsis from peripheral or central lines are other causes of infections in stroke patients. Infections or post-infectious vasculopathy may be found in relation to varicella-zoster virus, HIV infections, tuberculous and aspergillus meningitis, and neurosyphilis.

56.9.2. Monitoring

Measuring temperature, a full blood cell count, C-reactive protein, and occasionally the sedimentation rate on admission identifies patients with early inflammatory states. These tests should be repeated if fever or fluctuation of the neurological status is observed. Appropriate tests in search of sources of infections should be performed. If no infectious source for a systemic inflammation is found, tests for systemic vasculitis (such as giant cell arteritis, systemic lupus erythematosus, Takayasu's arteritis or Cogan's syndrome) and endocarditis should be performed.

56.9.3. Management

If no cause for persistent fever and inflammation is found after a thorough search, recurrent bronchoaspiration, pulmonary emboli, and systemic vasculitis may be suspected and treated. The choice of antibiotic depends on the site—whether the infections were acquired at home or in hospital—and on possible local resistance pattern and side-effects. A randomized trial of routine use of antibiotics during the first days after stroke has not shown a benefit (Chamorro et al., 2005). There is no convincing evidence to date for a clinical effect of anti-inflammatory drugs such as high-dose aspirin (Dutch TIA Trial Study Group, 1991) or statins (Montaner et al., 2004) in acute stroke patients.

56.10. Blood pressure

56.10.1. Overview and pathophysiology

During acute stroke, the majority of patients have increased blood pressure (>140/90), even if they are not hypertensive before the stroke (Yatsu and Zivin, 1985; Leonardi-Bee et al., 2002b). Although the exact

mechanisms for this observation are not well understood, several factors may be involved such as activation of neuro-endocrine systems (corticotrophic, sympathetic, renin–angiotensin), increase in cardiac output, high blood pressure secondary to increased intracranial pressure (Cushing reflex), pain, and urinary retention (Carlberg et al., 1991). Cardiac baroreceptor sensitivity is impaired after acute stroke and may explain increased blood pressure variability (Robinson et al., 1997). It also appears that persistent cerebral arterial occlusion contributes to persistent elevation of blood pressure in acute stroke patients (Mattle et al., 2005).

Cerebral blood flow (CBF) autoregulation is frequently defective in an area of evolving infarction (Eames et al., 2002). This leads to a direct dependency on the mean arterial pressure (MAP) of blood flow in the ischemic tissue. Maintenance of CBF above the infarction threshold is facilitated by high blood pressure. A drop of blood pressure and therefore of flow below critical thresholds in the penumbra zone may explain the relationship between low blood pressure at hospital admission and stroke progression (Dávalos et al., 1990; Powers, 1993; Jorgensen et al., 1994) and bad outcome (Ahmed et al., 2000; Leonardi-Bee et al., 2002a; Willmot et al., 2004). In addition to poor autoregulation of blood flow in ischemic areas, many stroke patients are chronically hypertensive and their brain autoregulatory curve is shifted to the right. Therefore hypertensive stroke patients may better tolerate higher blood pressure levels. Blood pressure decreases spontaneously and gradually in most hypertensive stroke patients after the first hours and days (Britton et al., 1986; Broderick et al., 1993), which may partially be explained by (spontaneous) recanalization (Mattle et al., 2005).

The relationship between blood pressure during the acute phase and prognosis is a U-shaped curve (Leonardi-Bee et al., 2002a; Bath, 2004; Willmot et al., 2004). High blood pressure in ischemic stroke appears to be associated with early recurrence and cerebral edema (Hatashita et al., 1986; Leonardi-Bee et al., 2002a). It remains controversial whether hemorrhagic transformation of the infarct is also facilitated by persistent hypertension in non-thrombolyzed patients (Bowes et al., 1996; Leonardi-Bee et al., 2002a). In spontaneous intracerebral hemorrhage, however, it is more evident that elevated blood pressure promotes hematoma growth (Arakawa et al., 1998).

Treatment of extremely high blood pressure is indicated because this puts not only the brain but also the heart and kidneys at risk. Nonetheless, if blood pressure is lowered in unselected hypertensive patients in the acute phase, early neurological deterioration, increased infarct volume, and poorer outcome at 3 months have been described, especially if systolic blood pressure reduction is more than 20 mmHg (Castillo et al., 2004). Rapid fall of blood pressure induced by nimodipine explained the bad outcome in the Intravenous Nimodipine West European Stroke Trial (Ahmed et al., 2000). A randomized controlled study using oral candesartan during the first 7 days after ischemic stroke has shown good tolerability and a decrease of cardiovascular events over the following 12 months (Schrader et al., 2003). The mechanisms of this observation was questioned, because no significant lowering of peripheral blood pressure was observed, effects on the outcome of the stroke were not described, and an effect produced weeks and months after the treatment on other organs seems unlikely (Michel and Bogousslavsky, 2003).

More aggressive blood pressure treatment is indicated in patients undergoing thrombolysis or having particular concomitant medical conditions. Because of the above-mentioned risk of early rebleeding, blood pressure should also be treated more aggressively in hypertensive patients with spontaneous intracerebral hemorrhage and subarachnoid hemorrhage.

56.10.2. Monitoring

Blood pressure can usually be measured with sufficient precision with an arm cuff adapted to the patients arm circumference. It should be compared between both arms at least once in the acute phase; a difference may suggest stenosis of subclavian or axillary arteries in relation to dissections of aortic aneurysms, with severe atherosclerosis, or rarely arteritis. Intra-arterial blood pressure monitoring may occasionally be required in patients with very high blood pressure resisting initial treatment, with requirements for aggressive intravenous blood pressure-lowering, and with concomitant acute medical conditions.

If measured non-invasively, the frequency of blood pressure measurements should initially be every 3–5 minutes. If the patient and the blood pressure remain stable, the frequency can be decreased to every 15–30 min. Specific recommendations are available for blood pressure-monitoring during thrombolysis (Brott et al., 1998; Adams Jr et al., 2003).

The ideal target blood pressure may be quite variable from one acute stroke patient to the other. Continuous monitoring of cerebral tissue perfusion at the bedside could potentially help in finding the best blood pressure and cardiac output for an individual situation. Tissue harmonic imaging by transcranial Doppler (Seidel et al., 2004) or repeat perfusion imaging by MRI or perfusion-CT may become useful for this in the future.

56.10.3. Management

Because of the lack of unambiguous data, the appropriate treatment of blood pressure in the setting of acute ischemic stroke remains controversial. A systematic review concludes that to date there is not enough evidence to evaluate the effect of lowering the blood pressure after acute stroke (Blood Pressure in Acute Stroke Collaboration [BASC], 2000).

Despite the absence of randomized trials, a number of recommendations can be given that are based on clinical observation and case series. In most cases of acute ischemic stroke, the blood pressure should not be lowered. It is only recommended to treat systolic blood pressure values over 220 mmHg or diastolic blood pressure values over 120 mmHg (Adams Jr et al., 2003; Toni et al., 2004). If treatment is considered necessary, target systolic blood pressures of about 180 mmHg and diastolic blood pressure of about 105 mmHg are recommended (Toni et al., 2004; Adams et al., 2005). In patients undergoing thrombolysis or heparin administration, systolic blood pressure above 185 mmHg and diastolic blood pressure above 105 mmHg should be avoided because of increased risk of parenchymal hemorrhage (NINDS Study Group, 1997; Larrue et al., 2001). The latter thresholds have also been recommended for hypertensive patients with acute intracerebral hemorrhage. Recent guidelines recommend avoiding systolic blood pressure above 160 and diastolic blood pressure above 95 in intracerebral hemorrhage patients without known hypertension (Steiner et al., 2006).

Specific causes such as pain, anxiety, urinary retention, and increased intracranial pressure should always be sought and treated. If the upper limits are trespassed, short-acting parenteral drugs that may be titrated over a venous line allow best control of blood pressure. Suitable medications are labetolol, uradipil, clonidine, nitroglycerin, and sodium nitroprusside, although the latter two have the potential to increase intracranial pressure. Captopril can be given as intravenous boluses.

Oral medications such as captopril or nicardipine and percutaneous nitroglycerin preparations may suffice occasionally. Their drawback is the imprecise absorption and duration of action. Independently of the route of administration, blood pressure should be lowered gradually, by no more than 20 mmHg and under frequent monitoring (Toni et al., 1996; Brott et al., 1997; Adams Jr et al., 2003; Toni et al., 2004). Hence, sublingual and intravenous calcium antagonists should be avoided as they carry a considerable risk of abrupt reduction of blood pressure (Wahlgren et al., 1994), and of possible ischemic steal (Jorgensen et al., 1994; Ahmed et al., 2000).

Certain concomitant medical conditions, such as acute myocardial ischemia, cardiac insufficiency, acute renal failure, acute hypertensive encephalopathy, or aortic arch dissection require blood pressure lowering. Again, a precipitous blood pressure drop should be avoided and drugs suitable for both the stroke and the acute medical condition should be selected. In subarachnoid hemorrhage, oral nifedipine is given routinely for several days as it has been shown to reduce vasospasm-related morbidity and improve outcome (Mayberg et al., 1994a).

56.10.4. Management of hypotension

Low blood pressure in acute and subacute stroke is typically seen in younger patients with cardio-embolic sources. Specific causes of hypotension should be sought, however. They include volume depletion, gastrointestinal bleeding, sepsis, aortic dissection, decreased cardiac output secondary to myocardial ischemia, cardiac arrhythmias, and pulmonary embolism. Low blood pressure and cardiac output will affect regional cerebral blood flow particularly in areas of ischemia and in patients with chronic hypertension, as discussed above. Correction of hypovolemia by administering adequate amounts of normal saline is indicated in volume depletion, sepsis, and acute extracranial hemorrhage.

Treatment of the underlying cause of low cardiac output includes correction of cardiac arrhythmias, and treatment of myocardial ischemia and pulmonary embolism. Among the inotropic agents, dobutamine in doses of 5–50 mg/hour (Toni et al., 2004) seems to be suitable as it increases cardiac output without substantially affecting heart rate or blood pressure. Dopamine may be particularly useful in patients with hypotension or renal insufficiency. Positioning of the body in a horizontal or even in a head down (Trendelenburg) position may increase regional cerebral blood flow in vasoactively impaired tissue (Novak et al., 2003; Diserens et al., 2006) and may be useful during periods of hypotension.

Drug-induced hypertension in patients with acute stroke may be of particular value in the very acute phase where the proportion of penumbra tissue is highest, and in patients with clinical worsening due to persistent arterial occlusion or locally low flow. It may however increase the risk of brain edema, hemorrhagic transformation, cardiac ischemia or arrhythmias. The intervention also requires quite intensive close monitoring. Drugs that have been used for this purpose include intravenous phenylephrine, epinephrine, norepinephrine, and oral midodrine (Rordorf et al., 2001; Hillis et al., 2003; Marzan et al., 2004). These trials have shown that this intervention is feasible and safe

as long as hypertension remains moderate. In a randomized pilot study, Hillis et al. (2003) found that drug-induced hypertension can improve blood flow in ischemic tissue and lessen the neurological consequences of stroke. Before data from several larger, randomized trials are available, drug treatment of patients with low blood pressure in the acute stroke phase has to be individualized.

56.11. Fluid and electrolyte management

56.11.1. Overview and pathophysiology

Both hyper- and hypovolemia have negative effects on cerebral perfusion and homeostasis of other organs. Therefore the main goal of fluid management in the acute phase is to establish and to maintain normovolemia. A continuous intravenous infusion of isotonic fluids without glucose is best suited for this purpose (Brainin et al., 2004). Moderate or severe dehydration on admission is not uncommon and may be related to bad outcome (Bhalla et al., 2000). It can be due to fever and infections, to prestroke use of diuretics or late admission after stroke onset.

Hypervolemia is usually due to cardiac failure, overtreatment with fluids or inappropriate antidiuretic hormone secretion. A slightly negative fluid balance is often desirable in patients at risk for cardiac failure and mass effect from stroke. Major dehydration should be avoided, however, as other measures to improve cardiac output and to decrease intracranial pressure are available.

Hypotonic solutions (NaCl 0.45% or glucose 5%) are contraindicated due to the risk of brain edema increase as consequence of reduced plasma osmolality (Adams Jr et al., 2003; Toni et al., 2004). Moreover, glucose solutions are not recommended due to the detrimental effects of hyperglycemia.

Severe electrolyte abnormalities are not frequent in patients with ischemic stroke (Diringer, 1992). Still, hyperosmolality in dehydrated patients, hyperkalemia in acute renal failure, or hypokalemia in patients on diuretics may be present. Hypo-osmolality due to the syndrome of inappropriate antidiuretic hormone secretion or to the cerebral salt wasting syndrome can occur during the first days after stroke onset, especially in patients with subarachnoid hemorrhage.

Trials using volume expansion or isovolemic hemodilution by infusing crystalloids or colloid solutions for acute ischemic stroke have been negative (Scandinavian Stroke Study Group, 1987; Italian Acute Stroke Study Group, 1988). Because of the risk of myocardial ischemia, congestive heart failure, pulmonary edema, hypertensive encephalopathy, or increased brain edema, this approach would also require close cardiovascular monitoring. At present, these strategies to improve blood flow are not recommended for acute ischemic stroke, even though isovolemic or hypervolemic hemodilution have been used successfully to prevent ischemia secondary to vasospasm following subarachnoid hemorrhage (Mayberg et al., 1994b).

56.11.2. Monitoring

In most patients, fluid balance does not need to be measured, but hydration status can be estimated clinically from vital signs, cardiorespiratory examination, dryness of mucosae, and an estimation of urinary output. In patients who have manifest volume deficiency or overload or who are at risk for it (see above), measuring input and output using a urinary catheter, and measuring central venous pressure may be necessary. The latter should be maintained at approximately 8–10 cm H_2O. Monitoring of electrolytes should be adapted to initial abnormalities, stroke severity, and concomitant medical conditions. When major corrections of fluids and electrolytes are required, continuous clinical and ECG monitoring must be available.

56.11.3. Management

Peripheral venous access is sufficient for initial fluid management in most patients. There is no consensus of whether the access should preferably be on the paretic or on the other side. A central venous catheter is indicated in case of infusion of larger volumes of fluids, high osmolality solutions or irritant substances, or in unstable patients. It also allows measures of central venous pressure (Toni et al., 2004). In a euvolemic patient with no other specific conditions, initial intravenous isotonic saline or Ringer's solution should be given at approximately 25 ml per kg per 24 hours. Reasons to increase or decrease this rate are mentioned in the above paragraph.

The usual cause for hypovolemia with hyperosmolality is insufficient hydration of a patient with increased demands, often pneumonia and fever. The free water deficit can be calculated in this situation, and the patient may transiently receive glucose-free hypotonic solution to correct it. Normo-osmolar hypovolemia due to insufficient hydration or sepsis should be treated with a high rate infusion or repeat boluses of isotonic fluids. Hyperosmolar hypovolemia may be related to dehydration. If cerebral salt wasting syndrome is the cause of hypovolemia (which is usually hypo-osmolar), increases in input volume and sodium loading are required.

Hypervolemia from cardiac failure requires salt and fluid restriction. Diuretics given as boluses or continuous

intravenous infusion may be necessary in order to achieve a negative fluid balance. And rate-controlling medication, positive inotropic medication, or reduction of afterload will improve cardiac function. Hypervolemia due to the syndrome of inappropriate antidiuretic hormone secretion is managed by fluid restriction or administration of hypertonic saline.

Electrolyte abnormalities should be investigated and corrected according to severity and suspected duration. Precipitated increase of natremia may result in pontine or extra-pontine myelinolysis. Potassium disturbances increase cardiac arrhythmias. Severe hyperkalemia may require transient intravenous glucose and insulin treatment. Hypokalemia is corrected with oral or intravenous potassium.

56.12. Blood glucose

56.12.1. Overview and pathophysiology

Hyperglycemia is defined as plasma glucose levels above 6.7 mmol/l (120 mg/dl). Patients with hyperglycemia in the acute stage of stroke may be divided into four groups: (1) patients with known diabetes, (2) with undiagnosed newly discovered diabetes, (3) with impaired fasting glucose, and (4) without any of these underlying conditions (also called "pure stress hyperglycemia"). Between 5% and 28% of stroke patients have previously undiagnosed diabetes (Gray et al., 1987; Kiers et al., 1992).

Hyperglycemia is present on admission in about two-thirds of diabetics and in about 40% of non-diabetics, with an overall incidence for hyperglycemia in about 50% of patients (Capes et al., 2001; Muir et al., 2007). It affects all clinical subgroups of stroke, including hemorrhagic and lacunar strokes (Scott et al., 1999).

The pathogenesis of hyperglycemia in patients without diabetes is incompletely understood. Based on the correlation between the severity of stroke, glycemic serum levels (Candelise et al., 1985; Jorgensen et al., 1994) and the elevation of hormones such as cortisol (Mitchell and Kirckpatrick, 1997), a stress response is likely. The latter may be further enhanced by concomitant cardiac disease, aspiration pneumonia, or other infections. Most often these patients do actually have some degree of insulin resistance and impaired insulin secretion, which explains why they are not able to maintain normoglycemia during the stress response. Moreover, it can be seen as a prediabetic stage with an increased risk of overt diabetes in the future. This risk can however be reduced efficiently by medical and lifestyle interventions. Hypoglycemia may be caused by advanced liver disease, insulin secretagogues, long-acting insulin preparations, malnutrition, and more rarely by endocrine diseases like adrenal insufficiency or insulinoma.

Hypoglycemia can rarely mimic an acute ischemic infarction (Huff, 2002). Alterations in behavior, worsening neurological deficits, and decreased levels of consciousness may indicate hypoglycemia and is usually rapidly detected and corrected in a monitored stroke unit. Prolonged and profound hypoglycemia may lead to irreversible brain damage in patients without stroke. The influence of hypoglycemia on acutely ischemic tissue is unknown in humans.

Stroke severity of diabetic and non-diabetic patients is similar in most studies (Toni et al., 1992; Jorgensen et al., 1994; Karapanayiotides et al., 2004). Hyperglycemia in non-diabetics during the acute phase of ischemic stroke is an independent prognostic factor for a poor outcome, regardless of age, severity of stroke, or type of stroke (Candelise et al., 1985; Weir et al., 1997; Bruno et al., 1999; Capes et al., 2001; Muir et al., 2007). A negative influence on prognosis is less clear for hemorrhagic stroke (Capes et al., 2001). In diabetic patients, most studies show that initial hyperglycemia and its severity do not influence prognosis independently of other factors (Murros et al., 1992; Capes et al., 2001; Karapanayiotides et al., 2004). Still, in a few studies, early mortality was higher in diabetic patients (Toni et al., 1992; Jorgensen et al., 1994) and recovery was slower (Jorgensen et al., 1994). Differences in patient population, functional outcome scales used, and follow-up duration may account for the contradictory results.

Several reasons why hyperglycemia leads to poorer outcome in non-diabetics are cited: increasing tissue acidosis secondary to anerobic glycolysis, increased blood–brain barrier permeability (Adams Jr et al., 2003), and decreased fibrinolysis. These and possibly other mechansims (protein catabolism, oxidative stress, endothelial dysfunction) lead to less penumbra survival (Parsons et al., 2002) and to larger stroke volumes (Candelise et al., 1985; Toni et al., 1994). Furthermore, hyperglycemia decreases the efficacy and increases the hemorrhage rate of thrombolysis (Bruno et al., 1999; Kase et al., 2001).

Which level of hyperglycemia is harmful and the degree to which blood sugar should be lowered remains unknown. The meta-analysis by Capes et al. (2001) has shown a correlation between even mildly elevated glucose levels of 6.1–7 mmol/l on admission and an increased risk of 30-day mortality and poor functional recovery.

Data on the effect of treatment of acute hyperglycemia are scarce. A pilot study on patients with mild to moderate hyperglycemia randomized to saline or a

10% glucose potassium insulin infusion, showed that glucose–potassium–insulin infusion was safe, despite a significant decrease in blood pressure (Scott et al., 1999). Trials with strict control of blood sugar (aim: 4–6 mmol/l) in critically ill patients with diverse pathologies have shown reduced morbidity (Van den Berghe et al., 2001, 2006) and mortality (Van den Berghe et al., 2001). Although there is general agreement to recommend control of hyperglycemia following stroke, currently recommended treatment thresholds reflect this uncertainty. They vary between 8.3 mmol/l (150 mg/dl) (Diez-Tejedor and Fuentes, 2004), and 16.6 mmol/l (300 mg/dl) (Adams Jr et al., 2003). Among several ongoing trials, the United Kingdom Glucose Insulin in Stroke Trial (GIST-UK) is the first one to have reported results (Gray, 2007). A protocol of combined insulin–glucose–potassium infusion did not change the mortality or other outcomes significantly. Reasons for the absence of an effect may have been the relatively mild initial hyperglycemia, a significant blood pressure lowering effect of the treatment, the relatively late onset of treatment (median of 13 hours) when penumbra had already disappeared, and an insufficiently aggressive adoption of treatment.

56.12.2. Monitoring

Glycemia fluctuates during the acute phase of stroke and detection of hyperglycemia increases with the frequency of blood glucose measurements. After an initial blood glucose measure in the prehospital phase, monitoring of capillary serum glucose by venous puncture or fingerstick with a bedside device (standardized to plasma values) is recommended. If the initial value is normal, measures may be repeated at 4–6 hour intervals during the first 24 hours, then once to twice daily. If they are elevated and treatment with intravenous insulin is initiated, initial frequency of measures should be hourly, then every 2–4 hours once glycemia and infusion rate are stable. Devices that allow continuous subcutaneous glucose measurements are now being tested in the hospital setting.

56.12.3. Management of hyperglycemia

To prevent hyperglycemia, any use of solutions containing glucose should be avoided. Infections and fever should be treated promptly. Prehospital treatment of hyperglycemia has not yet been tested and cannot be recommended at this stage. Hyperglycemia upon arrival in the hospital is best managed by continuous intravenous insulin administration. This approach is necessary to allow safe and rapid enough (within hours) achievement of persistent normoglycemia. Intermittent subcutaneous treatment in contrast takes usually several days to obtain glycemic control. As discussed above, hyperglycemia should certainly be treated above 10.0–16.6 mmol/l (180–300 mg/dl) (Adams Jr et al., 2003; Toni et al., 2004). Different schemes of intravenous insulin administration are published and acceptable (Trence et al., 2003; Goldberg et al., 2004). During continuous insulin infusion, hypokalemia should be sought actively and treated. The addition of glucose to the insulin infusion (Scott et al., 1999) does not seem necessary (Trence et al., 2003; Goldberg et al., 2004).

56.12.4. Management of hypoglycemia

Hypoglycemia should be treated promptly by an intravenous bolus of dextrose or infusion of 10–20% glucose, independently of whether it is spontaneous or caused by hypoglycemic treatment. Oral glucose or dextrose are alternatives for awake patients without major dysphagia. Fingerstick glucose measurements should initially be repeated frequently after an episode of hypoglycemia.

56.13. Body position and mobilization

56.13.1. Overview and pathophysiology

A benefit of early mobilization in bed (after the first few hours) and out of bed (after the first few days) is likely based on observational studies, showing that thromboembolic complications, pneumonia, and pressure sores can be reduced (Hacke et al., 2003). Inappropriate mobilization and positioning during bed rest contribute to the development of algoneurodystrophy (CRPS I, complex regional pain syndrome of type I) (Braus et al., 1994), contractures, orthopedic complications, and pressure palsies. A theoretical concern of too-rapid verticalization of the acute ischemic stroke patient is hypoperfusion in the ischemic stroke tissue where autoregulation is abnormal, leading to infarct growth. It seems that verticalization of acute stroke patients does not lower systemic blood pressure (Panayiotou et al., 1999), but decreases intracranial blood flow (Wojner et al., 2002) months after the stroke (Novak et al., 2003).

56.13.2. Monitoring

Although body position should be regularly monitored by nurses and physicians, patients who are not compliant with prescribed positions should not be restrained or sedated. Surveillance of the skin helps prevent development of pressure sores. Close clinical monitoring by neurological nurses, physiotherapists, or doctors

during the verticalization may permit the detection of clinical worsening, indicating critical local hypoperfusion. This observation should lead to a slower pace of verticalization (see below).

56.13.3. Management

There are no randomized studies comparing early (for example, 1–3 days) versus late (for example, 10 days) mobilization on the outcome in stroke patients. Mobilization and regular positioning (at least every 2–4 hours) while the patient is in bed is critical to reduce the risk of pressure sores. Mobilization out of bed within the first days after stroke is recommended (Adams Jr et al., 2003; Toni et al., 2004), and a practical scheme based on pathophysiological considerations has been published recently (Diserens et al., 2006). It is recommended that patients with TIAs or with intracerebral hematomas without mass effect be mobilized immediately and according to their tolerance. Patients with acute ischemic stroke may be left at 0° for the first 24 hours when sufficient local cerebral blood flow may be most likely to prevent transformation of penumbra into infarct. It is felt that this potential salvage of tissue is more important than the risk of bronchoaspiration during this phase. Thereafter the patient can be verticalized progressively on day 2 and get out of bed on day 3 unless worsening occurs on mobilization. If mass effect is present, a 30° position is recommended until its resolution. Once out of bed, measures to avoid falls are an important part of mobilization (Tutuarima et al., 1997).

56.14. Dysphagia, bronchoaspiration, and nutrition

56.14.1. Overview and pathophysiology

Malnutrition is present in up to 34% of stroke patients on admission (Dávalos et al., 1996; FOOD Trial Collaboration, 2003), both in the form of obesity and malnourishment. Although obesity and diabetes are over-represented in stroke patients (Lees and Walters, 2005), malnourishment is of greater concern following an acute stroke. Weight loss beyond 5–10% is frequent in the first weeks after stroke (Finestone et al., 1995). Malnutrition and in particular hypoalbuminemia increases the risk of complications, independently of the body mass index (BMI) (Gariballa et al., 1998; FOOD Trial Collaboration, 2003).

Dysphagia occurs in about 50% of stroke patients in the acute phase (Martino et al., 2005), and then decreases at various rates. Its detection depends on the type of evaluation and may often be clinically silent, even weeks after the stroke (Horner and Massey, 1988; Martino et al., 2005). Like malnutrition, dysphagia is a predictor of complications, delayed recovery, and poor outcome (Mann et al., 1999; Sharma et al., 2001). Patients with brainstem stroke, multiple or pre-existent lesions, and large hemispheric lesions are at greatest risk for bronchoaspiration (Smithard, 2002).

56.14.2. Monitoring

Decreased level of consciousness, a high NIHSS, cognitive impairment and hemineglect, oral apraxia, dysarthria, dysphonia, impaired voluntary cough, and respiratory distress indicate a patient at high risk for dysphagia. Signs of bronchoaspiration should be sought daily including a cough or change of voice after swallowing, new, recurrent or persistent fever, abnormal percussion or auscultation of the chest, oxygen desaturation, tachypnea, and tachycardia.

If the patient can swallow small amounts of water in increasing volumes without coughing or changing of the voice (DePippo et al., 1994), normal diet may be attempted. If liquids cannot be swallowed safely, thickened liquids may be tried. A preserved gag reflex does not indicate safety from aspiration. Videofluoroscopic swallowing evaluation with modified barium may be indicated after evaluation by a swallowing specialist, especially if there is persistent or unusual dysphagia.

Evaluation of the nutritional status on admission includes calculation of the BMI, measurements of blood cell count, albumin, creatinine, and vitamins in selected patients. Thereafter, patients may be monitored for insufficient nutrition by an estimation of daily calorie intake, or by systematic calorie counts. Combined with weekly weighing, this information can be used to detect patients at risk for malnourishment, for example by using the Kondrup score (Kondrup et al., 2003). Other than dysphagia, patients with a low BMI on admission, medical complications, poor appetite, and cognitive dysfunction may be at particular risk for malnutrition after stroke. When nutrition is reintroduced, blood sugar should be actively monitored and hyperglycemia treated, especially in patients with hyperglycemia on admission.

56.14.3. Management

After performing bedside evaluation for dysphagia (see above), it can be determined whether the patient can safely swallow any food (including liquids), thickened food, or nothing at all. In the latter case, patients should receive intravenous saline, and the bedside water swallow test should be repeated daily. Patients

with persistent dysphagia are not only at risk of aspirating their own saliva and gastric juice, but also food given by gastric tubes. The evaluation and swallowing training by specialized nurses or logopedic ergotherapists for patients with persistent dysphagia may contribute to the management of dysphagia (Carnaby et al., 2006).

General measures in patients with dysphagia include elevation of the head off the bed as soon as possible (see section on mobilization, below) and for most of the day and night. Mobilization out of bed, avoidance of sedating medication, good oral hygiene, adaptation of texture, temperature, and taste of food may help with swallowing and its rehabilitation. Hypersalivation, hiccup, and nausea should be treated promptly.

Nutritional consultation should be obtained if chronic or acute malnutrition is suspected (Kondrup score) (Kondrup et al., 2003), if oral feeding is impossible for a prolonged phase, or if poor eating habits are considered an etiological factor in the current stroke. In the largest randomized trial to date, routine nutritional supplementation has not improved outcome (Dennis et al., 2005b).

If major dysphagia persists, gastric or jejunal tube feeding is started about day 5 or later depending on the estimated risk of malnourishment. This approach showed a trend of decreased mortality and poor outcome (Dennis et al., 2005a; Nakajima et al., 2006). Enteral nutrition is introduced progressively through the tube, watching for regurgitation, diarrhea and hyperglycemia. Tube feeding should probably be halted for at least 4 hours during night hours when the risk of gastric reflux is higher. This will also allow physiological acidification of gastric juice. Feeding through a small nasogastric or a percutaneous tube does not prevent rehabilitation of dysphagia, and may allow progressive transition of percutaneous to oral feeding. Patients with potential or manifest mass effect from the stroke should not be given enteral nutrition until resolution of this threat.

If oral nutrition cannot be resumed within 2–4 weeks, percutaneous placement of an endogastric tube (PEG) may prevent more denutrition than nasogastric tube feeding in some studies (Norton et al., 1996), but not in others (Dennis et al., 2005a). The decision to place a PEG may be taken earlier if the likelihood of persistent dysphagia and malnourishment is considered high after the first week or so. Placing the end of the tube into the jejunum decreases the risk of aspiration of gastric material in some preliminary studies (Montejo et al., 2002), but cannot be recommended routinely as yet. Patients with a tracheal cannula are not protected from bronchoaspiration, even if a balloon is inflated. Swallowing should be evaluated and managed as in any other patients, although it may be more difficult (Murray and Brzozowski, 1998). Parenteral nutrition in patients with persistent dysphagia or with malnutrition potentially carries more risks than benefits and is very rare needed.

56.15. Brain edema, increased intracranial pressure, and hemicraniectomy

56.15.1. Overview and pathophysiology

Edema of the ischemic brain is frequent and mainly of the cytotoxic type. “Malignant” cerebral edema has been defined as a clinico-radiological syndrome characterized by a decrease of the level of consciousness and oculocephalic deviation with progressive truncal encephalic involvement. It usually occurs between the third and fifth day after stroke onset, but occasionally starts within the first 24 hours. It carries a dismal prognosis, with more than half of the patients dying, usually from brain herniation (Hacke et al., 1996). Risk factors for malignant brain edema are, other than younger age, multiple territory strokes (Kasner et al., 2001), a high initial NIHSS (Krieger et al., 1999), severe hypertension during the acute phase of stroke (Krieger et al., 1999), and large hypodensity on CT scanner (Kasner et al., 2001). Large DWI volumes and very low apparent diffusion coefficient (ADC) values on MRI may also predict edema (Oppenheim et al., 2000; Thomalla et al., 2003). In cerebellar lesions, decreased level of consciousness (Jauss et al., 1999), and radiological signs of mass effect (Koh et al., 2000) may predict herniation.

56.15.2. Monitoring

As there are no reliable non-invasive measurements of intracranial pressure to date, clinical monitoring remains of great importance. Increased headaches, yawning, decreased level of consciousness, ipsilateral corticospinal signs from compression of the (mesencephalic) cerebral peduncles (“Kernohan’s notch”), and (usually) contralateral mydriasis indicate progressive and dangerous mass effect (Ropper and Shafran, 1984). Invasive measurement of intracranial pressure has been found to be of modest value in predicting complications and outcome (Schwab et al., 1996). It may be indicated in patients who are difficult to monitor clinically, or after craniectomy for mass effect. Whenever there is a worsening of the neurological status without an obvious cause, neuroimaging should be performed urgently. The signs associated with mass effect in the posterior fossa have been well described by Koh et al. (2000).

56.15.3. Management

An early decision about craniectomy can and should be taken during the hyperacute ("honeymoon") period where even patients (with right hemispheric lesions) may participate in the decision making. A joint discussion of the stroke specialist, the neurosurgeon, and the neurointensivist with the patient and the family will help to take appropriate decisions. Good candidates for decompressive craniectomy are younger patients (especially below 50 years of age) (Gupta et al., 2004; Uhl et al., 2004) with an intermediate level of consciousness and no mydriasis at the time of intervention. Contrary to common belief, the side of the lesion does not seem to influence outcome in the long term (Gupta et al., 2004; Uhl et al., 2004). Despite the success of craniectomy in the combined analysis of randomized controlled trials (Vahedi et al., 2007) in terms of survival and handicap, it should be remembered that these patients have severe strokes and that they rarely return back to their usual activities in the long term. The threshold for posterior craniectomy which is usually combined with cerebellectomy should be low for mass effect in the cerebellum (Krieger et al., 1992).

General measures for patients with intracranial hypertension include avoidance of fever, hyperhydration and hypotonic fluids, vasodilating medications, elevation of bed at about 30°, and no enteral nutrition. Severe hypertension should be treated carefully, as cerebral perfusion pressure needs to be maintained.

It may be decided to withhold aspirin (but not the prophylaxis against venous thrombosis) for a few days, as craniectomies under aspirin probably have a higher risk of bleeding complications. If craniectomy is performed for the anterior circulation, a large (about 12 cm long) bone flap should be removed and the brain covered with dura only. Ischemic tissue is usually not removed in the anterior fossa. If hydrocephalus is present, drainage of cerebrospinal fluid via an intraventricular catheter can rapidly lower intracranial pressure.

If potentially life-threatening cerebral edema is identified, medical measures to decrease intracranial pressures should be considered. As most of these measures decrease pressure only transiently and may have profound rebound effects, they should preferentially be offered to patients awaiting urgent craniectomy. Osmotic diuresis with mannitol can be effective (25–50 g given intravenously every 3–5 hours), as can furosemide. Glucocorticoids are not recommended as they may be harmful. Tracheal intubation and mechanical ventilation to achieve a partial pressure of carbon dioxide around 30–35 mmHg may lower the intracranial pressure. Hypothermia may be partially effective for reduction of mass effect (Schwab et al., 2001; Georgiadis et al., 2002; De Georgia et al., 2004), but also show a rebound effect when discontinued.

56.16. Hemorrhagic transformation

56.16.1. Overview and pathophysiology

Hemorrhagic infarct, that is, patchy and minor bleeding into ischemic tissue, is fairly frequent, especially if sought with gradient-echo MRI or on autopsy. Blunt hematoma (also termed "Parenchymal hemorrhage type II", (Larrue et al., 2001) occurs rarely but is a catastrophic event in a patient about to recover from a very recent ischemic stroke. Risk factors for hemorrhagic transformation are strokes due to cardio-embolism, particularly endocarditis. Early and excessive anticoagulation after acute stroke (Gubitz et al., 2004; Paciaroni et al., 2007) and of course intravenous thrombolysis (Hacke et al., 2004) increase the risk of hemorrhagic transformation. Thrombolysis-related hemorrhage is discussed in Chapter 57. Interestingly, series of patients with local (intra-arterial) thrombolysis (PROACTII) (Furlan et al., 1999) and even with pure mechanical recanalization (Smith et al., 2005) have similar hemorrhage rates as patients thrombolyzed intravenously. This suggests that the breakdown of the ischemic endothelium and blood–brain barrier may be particularly related to ischemia and reperfusion with high blood pressure rather than to thrombolysis itself (Khatri et al., 2007).

56.16.2. Hemorrhagic transformation—monitoring

Any worsening of the neurological status, especially when accompanied by signs of intracranial hypertension (see above), may indicate hemorrhagic transformation. Repeat imaging by CT or gradient-echo MRI usually differentiates between mass effect from ischemic edema and from hematoma formation.

56.16.3. Management

If hemorrhagic transformation is symptomatic, antithrombotics are usually stopped for a few days or weeks. Acute platelet and fresh frozen plasma transfusions are of unproven value. They may be considered if an underlying coagulation abnormality is present (such as after thrombolysis). Severity of bleeding, of the underlying stroke, and age will dictate invasive measures such as decompressive craniectomy or hematoma removal. These interventions may be performed a few hours after thrombolysis if coagulation parameters (including fibrinogen) and platelet counts remain within normal limits.

56.17. Cardiac diseases and complications

56.17.1. Overview and pathophysiology

Myocardial ischemia, cardiac arrhythmias, and cardiac failure may be the cause or consequence of acute stroke. Sudden death, arrhythmias, heart failure, and acute myocardial infarction (Broderick et al., 1992; Vingerhoets et al., 1993) may be triggered by neurogenic (Oppenheimer, 2006), by endocrine mechanisms (Kolin and Norris, 1984), or by medication withdrawal. Multiple ECG and cardiac enzyme abnormalities have been described in relation to stroke, sometimes reflecting cardiac disease, sometimes mimicking it (Chalela et al., 2004; Jensen et al., 2007). An elevation of troponin-T seems to be associated with an increased mortality after stroke (James et al., 2000; Jensen et al., 2007). While the ischemic-like changes and QT prolongation in patients with subarachnoid hemorrhage are mainly a direct consequence of the neurological disease, they seem more often related to pre-existing coronary artery disease in patients with ischemic and hemorrhagic stroke (Khechinashvili and Asplund, 2002). Lesions affecting the right or left insula and the medulla oblongata (Oppenheimer, 2006) may carry a higher risk for inducing cardiac complications due to their importance in central autonomic control.

56.17.2. Monitoring

Patients are regularly assessed by physicians and nurses for the presence of retrosternal pain, tachypnea, tachycardia, jugular venous distension, peripheral edema, or a third heart sound. Every stroke patient should have an initial 12-lead ECG and chest x-ray, followed by continuous ECG monitoring for 24 hours (Toni et al., 2004), or longer if at risk of cardiac complications. Threshold for serial troponine and creatinine-kinase MB in the serum should be low. Echocardiography may be necessary on an urgent basis in the case of cardiac decompensation, and coronary angiography should be rapidly available for patients with a high likelihood of unstable coronary disease.

56.17.3. Management

Restoration of normal rhythm by drugs, cardioversion or pacemaker is mandatory if the patient is hemodynamically unstable. In stable acute stroke patients with arrhythmia, electrical cardioversion and full dose anticoagulation before cardioversion may not be safe in the presence of large volume infarcts. Persistent tachycardia should be slowed with medications even if asymptomatic. Treatment of stroke-related ECG-phenomena with beta or alpha/beta blocking has been recommended when not contraindicated (Toni et al., 2004).

Acute coronary syndromes usually require aggressive intervention, including nitroglycerin, lowering of high blood pressure, double or triple antiplatelet treatment, intravenous heparin, beta-blocking agents, converting enzyme inhibitors, statins, and acute coronary stenting. Similarly, acute cardiac insufficiency usually requires lowering of high blood pressure, nitroglycerin, diuretics, beta-blocking agents, and continuous positive airway pressure treatment. Potential unfavorable effects of these treatments on the stroke have to be weighed against their potential benefits for the individual patient.

56.18. Deep venous thrombosis (DVT) and pulmonary embolism

56.18.1. Overview and pathophysiology

Despite progress in prevention and diagnosis, venous thrombo-embolic complications remain a significant reason for morbidity, prolonged hospitalization, and mortality in acute stroke patients. Although detection of a pulmonary embolism around the time of an acute ischemic stroke rises the possibility of a hypercoagulable state or a paradoxical embolus through a patent foramen ovale, immobilization-related thrombo-embolism is the much more frequent relationship between the two diseases. In acute stroke patients, advanced age, immobility, paralysis of the lower extremity, severe paralysis, and atrial fibrillation are associated with a increased risk of DVT. Including asymptomatic patients, up to half of moderately severely affected stroke patients have proximal DVT (Adams Jr et al., 2003).

56.18.2. Monitoring

Acute pulmonary embolism is suspected in patients with dyspnea, tachycardia, or thoracic pain, and DVT in patients with unilateral leg swelling. Clinical probability of pulmonary embolism is estimated for pulmonary embolism with the revised Geneva criteria (Le et al., 2006), and for DVT with the Wells criteria (Wells et al., 2000). D-dimers, multi-array CT of pulmonary arteries (van et al., 2006), or pulmonary scintigraphy, and venous duplex scanning of the legs are then performed in a stepwise fashion according to the level of suspicion.

56.18.3. Management

Administration of low-dose subcutaneous heparin, low-molecular-weight heparin, heparinoids (Gubitz et al., 2004) and/or oral aspirin (PEP study group, 2000) is beneficial for the prophylaxis of DVT and

pulmonary embolism in immobilized patients. Early mobilization, pressure stockings and intermittent pneumatic compression (Kamran et al., 1998) are probably also effective, and are the methods of choice for patients with acute subarachnoid and intracerebral hemorrhage (Lacut et al., 2005). For the latter condition, the subcutaneous administration of low-dose anticoagulants is recommended after 24 hours in stable patients (Steiner et al., 2006).

Treatment of uncomplicated cases consists of parenteral anticoagulation by intravenous heparin (or subcutaneous low-molecular-weight heparins) in therapeutic doses, even in patients with a large volume stroke and risk for hemorrhagic transformation. Patients can be mobilized without delay and oral anticoagulation can be started. Compression stockings and analgesics are added for TVP.

56.19. Antithrombotics in acute stroke

56.19.1. Overview and pathophysiology

Patients not thrombolyzed benefit from early treatment with aspirin (160–300 mg/day) (CAST Collaborative Group, 1997; IST Collaborative Group, 1997) given either orally or intravenously. Other oral antiplatelet regimens have not been tested in the acute phase of stroke, and two randomized trials of intravenous abciximab, an anti-glycoprotein IIb-IIIa antagonist, have not shown any benefit. Aggressive oral antiplatelet treatment for a limited time after TIA is undergoing clinical study.

Administration of low doses of subcutaneous heparin, low-molecular-weight heparin, or heparinoids (Gubitz et al., 2004) and/or oral aspirin (PEP study group, 2000) may be beneficial for prophylaxis of venous thrombosis and pulmonary embolism , but it is not for the stroke itself nor for prevention of early recurrences. Early anticoagulation after ischemic stroke from all causes or from atrial fibrillation has not shown any benefit because it increases the risk of hemorrhage (Paciaroni et al., 2007). It should therefore be the exception. It may be considered empirically in patients who are perceived as having a low risk of hemorrhagic transformation and a high risk of early stroke recurrence, such as in the presence of mechanical heart valves, intracardiac thrombi, severely depressed ejection fraction, acute myocardial infarction, antiphospholipid-antibody syndrome, extracranial or intracranial stenosis with recurrent embolic ischemic events, floating thrombi in the aortic arch or cervical arteries, and symptomatic dissection of extracranial arteries (Adams Jr, 2002). The larger the ischemic lesion, the higher the risk of hemorrhagic transformation seems to be and the more restrictive early anticoagulation should be used.

56.19.2. Monitoring

In the absence of clinically proven acute antiplatelet therapy other than aspirin, and of an established test to measure antiplatelet resistance, no specific blood test is required. Heparin-induced thrombocytopenia needs to be watched for in patients receiving this drug, and probably also its analogs.

Over-anticoagulation and very high blood pressure in anticoagulated patients increase the risk of hemorrhagic transformation. Therefore, these patients should be carefully monitored with coagulation tests and frequent BP monitoring.

56.19.3. Management

Unless the patients undergo intravenous thrombolysis, they should immediately receive aspirin in doses of 160–325 mg once acute ischemic stroke is confirmed. Prophylactic doses of heparin or low-molecular-weight heparin are also given. Patients considered at high risk for craniectomy may not receive aspirin for a few days to avoid bleeding complications during the intervention.

For patients with a definite indication for short- or long-term anticoagulation, there is no consensus about the timing when it should be started (Brott and Bogousslavsky, 2000; Paciaroni et al., 2007). Immediate treatment may be considered in patients without a significant morphological lesion, such as in most TIA patients. In patients with minor and large-size infarction, anticoagulation should probably be withheld for 3–5 and 7–10 days, respectively (Michel and Bogousslavsky, 2004b; Paciaroni et al., 2007).

If early anticoagulation is considered, a bolus is avoided, except in patients with cerebral sinus vein thrombosis. Intravenous heparin may be preferable to subcutaneous low-molecular-weight heparins as its action can be more rapidly reversed in the case of hemorrhagic complications. In the subacute phase of stroke, oral anticoagulation should be preceded by parenteral treatment because of transient hypercoagulability with vitamin K antagonists in some patients.

56.20. Early neurorehabiliation, neurobehavioral aspects, pain, and sphincter problems

56.20.1. Early neurorehabiliation

Early introduction of rehabilitation in acute stroke patients improves functional prognosis (Stroke Unit Trialists' Collaboration, 2000) and is one of the main contributing factors as to why patients treated in stroke units do

better than others (Jorgensen et al., 1999). Old age alone is no reason to exclude a patient from an effective rehabilitation program (Jorgensen et al., 2000). Such an early rehabilitation should include strategies to detect and manage dysphagia and immobility (see above), risk of falls (Tutuarima et al., 1997), injury to the skin, pain, shoulder injury (Braus et al., 1994), and depression.

56.20.2. Acute neurobehavioral aspects

Agitation may interfere greatly with care and early rehabilitation. It is usually due to a confused state, which itself may be related to the localization or type of stroke. Other frequent causes are pre-existing cognitive problems, retention of urine or stool, metabolic and infectious complications, use of psychoactive drugs, and drug or alcohol withdrawal. Underlying causes should be sought and treated, and a calm, reassuring environment be provided.

If treatment of the underlying cause of agitation is insufficient, a stepwise approach using increasing doses of oral neuroleptics (probably of the atypical type in patients with parkinsonism or gait problems), benzodiazepines (for withdrawal symptoms) or older-generation antihistamines may be tried. Some of these drugs may increase the risk of cardiovascular death and should be used carefully (Schneider et al., 2005). Over-sedation and drugs to increase sleep should be avoided in the acute phase of stroke. They may increase the functional deficit, mask neurological worsening, slow cognitive and neurological recovery, and increase medical complications.

Alcohol withdrawal should be treated with fluids, frequent and sufficient use of benzodiazepines according to the symptom severity, and vitamin supplements. Acute nicotine withdrawal may be prevented with oral or cutaneous nicotine preparations, and rarely with benzodiazepines. These, professional counseling, and certain serotoninergic drugs, may be useful in promoting long-term nicotine abstinence.

56.20.3. Pain

A careful history taking and clinical examination should be performed if the patient complains of or behaves like having pain. Headaches are related to mass effect, cervical artery dissection, subarachnoid blood, meningitis, arterial spasms, or vasculitis such as giant cell arteritis. A painful hemisyndrome related to a lesion in the central spinothalamic or lemniscal pathways may start in the first days after stroke. The most frequent causes of extremity pain in the subacute phase of stroke are arthritis (degenerative, gout, or chondrocalcinosis), fall-related fractures, paralysis-related distension of tendons and articular capsules, subluxations, and complex regional pain syndrome. As all of these painful conditions require specific treatments they are not described in detail here.

56.20.4. Urinary problems

Urinary retention due to weakened detrusor reflex may be triggered by bed rest and medications in patients with pre-existing neurological and urological conditions (Brittain et al., 1998). Urinary incontinence is usually due to supraspinal loss of inhibition. Indwelling urinary catheters should be avoided or withdrawn, except if the patient has major problems with communication, cannot be mobilized on a pan or toilet, has skin problems, or needs measurement of urinary output. There is no advantage of catheter clamping before withdrawal in non-chronic situations. If several trials of removing the catheter have been unsuccessful, an urology consult should be obtained.

56.20.5. Gastrointestinal problems

Gastrointestinal hemorrhage is infrequent in acute stroke patients, despite increased stroke-related stress and use of antithrombotics. Routine use of drugs that increase gastric pH is probably not beneficial in nasogastric tube feeding.

Stool frequency is usually decreased in the first days and weeks after stroke because of decreased nutrition, bed rest, and medication. Diarrhea may develop from tube feeding, and fecal incontinence may occur from central loss of sphincter control. Constipation can be prevented by early mobilization of the patient (see above) and avoidance of dehydration. Daily oral laxatives and high-fiber diet may be prescribed after 3 days without bowel movement, or before if abdominal discomfort develops. Rectal treatments may be added on an as-needed basis. In cases of major abdominal pain and ileus, laxatives should be suspended, and radiological investigations for constipation, abdominal or retroperitoneal pathology should be performed.

56.21. Conclusions

General measures during the acute phase of stroke improve patient outcome, probably through neuroprotective effects. An effective prehospital detection and triage system with immediate referral to a stroke center increases the number of patients that can be treated. Optimized management in the prehospital, ER, and early treatment phases contributes to large time savings, more accurate diagnosis, and more effective treatment. Most complications from acute stroke and its treatment

can now readily be detected, prevented, and treated, especially if the patient is surveyed by and treated by dedicated medical personnel that are well organized.

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Chapter 57

Thrombolytic therapy for acute stroke

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57.1. Introduction

Stroke is the third leading cause of death after myocardial infarction and cancer and the leading cause of permanent disability in Western countries (WHO Guidelines Subcommittee, 1999). Furthermore, it is the leading cause of disability-adjusted loss of independent life years. Aside from the tragic consequences for the patients and their families, the socio-economic impact of more or less disabled stroke survivors is evident as stroke patients with permanent deficits such as hemiparesis and aphasia will frequently not be able to live independently or pursue an occupation. The added indirect and direct cost estimates for a survived stroke vary between US$35,000 and US$50,000 per year. In the face of our aging population and the skewed population pyramid the incidence and prevalence of stroke is expected to rise. Therefore, an effective treatment for this devastating disease is desperately needed.

After introduction of thrombolytic therapy for the treatment of acute myocardial infarction in the early 1990s (GUSTO Angiographic Investigators, 1993), major trials for the evaluation of this new therapeutic approach to ischemic stroke were initiated. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction with a central infarct core of irreversibly damaged brain tissue and a more or less large area of hypoperfused but still vital brain tissue (the ischemic penumbra), which can be salvaged by rapid restoration of blood flow (Astrup et al., 1981; Schellinger et al., 2001c). Therefore, the underlying rationale for the introduction and application of thrombolytic agents is the lysis of an obliterating thrombus and subsequent re-establishment of cerebral blood flow by cerebrovascular recanalization.

The characterization of potentially reversible versus irreversible loss of function is based on the concept of the ischemic penumbra (Ginsberg and Pulsinelli, 1994). Until recently only positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging could approximately define ischemia and penumbra thresholds. This is however not feasible for emergency services for broad populations, where imaging in an acute setting is confined to computed tomography (CT) and also increasingly magnetic resonance imaging (MRI). Only the advent of new imaging techniques such as novel sequences and continuing improvement of imaging hardware allows the improvement of the diagnostic yield. An adequate therapy demands an adequate diagnostic workup initially (Davis et al., 2003; Fiebach and Schellinger, 2003; Hjort et al., 2005).

57.2. Initial patient assessment

In addition to standard care in acutely ill patients such as stabilization of vital parameters, application of venous lines and so on, an accurate assessment of the patient's neurological status is essential (Schellinger et al., 2001c). With the use of standard stroke scales such as the National Institutes of Health Stroke Scale (Lyden et al., 1994) stroke severity can be rapidly graded, with the goal of excluding small as well as too severe infarctions from a potentially hazardous therapy. Furthermore, information about the time-point of stroke onset is crucial as the therapeutic time window is small. Besides the usual contraindications for

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thrombolytic therapy in general, intracranial hemorrhage must be excluded by imaging procedures such as CT or MRI (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995). Proof of an occluded vessel by Doppler ultrasound, CT angiography (CTA), MR angiography (MRA) or digital subtraction angiography (DSA) should be established, at least when thrombolysis is performed later than 3 hours after symptom onset; however, it is not yet required for the indication of thrombolytic therapy. Overall, in unselected patients the proverb "time is brain" holds true; therefore, a rapid workup of the patient who is a potential candidate for thrombolytic therapy is mandatory. A rule of thumb adapted from the American Heart Association for timing from "door" in myocardial infarction is 10 minutes for seeing the doctor plus 15 minutes for getting the CT results and a maximum of 60 minutes total from arrival to bolus application of the thrombolytic. Although average door-to-needle times according to registries such as canadian alteplase for stroke effectiveness study (CASES) and safe implementation of thrombosis in stroke (SITS) (Hill and Buchan, 2005) exceed 60 minutes, there is a lot of room left for improvement. In fact, thrombolysis can be performed much faster than 60 minutes from arrival in the ER.

57.3. Thrombolytic agents in use

In 1933, Tillet and Garner reported that streptococci released a substance that dissolved blood clots. Streptokinase has a molecular weight of 47,000 Daltons; it is a single-chain protein with only minimal intrinsic enzymatic activity that combines with plasminogen and leads to its activation to plasmin. As streptokinase is not fibrin-specific, high concentrations may deplete coagulation factors V and VIII, plasminogen, α-II-antiplasmin and fibrinogen, which characterizes the lytic state that impairs plasmatic coagulation and platelet aggregation, and therefore may result in hemostatic failure.

Urokinase has a molecular weight of 54,000 Daltons; it is a double-chain, non-fibrin-specific serine protease that directly transforms plasminogen to plasmin (Bernik and Oller, 1973). As urokinase, like streptokinase, activates bound as well as circulating plasminogen, it may cause depletion of the aforementioned coagulation factors and hemostatic failure. Pro-urokinase or saruteplase is the inactive single-chain precursor of urokinase. It has a low intrinsic activity but the efficacy is approximately 100-fold less than that of urokinase. Pro-urokinase has a significant fibrin specificity, which may be due to a preferential conversion of pro-urokinase to urokinase at the fibrin surface (Lijnen et al., 1989).

Tissue plasminogen activator (tPA) is produced endogenously in physiologic concentrations, synthesized, and secreted by endothelial cells; is relatively fibrin-specific (presence of fibrin enhances tPA effect by three orders of magnitude), leading to a minimal consumption of circulating coagulation factors; and appears as a single- or double-chain polypeptide with a molecular weight of 70,000 Dalton (single-chain form) and a serum half-life of 4–6 minutes if not bound to a fibrin-clot (Rijken et al., 1982; Garabedian et al., 1987). The clinically available form of tPA (rtPA, alteplase) is produced by recombinant DNA techniques as its less commonly used double-chain form (duteplase). tPA is inactivated by plasminogen activator inhibitor type 1 (PAI-1), a 45,000 Dalton protein found in endothelial cells and platelets, which rapidly inhibits circulatory tPA, but only inhibits fibrin-bound tPA slowly (Wagner et al., 1989). In platelet-rich clots there may be enough PAI-1 to result in a significant inhibition of tPA, which may explain their potential resistance to thrombolysis (Potter van Loon et al., 1992; Levy et al., 1994).

Newer fibrinolytics include tenecteplase (TNK), reteplase (rPA), and desmoteplase (DSPA). All are produced recombinantly and their main differences are half-life and fibrin-specificity. TNK is an rtPA mutant with delayed clearance and increased half-life (del Zoppo and Hosomi, 2005) as well as an increased resistance to PAI-1 inhibition. TNK is applied as a double bolus with a 30 minute delay in between and in theory has better lytic properties than older components. It is widely used in acute myocardial infarction; however, it has yet to be tested for stroke beyond a pilot trial (Haley et al., 2005). rPA has been used in single series of intra-arterial thrombolysis for stroke and in pilot trials combining lytics and glycoprotein IIb/IIIa receptors. Although closely related to rtPA, it has a longer half life. rPA is approved for AMI. DSPA is a recombinant PA derived from the saliva of the vampire bat (*Desmodus rotundus*). The most prominent feature of DSPA is its fibrin specificity which is 200 times higher than for rtPA; that is, activation takes place only where fresh clots are formed (clot-selective), half life is longer than 2 hours compared to 8 minutes for rtPA, which allows for a single bolus. Furthermore DSPA is not activated by beta-amyloid, which is a potential advantage with regard to neurotoxicity (Stewart et al., 1998; Epple et al., 2004; Kruithof and Schleuning, 2004). Whether this translates into clinical efficacy with respect to lower bleeding rates remains to be seen.

57.4. Intravenous thrombolysis for ischemic stroke

Up to 85% of all strokes are of ischemic origin and mostly due to blockage of a cerebral artery by a blood clot. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction with a central infarct core of irreversibly damaged brain tissue and an area of variable size of hypoperfused but still vital brain tissue (the ischemic penumbra), which can potentially be salvaged by rapid restoration of blood flow. Therefore, the underlying rationale for the introduction and application of thrombolytic agents is the lysis of a thrombus and subsequent re-establishment of cerebral blood flow by cerebrovascular recanalization and consecutive brain reperfusion (Schellinger et al., 2001b,c). There are in general two strategies in thrombolytic therapy, a local (intra-arterial) approach and a systemic (intravenous) application of the thrombolytic agent. The local delivery of thrombolytic agents, at or within the thrombo-embolism (intra-arterial thrombolysis), has the advantage of providing a higher concentration of the particular thrombolytic agent where it is needed while minimizing the concentration systemically. Hence, local intra-arterial thrombolysis has the potential for greater efficacy with higher arterial recanalization rates and greater safety with lower risk of hemorrhage. Data are controversial, however, and compared to intravenous therapy small. The technique involves performing a cerebral arteriogram, localizing the occluding clot, navigating a microcatheter to the site of the clot, and administering the lytic agent at or inside the clot with or without mechanical destruction of the thrombus and with or without remodeling techniques (percutaneous transluminal angioplasty, stenting).

Grade of vessel occlusion is usually assessed in analogy to the Thrombolysis in Myocardial Infarction (TIMI) score, where TIMI 0 is complete occlusion, TIMI 1 minimal perfusion, TIMI 2 partial flow (recanalization), and TIMI 3 complete flow (recanalization) (TIMI Study Group, 1985). The agents most commonly used or which are under investigation are urokinase, tPA (alteplase), and pro-urokinase, all of which are usually administered at a lower dose than used in the intravenous treatment of acute ischemic stroke.

57.5. The early trials

The first anecdotal report of thrombolytic therapy for ischemic stroke dates back to the early 1960s (Meyer et al., 1963). Three trials in the early 1980s investigated the effect of low-dose intravenous urokinase for the therapy of acute ischemic stroke (Abe et al., 1981; Atarashi et al., 1985; Ohtomo et al., 1985). These trials are different from others for several reasons, such as a late time-point of randomization (up to 5 or 14 days after stroke onset, respectively), the exclusion of presumed cardio-embolic stroke, application of low doses of urokinase given daily for a period of several days, and the lack of assessment of clinical outcome except death and intracerebral hemorrhage.

In the early 1990s three small trials of intravenous thrombolysis with rtPA were carried out (Mori et al., 1992; Haley et al., 1993; Yamaguchi et al., 1993). These trials, though not large enough to prove the efficacy, very well demonstrated the feasibility of early thrombolytic therapy and also suggested a reasonable degree of safety and a potential benefit. All these trials were blinded or double-blinded, randomized, and placebo-controlled. Mori et al. randomized 31 patients with acute carotid artery territory stroke to treatment with either 20 or 30 mega-international units (MIU) duteplase (equivalent to 40 or 60 mg rtPA) or placebo given intravenously for 60 minutes in a time window of 6 hours after stroke onset (Mori et al., 1992). Baseline and post-infusion angiography demonstrated complete or partial reperfusion in 50% of patients treated with 30 MIU duteplase, 44% of those treated with 20 MIU duteplase, and 17% in the control group. Patients treated with 30 MIU duteplase showed earlier and better clinical improvement than those treated with placebo. There was one parenchymal hemorrhage in each group. Yamaguchi and colleagues randomized 98 patients into two treatment arms (20 MIU duteplase or placebo over 60 minutes) within 6 hours (Yamaguchi et al., 1993). According to immediate post-treatment angiography, recanalization rates were significantly better in the treatment group than in patients receiving placebo (21% versus 4%). In the treatment group, 16% of the patients experienced a marked clinical improvement as opposed to 6% in the placebo group; the rates of intracerebral hemorrhage, however, were similar in the two groups. The smallest randomized trial reported was that of Haley et al. (1993), who performed a pilot study with a time window to treatment of 3 hours in preparation for the NINDS rtPA trial (The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995). Twenty patients received 0.85 mg/kg bodyweight of rtPA within 90 minutes, another 7 patients within 91–180 minutes after stroke onset. Six patients in the 90-minute group improved by 4 or more NIH stroke scale (NIHSS) points at 24 hours compared with one patient in the placebo group ($p < 0.05$). There was no difference in the 91- to 180-minutes group, and one fatal intracerebral hemorrhage occurred in the placebo group. Although not large enough to prove the efficacy, they clearly showed the feasibility of early thrombolytic therapy and also

suggested a reasonable degree of safety and a potential benefit. All these trials were blinded or double-blinded, randomized, and placebo-controlled.

In the further course of the text, the following terms will be used: odds ratio (OR), 95% confidence interval (CI), relative risk (RR), events prevented per 1,000 patients treated (EP), number needed to treat to prevent an event (NNT) and p values. The 3- or 6-month outcome is frequently assessed with the modified Rankin scale (mRS) and dichotomized in favorable versus unfavorable outcome (mRS 0–1 versus 2–6) or independence versus dependence or death (mRS 0–2 versus 3–6). Zero points refer to the absence of any residual symptoms, 6 points to death (Rankin, 1957). Another outcome scale is the Barthel index (BI), which measures daily activity by utilizing 10 items, such as urinary and fecal continence and ability to walk (complete dependence = 0 points, functional independence = 100 points, favorable outcome ≥95 points) (Mahoney and Barthel, 1965).

57.6. The streptokinase trials

One pilot study and three large trials investigated the efficacy of streptokinase for acute ischemic stroke. Morris et al. (1995) evaluated 20 patients (10 streptokinase, 10 placebo) within 5.2 hours (placebo) and 5.8 hours (streptokinase). There were three deaths in each treatment group, with a higher incidence of hemorrhage in the streptokinase group ($n = 3$ versus $n = 1$ patients).

57.6.1. MAST-I

The Multicenter Acute Stroke Trial—Italy (MAST-I) was a non-placebo-controlled, randomized trial of streptokinase, which investigated whether, separately or together, streptokinase and aspirin have clinical benefits in acute ischemic stroke when given within 6 hours after symptom onset (Multicenter Acute Stroke Trial—Italy [MAST-I] Group, 1995). A total of 622 patients received either a 1-hour intravenous infusion of 1.5 MU streptokinase (157 patients), 300 mg/day aspirin for 10 days (153 patients), both active treatments (156 patients), or neither (156 patients); intravenous or oral anticoagulation and other antiplatelet agents were to be avoided, and subcutaneous heparin was allowed. MAST-I aimed for 500 patients in each subgroup but had to be stopped because of excessive early hazard in the groups allocated to streptokinase treatment (Hommel et al., 1995). Streptokinase (alone or with aspirin) was associated with high rates of death at 10 days (odds ratio 2.7; 95% confidence interval 1.7–4.3; $2p < 0.001$). Streptokinase (alone or with aspirin) and aspirin (alone or with streptokinase) reduced, albeit not significantly, the incidence of combined 6-month mortality and severe disability: OR for streptokinase 0.9 (95% CI 0.7–1.3) and OR for aspirin 0.9 (95% CI 0.6–1.3). There was a substantial disagreement among the investigators with regard to interpretation of the results of MAST-I. The biostatisticians separately reported a different interpretation, mainly indicating that the excess risk of fatal and disabling hemorrhage is understated and that a potential trend towards benefit of stroke therapy with streptokinase is overestimated (Tognoni and Roncaglioni, 1995): in absolute numbers, 196 of 313 (62.6%) patients treated with streptokinase were dead or disabled at 6 months, which is a negligible difference compared to the 65.7% of patients not receiving streptokinase (203 of 309 patients).

57.6.2. MAST-E

The Multicenter Acute Stroke Trial—Europe (MAST-E) was a placebo-controlled trial that randomized patients with carotid territory stroke to either treatment with 1.5 MU intravenous streptokinase over 1 hour or placebo within 6 hours after stroke onset (Multicenter Acute Stroke Trial—Europe Study Group, 1996). The primary efficacy endpoint was combined mortality and severe disability (Rankin ≥3) at 6 months. The primary safety outcomes were death at 10 days and intracerebral hemorrhage. Because of an increase in mortality in the treated group, the trial was stopped after 310 of the planned 600 patients had been recruited. The incidence of the primary efficacy outcome was similar in the two groups (124 patients in the streptokinase group/126 in the placebo group with Rankin ≥3); however, the early mortality was significantly higher in the streptokinase group (day 10: 34.0% versus 18.2%, $p = 0.002$; 6 months: 46.8% versus 38.3% of patients, $p = 0.06$), which was mainly due to fatal intracerebral hemorrhage. One has to consider, though, that MAST-E allowed early anticoagulation, which was given to 31% of the streptokinase—but only 12% of the placebo-treated patients within 12 hours ($p = 0.04$), and this may have contributed to the high rate of intracerebral hemorrhage in the streptokinase group.

57.6.3. Australian Streptokinase Trial

The Australian Streptokinase Trial (ASK), a randomized, double-blind, placebo-controlled trial with a 3-month follow-up, had a time window of 4 hours for patient recruitment (Donnan et al., 1996). The ASK aimed to determine whether the administration of 1.5 MU streptokinase within 4 hours of the onset of acute ischemic stroke would reduce morbidity and mortality at 3 months (Barthel index ≤60). In addition, a prospective comparison of the patients

randomized within 3 hours and those randomized within 3–4 hours was performed. A total of 340 patients were recruited before the safety committee advised trial suspension because of significantly ($p = 0.04$) poorer outcomes in patients ($n = 270$) treated between 3 and 4 hours after symptom onset (<3 hours: RR 0.66, 95% CI, 0.28–1.58; 3–4 hours: RR 1.22, 95% CI 0.80–1.86), and because of the low recruitment rate in the <3 hours group (70 patients). Streptokinase resulted in too many deaths in the group treated after 3 hours (RR 1.98; 95% CI 1.18–3.35), but not among those treated within 3 hours (RR 1.11; 95% CI 0.38–3.21). There was a non-significant overall trend toward unfavorable outcomes for streptokinase versus placebo (48.3% versus 44.6%; RR: 1.08; 95% CI: 0.74–1.58) and a high rate of intracerebral hemorrhage in the drug-treated group (13.2% versus 3%; $p < 0.01$).

In summary, all of the trials using streptokinase for acute ischemic stroke were prematurely stopped due to a high rate of early death, mostly due to intracerebral hemorrhage, and because of a lack of benefit at outcome in a meta-analysis as well (Cornu et al., 2000). In the streptokinase trials together there were 92 (95% CI 65–120) additional fatal intracerebral hemorrhage per 1,000 treated patients (OR 6.03, 95% CI 3.47–10.47) (Wardlaw et al., 2002). The higher bleeding rate may be due to pharmacological properties of streptokinase other than, for instance, rtPA, additional anticoagulation (MAST-E), a rather small fraction of patients treated within 3 hours, and a rather high dose of 1.5 MU, which is identical to the dose used in myocardial infarction (MI), whereas the rtPA studies (see below) chose approximately two-thirds of the dose used in MI. Other side-effects of streptokinase are a decrease in systolic blood pressure of more than 20 mmHg in 33% (only 6% in the placebo group) as well as anaphylaxis in 2.2% of the patients. Therefore, intravenous administration of streptokinase, outside the setting of a clinical investigation, is dangerous and not indicated for the management of patients with ischemic stroke.

57.7. The rtPA trials

In 1995, the results of the ECASS I and NINDS trials of intravenous rtPA for acute ischemic stroke were published (Hacke et al., 1995; National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995) and followed by ECASS II in 1998 (Hacke et al., 1998) and ATLANTIS in 1999 and 2000 (Clark et al., 1999, 2000). These four trials randomized a total of 2,657 patients to treatment with placebo ($n = 1316$ patients) or intravenous rtPA ($n = 1341$ patients) within 0–3 hours (NINDS), 3–5 hours (ATLANTIS), or 0–6 hours (ECASS I and II) after symptom onset. All four studies required a baseline CT scan to exclude intracerebral hemorrhage, and except for the NINDS study all others also established CT exclusion criteria such as major early signs of infarction. All trials used the 0.9 mg/kg bodyweight dose up to a maximum of 90 mg rtPA, except ECASS I, in which 1.1 mg/kg up to a maximum dose of 100 mg was given. Ten percent of the total dose was given as a bolus; the rest was infused over 1 hour in all four trials.

57.7.1. National Institute of Neurological Disorders and Stroke trial

The National Institute of Neurological Disorders and Stroke (NINDS) trial randomized 624 patients (312 each placebo and intravenous rtPA) within a time window of 3 hours after stroke symptom onset (National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group, 1995). Half of the patients were treated within 0–90 minutes, the other half within 91–180 minutes. The trial had two parts. Part 1 (in which 301 patients were enrolled) tested whether rtPA demonstrated a clinical effect, as indicated by an improvement of 4 points over baseline values in the NIHSS score or the resolution of the neurologic deficit within 24 hours of the onset of stroke (primary endpoint). Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at 3 months, according to scores on the BI, mRS, Glasgow Outcome Scale (GOS), and NIHSS, evaluating each single score and all four as a combined endpoint. A good outcome was defined as a NIHSS score of ≤ 1, GOS $= 1$, BI ≥ 95, and mRS ≤ 1. The median baseline NIHSS score was 14 (rtPA group) versus 15 (placebo group). There was no significant difference between the drug treatment and placebo group in the percentages of patients with neurologic improvement at 24 hours (rtPA 47% versus placebo 57%; RR 1.2, $p = 0.21$), although a post hoc analysis comparing the median NIHSS scores at 24 hours showed a median of 8 in the rtPA-treated group versus 12 in the placebo group ($p < 0.02$). Furthermore, a benefit was observed for the rtPA group at 3 months for all four outcome measures. In part 2, the long-term clinical benefit of rtPA predicted by the results of part 1 was confirmed in all single scores as well as in the global test: BI (50% versus 38%, OR 1.6 [1.1–2.5], $p = 0.026$); mRS (39% versus 26%, OR 1.7 [1.1–2.5], $p = 0.019$); GOS (44% versus 32%, OR 1.6 [1.1–2.5], $p = 0.025$); NIHSS (31% versus 20%, OR 1.7 [1.0–2.8], $p = 0.033$); and combined endpoint (OR 1.7 [1.2–2.6], $p = 0.008$). For every

100 patients treated with rtPA, an additional 11 to 13 will have a favorable outcome as compared to 100 not treated with rtPA. The combined analysis of all 624 patients of parts 1 and 2 together yielded results which were nearly identical to those of part 2 alone; interestingly, however, outcome did not vary by stroke subtype at baseline, meaning that patients with small vessel disease benefited as well as patients with, for instance, cardio-embolic stroke. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4% of patients given rtPA but only in 0.6% of patients given placebo ($p < 0.001$). Nevertheless, severe disability and death were higher in the non-treated group (mortality at 3 months: rtPA 17% versus placebo 21%, $p = 0.30$). After publication of the NINDS trial in 1996, rtPA received Food and Drug Administration (FDA) approval for the treatment of acute ischemic stroke in a time window of 3 hours.

57.7.2. ECASS I

ECASS I, a prospective, multicenter, randomized, double-blind, placebo-controlled trial, recruited 620 patients for treatment either with 1.1 mg/kg rtPA or placebo within 6 hours after stroke symptom onset (Hacke et al., 1995). Anticoagulants, neuroprotectants, and rheologic therapy were prohibited during the first 24 hours. Patients with a severe deficit (hemiplegia, forced head- and eye movement, impairment of consciousness), with only mild or improving stroke symptoms, or CT signs of early infarction exceeding 33% of the middle cerebral artery territory were excluded. Primary endpoints included a difference of 15 points in the BI and 1 point in the mRS at 90 days in favor of rtPA. Secondary endpoints included combined BI and mRS, Scandinavian Stroke Scale (SSS) at 90 days, and 30-day mortality. In anticipation of a substantial number of protocol violations due to the first time early CT signs of infarction were being used as an inclusion criterion, the investigators prospectively specified a target population analysis in addition to the primary intention-to-treat analysis, which was performed at the end of the trial. The median NIHSS score at baseline was 13 (rtPA patients) and 12 (placebo group), respectively. ECASS I was the first trial of thrombolysis to use CT exclusion criteria (Von Kummer et al., 1994, 1996, 1997; Von Kummer, 1998). In spite of these predefined parameters there were 109 protocol violations in ECASS I (17.4%), 66 (11%) of which were CT protocol violations and 52 (8.4%) of these due to maldetection of early infarct signs. There was no difference in the primary endpoints in the intention-to-treat analysis, while the target population analysis revealed a significant difference in the mRS (but not BI) in favor of rtPA-treated patients ($p = 0.035$). Of the secondary endpoints, the combined BI and mRS showed a difference in favor of rtPA-treated patients ($p < 0.001$). Neurologic recovery at 90 days was significantly better for rtPA-treated patients in the target population ($p = 0.03$). There was a non-significant trend towards a higher mortality rate at 30 days ($p = 0.08$) and a significant increase in parenchymal intracerebral hemorrhage (19.8% versus 6.5%, $p < 0.001$). There was a significant inverse relationship between protocol violation in rtPA patients and 7-day survival. A post hoc analysis of the ECASS I 3-hour cohort ($n = 87$ patients) did not reveal a significant difference between rtPA and placebo group outcomes (Steiner et al., 1998).

57.7.3. ECASS II

The results of ECASS I and NINDS led to the design of ECASS II, which was conducted from October 1996 to January 1998 in 108 centers in 16 countries in Europe, New Zealand, and Australia (Hacke et al., 1998). The primary endpoint was the modified rankin scale (MRS) at 90 days, dichotomized for favorable (score 0–1) and unfavorable (score 2–6) outcome. Analyses were by intention-to-treat and an 8% absolute difference was aimed for in the primary endpoint. Secondary endpoints were a combined BI and MRS at day 90 and the NIHSS at day 30. A post hoc analysis requested by the board of reviewers was performed for an alternative dichotomization into independent versus death and dependent outcome (MRS 0–2 versus 3–6). Baseline median NIHSS was 11 in both groups, which is 2–3 points less than in NINDS and ECASS I. The safety analysis showed a similar mortality in the two groups (10.5% versus 10.7%). There was a substantially larger number of fatal intracerebral hemorrhage in the rtPA group (11 versus 2 patients) whereas more patients died due to space-occupying brain edema (8 versus 17 patients) in the placebo group. There was a four-fold increase in symptomatic parenchymal intracerebral hemorrhage (48 versus 12 patients) in the rtPA group, which was a far lower rate than in ECASS I. The primary endpoint was negative for rtPA (mRS 0.1: 40.3% versus 36.6%; delta = 3.7%; $p = 0.277$). There was a trend for the combined BI/MRS endpoint ($p = 0.098$) and a significant difference in day 30 NIHSS ($p = 0.035$). With the alternative dichotomization, a significant advantage for patients treated with rtPA (MRS 0–2: 54.3% versus 46.0%; delta = 8.3%; $p = 0.024$) was demonstrated. Like in ECASS I, the 3-hour cohort did not show

any significant differences due to the small patient numbers ($n = 80$ patients per group). Symptomatic intracerebral hemorrhage occurred in 36 (8.8%) rtPA patients and 13 (3.4%) placebo-treated patients. Interestingly, there was a high number of benign spontaneous disease courses in the placebo group (36.6%), which is larger than the favorable outcome rate in the ECASS I rtPA group (35.9%). Furthermore, a comparison of the 3-hour cohorts of ECASS I and II and NINDS demonstrates a surprisingly high number of favorable outcomes among the placebo group patients in ECASS II (ECASS I rtPA: 38.5%; NINDS rtPA: 38.7%; ECASS II placebo: 37.7%). Whether this is due to general improvements in the treatment of acute stroke patients, a less severe baseline deficit, or other factors is unclear. While negative for the primary endpoint, ECASS II was a clinically highly relevant study and showed that treatment of ischemic stroke with rtPA in a time window of less than 6 hours may lead to an improved outcome if given to selected patients in experienced centers.

57.7.4. ATLANTIS

The ATLANTIS study began in 1991 and originally was designed to assess efficacy and safety of thrombolytic therapy with rtPA within 0–6 hours after stroke symptom onset (Clark et al., 1999). In 1993 the time window was changed due to safety concerns to 0–5 hours and restarted as part B (intention-to-treat), only to be further modified in 1996 to a 3–5 hour window (target population) after rtPA had been approved by the FDA. Part A enrolled 142 patients ($22 < 3$ hours; $46 > 5$ hours) (Clark et al., 2000). The primary endpoint was an improvement of 4 or more points on the NIHSS at 24 hours and day 30; secondary endpoints included functional outcome (BI and MRS) at days 30 and 90. There was a significant improvement at 24 hours in the rtPA group (40% versus 21%, $p = 0.02$); this effect, however, was reversed at day 30 (60% versus 75%, $p = 0.05$). rtPA significantly raised the rate of symptomatic intracerebral hemorrhage (11% versus 0%, $p < 0.01$) and mortality at 90 days (23% versus 7%, $p < 0.01$). The primary endpoint for part B was a NIHSS score of ≤ 1 at 90 days; secondary endpoints were outcome at days 30 and 90 according to BI, MRS, and GOS. An intention-to-treat population of 613 acute ischemic stroke patients was enrolled, with 547 of these treated as assigned within 3–5 hours of symptom onset (target population). There were no differences on any of the primary (34% versus 32%, $p = 0.65$) or secondary functional outcome measures; however, there was a significant difference in the rate of major neurologic recovery (complete or ≥ 11 NIHSS points improvement: 44.9% versus 36%, $p = 0.03$), which did not affect overall outcome. Treatment with rtPA significantly increased the rate of symptomatic intracerebral hemorrhage (7.0% versus 1.1%, $p < 0.001$). As in ECASS II (median baseline NIHSS: 11 points), the median baseline NIHSS score was substantially lower than in the NINDS trial (10 versus 14 points), which (as in ECASS II) may have led to a better than expected outcome in the placebo group. In contrast to ECASS II, ATLANTIS was negative for the alternate outcome measurement independence (MRS 0–2) versus dependence or death (MRS 3–6) (rtPA 54% versus placebo 56%, $p = 0.75$). The authors conclude that thrombolysis with rPA for acute ischemic stroke later than 3 hours after symptom onset cannot be recommended.

57.7.5. Post-hoc analyses, old age, and mild strokes

After FDA approval in 1996 the use of rtPA was limited, a survey from 2001 indicating that less than 2% were treated (Reed et al., 2001). Because of reports of safety problems mostly caused by protocol violations (Katzan et al., 2000), the American Academy of Emergency Medicine stated that objective evidence regarding the safety, efficacy, and applicability of rtPA for ischemic stroke was insufficient to warrant its classification as a standard of care (American Academy of Emergency Medicine Work Group on Thrombolytic Therapy in Stroke, 2002). These and other concerns led to series of commentaries mainly published in the *British Medical Journal* that raised concern about the conduct of the NINDS trial (Lenzer, 2002; Warlow, 2002), as a response to which the NINDS commissioned an independent committee to address these concerns and critiques (Ingall et al., 2004). The committee was asked "to address whether there is concern that eligible stroke patients may not benefit from tPA given according to the protocol used in the trials and, whether the subgroup imbalance (in baseline stroke severity) invalidates the entire trial." Therefore the original NINDS trial data were reanalyzed to assess the rtPA treatment effect, the effect of the baseline imbalance in stroke severity between the treatment groups on the rtPA treatment effect, and whether subgroups of patients did not benefit from receiving rtPA. While median NIHSS values did not differ in between placebo and treatment arms, they did in NIHSS subgroups (0–5, 6–10, 11–15, 15–20, >2, $p = 0.005$). The adjusted odds ratio (OR) for a favorable outcome at 3 months was 2.1 (95% CI, 1.5–2.9) in favor of rtPA. The absolute treatment benefit varied for the different outcome scales from 15.6% (NIHSS) to 20.2% (mRS), all of these being highly statistically significant in favor of rtPA (Ingall et al., 2004).

The baseline differences in NIHSS was tested for all five categories of NIHSS score ranges and only for the 0–5 and the >20 point groups were there no significant effect in favor of rtPA; for the latter however, there was a strong trend. One has to bear in mind that this is a post hoc analysis of an underpowered study sample. In a complex statistical approach the committee then tested interactions involving, amongst others, age, baseline NIHSS, and rtPA for a differential treatment effect related to baseline stroke severity, which yielded negative results and therefore does not support the presence of a clinically relevant interaction between baseline NIHSS and rtPA. Also, the presence and number of risk factors such as age >70, hyperglycemia, and baseline NIHSS >20 did increase the likelihood for intracerebral hemorrhage but did not affect the OR for a favorable outcome when treated with rtPA as opposed to placebo (Ingall et al., 2004). These findings support the use of rtPA to treat patients with acute ischemic stroke within 3 hours of onset under the NINDS tPA trial protocol.

Saver and Yafeh (2006) presented another analysis of the NINDS data by using a baseline severity-adjusted endpoint analysis. This means that patients with a NIHSS score of 0–7 have to get to a day 90 mRS of 0 to be scored as favorable outcome. As an analogy, NIHSS scores of 8–14 have to be mRS 0–1 and NIHSSS 15 or greater to achieve mRS 0–2, which is also called a sliding dichotomy (Abciximab Emergent Stroke Treatment Trial Investigators, 2005). Severity-adjusted analysis is also a novel means of adjusting trial analysis for baseline imbalances in presenting stroke severity among treatment groups, a factor that has complicated interpretation and reception of the results of the pivotal NINDS-tPA trials (Ingall et al., 2004). Both of the NINDS rtPA stroke trials showed a statistically significant beneficial treatment effect of rtPA using the sliding dichotomy. In trial 1, good outcomes in rtPA versus placebo patients were 39.6% versus 28.6%, OR 1.64, $p = 0.049$; in trial 2, 35.7% versus 24.2%, OR 1.74, $p = 0.024$. Among all 624 patients in trials 1 and 2 combined, good outcomes occurred in 37.5% versus 26.3% patients, OR 1.68, $p = 0.0034$. There was an imbalance with regard to baseline severity in NINDS patients in the early (≤90 minutes) treated group. Therefore, the 0–90 and 91–180 minute groups were also analyzed separately. In the 0–90 minute group, good outcomes in rtPA versus placebo patients were noted in 38.9% versus 29.0%, OR 1.56, $p = 0.089$; in the 91–180 minute cohort, 36.1% versus 24.0%, OR 1.80, $p = 0.021$. Odds ratios favoring rtPA further increased after adjustment for 15 additional covariates known to predict acute stroke outcome from OR 1.7 (unadjusted) to OR 2.32 (adjusted, CI 1.36–3.95). This reanalysis again confirms a robust beneficial treatment effect of intravenous rtPA throughout the full 3-hour time window (Saver and Yafeh, 2006).

57.7.5.1. Old age

One real advantage of the IST-3 trial (see below) is the large number of old patients, where there is only a small amount of evidence available at present. Old age has been argued to be a poor prognostic factor for outcome regardless of therapy and the use of rtPA has been discouraged because of fear of hemorrhage and supposed lack of effect (Heuschmann et al., 2004). However, more recent studies support the treatment of older patients (Barber et al., 2004). The CASES study showed that thrombolytic therapy can be performed in daily routine without losing safety or efficacy and without a higher risk of intracerebral hemorrhage in older patients (Hill and Buchan, 2005). It may be unjustified withholding a therapy that, based on the current data, is the only effective therapy for acute ischemic stroke. Some authors believe that there is a lack of a more positive attitude towards a therapy that is uncommonly invasive for neurologists (Kaste, 2005). Older patients per se do have a higher risk of not recovering from ischemic stroke. This risk is not reduced by withholding thrombolytic therapy. Another recent study compared patients older ($n = 38$) and younger ($n = 287$) than 80 years treated with rtPA (Engelter et al., 2005). While there was a higher 3-month mortality in older patients, favorable outcomes (mRS 0–1) and intracerebral hemorrhage were similarly frequent in both groups. A logistic regression analysis showed that stroke severity, time to thrombolysis, glucose level, and history of coronary heart disease independently predicted outcome, whereas age did not. Trials and registries such as IST-3 and SITS-ISTR will answer this question within the next few years.

57.7.5.2. Mild strokes

Patients are frequently not considered for thrombolytic therapy because of a mild or rapidly improving deficit (Barber et al., 2001). Barber and colleagues investigated why patients with ischemic stroke did not receive rtPA in 1,168 consecutive patients with acute ischemic stroke. They found that 73.1% (854/1,168) of the patients were not eligible for rtPA because they arrived after 3 hours. Major reasons for delay included uncertain time of onset (24.2%), patients waited to see if symptoms would improve (29%), delay caused by transfer from an outlying hospital (8.9%), and inaccessibility of treating hospital (5.7%). Twenty-seven

percent (314/1,168) of patients with ischemic stroke were admitted within 3 hours of symptom onset and of these, 84 (26.7%) patients received rtPA. The major reasons for exclusion in this group of patients were mild stroke (13.1%), clinical improvement (18.2%), perceived protocol exclusions (13.6%), emergency department referral delay (8.9%), and significant comorbidity (8.3%). Of those patients who were considered too mild or were documented to have had significant improvement, 32% either remained dependent at hospital discharge or died during hospital admission. This brings into question the initial decision not to treat (Barber et al., 2001).

Gonzalez presented another study of mild strokes, comparing patients who received IV rtPA with patients who did not (Gonzales et al., 2006). Consecutive patients with NIHSS $\leq$7 were identified. Baseline NIHSS, use of thrombolytics, and the reason for thrombolytic exclusion were recorded. Patients were further divided into two groups: minimal symptoms (NIHSS 1–3) and mild symptoms (NIHSS 4–7). Excellent outcome was defined as a discharge mRS of 0–1. Of the 885 patients with AIS that were screened, 238 had NIHSS $\leq$7 (103 NIHSS 1–3, 135 NIHSS 4–7). Forty-one patients (17%) were treated with rtPA. Of those presenting within 3 hours and not treated, the most common reason for exclusion was minor symptoms (59%). Only 10% of patients with minimal symptoms received rtPA compared to 23% with mild symptoms ($p < 0.01$). Patients treated with rtPA were more likely to have an excellent outcome, OR 2.48 (CI 0.17–0.52, $p = 0.01$). As a whole, 59% of the rtPA group had an excellent outcome compared to 44% of the untreated group. When treated with rtPA, 90% of patients with minimal symptoms had an excellent outcome compared to only 58% of the untreated group. This effect was also seen in the "mild symptom" group: those treated with rtPA had a 48% chance of an excellent outcome compared to only 32% in the untreated group. No patients in the rtPA-treated group died compared to 1% in the untreated group. The authors concluded that patients presenting within 3 hours are frequently excluded from thrombolytics for minor symptoms although they would have profited from therapy. Mild strokes are no reason for withholding thrombolytic therapy (Gonzales et al., 2006).

57.7.6. Meta-analyses

A search of the literature revealed three large meta-analyses. The first meta-analysis by Hacke et al. (1999) covered the NINDS study and both ECASS trials, with a total of 2,044 patients included (1,034 rtPA patients versus 1,010 placebo patients). The authors assessed the benefit of rtPA, and dichotomized the outcome into dependent versus independent or dead (mRS 0–2 versus 3–6) and favorable versus unfavorable (mRS 0–1 versus mRS 2–6). Risk in these three trials can be defined as intracerebral hemorrhage and mortality. Differences between the trials such as the dose of rtPA (1.1 mg/kg in ECASS I versus 0.9 mg/kg in NINDS and ECASS II) and the therapeutic time window (3 hours in NINDS versus 6 hours in ECASS I and II) were taken into account. Intracerebral hemorrhage occurred significantly more often in patients receiving rtPA (144/1,034 versus 43/1,010; OR 3.23, CI 2.39–4.37), and was slightly less increased in the 3-hour time window and at the lower dosage (41/393 versus 15/389; OR 2.68, CI 1.56–4.62). There was no significant difference in mortality between rtPA and placebo (OR 1.07, CI 0.84–1.36) but a slight trend towards a lower mortality in the 0.9 mg/kg and 3-hour group (OR 0.91, 0.63–1.32). rtPA, on the other hand, led to a 37% reduction in death and dependence regardless of dose and time window (OR 0.63, CI 0.53–0.76). If treated with the lower dose and within 3 hours the chance of an unfavorable outcome was reduced by 45% (OR 0.55, CI 0.41–0.72). For every 1,000 patients treated with either dose there were 90 fewer patients who are dead or disabled but 96 hemorrhages more than expected with placebo. Conversely, for 1,000 patients treated with 0.9 mg/kg and within 3 hours, there were 65 additional intracerebral hemorrhages and 140 fewer patients dead or disabled. The number-needed-to-treat for all doses and time windows was 11; for the 3-hour and 0.9 mg/kg group it was 7. These numbers are far better than the number-needed-to-treat for thrombolysis in myocardial infarctions, which is 30–40 (Hacke et al., 1999).

Wardlaw et al. included in their Cochrane Library meta-analysis (2002) all randomized trials of thrombolysis regardless of time window, dosage, administration route, and substance. Seventeen trials with a total of 5,216 patients (2,889 of which were from rtPA trials) were included. The main objectives were to show that thrombolytic therapy reduces the risk of late death, may increase the risk of early and fatal intracerebral hemorrhage, and that the benefit at outcome (reduction of death and dependence) offsets any early hazard. Symptomatic and fatal intracerebral hemorrhage were significantly more common as a result of thrombolytic therapy (symptomatic intracerebral hemorrhage: OR 3.53, CI 2.79–4.45, $p < 0.000001$; fatal intracerebral hemorrhage: OR 4.15, CI 2.96–5.84). This translates into 70 additional instances of symptomatic intracerebral hemorrhage for patients receiving thrombolysis and 29/1,000 (OR 3.2) additional instances of fatal intracerebral hemorrhage in

rtPA patients but 92/1,000 (OR 6.03) additional intracerebral hemorrhage in those patients receiving streptokinase as opposed to placebo. Despite this, thrombolytic therapy, administered up to 6 hours after ischemic stroke, significantly reduced death or dependence at the end of follow-up (55.2% versus 59.7%, OR 0.83, CI 0.73–0.94, $p = 0.0015$), which is equivalent to 44 fewer patients being dead or dependent per 1,000 treated (CI 15–73). For patients treated with rtPA only, the OR was 0.79 (CI 0.68–0.92, $p = 0.001$) or 57 deaths/dependence prevented per 1,000 patients treated (CI 20–93). An alternative endpoint analysis yields similar results for favorable versus unfavorable outcome (OR 0.79 for all patients and 0.76 for rtPA patients). When treatment was given within 3 hours after stroke onset, there was an even better risk reduction for dependency or death (55.2% versus 68.3%; OR 0.58, CI 0.46–0.74, $p = 0.00001$) or 126 fewer dead or dependent patients per 1,000 treated. The difference of benefit of rtPA in the 0–3 hour window or 3–6 hour window was non-significant but showed a trend towards better improvement with early therapy (OR 0.7 versus 0.76). The authors conclude that the significant increase in early death and fatal and nonfatal symptomatic intracerebral hemorrhage are offset by the significant reduction of disability in survivors. Therapy with rtPA is associated with less risk and more benefit than with other substances.

In 2004, a new combined analysis of the data from the NINDS, ECASS I and II, and ATLANTIS studies aimed to confirm the importance of rapid treatment and influence of time was published (Hacke et al., 2004). Common data elements from the major thrombolysis trials were pooled and analyzed using multivariable logistic regression to assess the relationship of the interval from stroke onset to start of treatment on favorable 3-month outcome and on the occurrence of clinically relevant parenchymal intracerebral hemorrhage. From these six trials (NINDS Parts 1 and 2, ATLANTIS Parts A and B, ECASS I and II), 2,775 patients were randomly allocated to rtPA or placebo (median age 68 years, median baseline NIHSS 11). Odds of a favorable 3-month outcome decreased as onset to treatment time increased ($p = 0.005$). Odds were 2.8 (95% CI 1.8–4.5) for 0–90 minutes, 1.6 (1.1–2.2) for 91–180 minutes, 1.4 (1.1–1.9) for 181–270 minutes, and 1.2 (0.9–1.5) for 271–360 minutes in favor of the rtPA group. The hazard ratio for death adjusted for baseline NIHSS was not different from 1.0 for the 0–90, 91–180, and 181–270 minutes intervals; for 271–360 minutes it was 1.45 (1.02–2.07). Intracerebral hemorrhage was seen in 82 (5.9%) rtPA patients and 15 (1.1%) controls ($p < 0.0001$). Intracerebral hemorrhage was not associated with onset to treatment time (OTT) but was with rtPA treatment ($p = 0.0001$) and age ($p = 0.0002$). Most interestingly the significant effect in favor of rtPA was mainly on the cost of patients in the mRS range from 2 to 5. The authors concluded that the sooner rtPA is given to stroke patients, the greater the benefit, especially if treatment is started within 90 minutes. Thus the negative correlation of time and outcome again could be established ("lost time is lost brain"). Another interesting aspect of this analysis refers to the degree of severity frequently used as an exclusion criterion for rtPA. Within the first 90 minutes patients with a moderate baseline severity (NIHSS 6–10) predominantly showed a good effect after rtPA. In contrast to this, within 91–180 minutes, which is the maximum time window as per approval, only patients with very severe hemispheric strokes (NIHSS >20) showed any benefit. Interestingly, there was no difference in treatment effect with regard to baseline severity within 181–270 minutes, but again from 271–360 minutes in favor of the more severely affected patients (NIHSS 16–20). Therefore there seems to be no justified reason to withhold thrombolysis from patients with a severe stroke syndrome within the first 3 hours, especially if the CT scan does not show any major early changes. Also the NINDS study did not apply an upper NIHSS limit as an exclusion criterion. Recommendations not to treat more severe strokes are mostly derived from the ECASS studies and not from a patient collective treated within 3 hours after stroke onset.

57.7.7. New intravenous thrombolysis studies, new thrombolytics and add-on therapies for intravenous thrombolysis

57.7.7.1. ECASS III

After conditional approval of rtPA in many European countries by the European Medicines Agency (EMEA) in addition to an international registry (SITS, see below) another trial of rtPA for ischemic stroke—ECASS III—was demanded by these European authorities, and started to randomize patients in July 2003. Because many patients do not arrive in the hospital within 3 hours, the aim of ECASS III is to extend the treatment window by showing that rtPA is effective beyond 3 hours. The original protocol was designed to include patients up to 4 hours. This was changed in early 2005 adapting to low recruitment rates and the detection of the effectiveness of the 4.5-hour time window in the combined analysis of NINDS, ECASS I and II, and ATLANTIS (Hacke et al., 2004). ECASS III is a double-blind, randomized, placebo-controlled trial of rtPA 0.9 mg/kg body weight in the 3–4.5-hour time window with 400 patients per study arm to be included by the end of

2007. The primary endpoint is an mRS score of 0–1 at day 90, the secondary endpoint is a global outcome (mRS 0–1, BI 95–100, GOS 0–1, NIHSS 0–1) at day 90. A tertiary endpoint is an mRS score of 0–1 at day 90 stratified by admission NIHSS. Safety parameters include symptomatic intracerebral hemorrhage rate, survival at day 90, and also rates of brain herniation and symptomatic brain edema. Inclusion criteria are age 18–80, clinical diagnosis of stroke (NIHSS score $\leq$24) without significant improvement, informed consent, treatment possible within 3–4.5 hours. Exclusion criteria are similar to ECASS II including early CT signs of intracerebral hemorrhage or extensive infarction. Recruitment was finalized at the end of 2007 and the results will be presented in fall 2008.

57.7.7.2. Third International Stroke Trial

The Third International Stroke Trial (IST-3) aims to recruit a large number of patients (n = 6,000) into thrombolysis with rtPA against placebo within the 6-hour time window (IST3 Study Group, www.ist3.com). IST-3 is a randomized controlled multicenter trial. The rationale is that within 3 hours only a highly selected patient clientele can be treated. IST-3 according to the investigators also aims to determine whether a larger variety of patients, especially with regard to age and concomitant morbidity, can profit. The primary measure of outcome is the proportion of patients alive and independent (mRS 0–2) at 6 months. Secondary outcomes include: events within 7 days (death, recurrent stroke, symptomatic intracranial intracerebral hemorrhage), outcome at 6 months (death, functional status, EuroQol). Planned subgroup analyses include an assessment of the effect of: age, stroke severity, time to randomization, CT appearances, blood pressure, and other factors on the risks and benefits of treatment. While this rationale is sound, reasonable considerable dissent exists with regard to the methodological study design. As of August 2005 more than 400 patients had been enrolled, 67% older than 70 years and 55% with a total anterior circulation syndrome (Kane et al., 2005). The number as of February 2006 exceeded 500 patients. The problem with IST-3 is the uncertainty principle, which is based on the possibility that the recruiting physician is supposed to treat the patients in whom he thinks thrombolysis is indicated and not to treat those where he thinks it is contraindicated. In those patients where he or she is uncertain whether to treat or not randomization and recruitment into IST-3 is the aim. This per se is a negative patient selection and also other open label series have shown that inexperience and not knowing whom to treat or not to treat is associated with a poor performance in thrombolysis for stroke regarding safety and efficacy (Katzan et al., 2000; Heuschmann et al., 2003, 2004). Furthermore, at the current inclusion rate of 100 patients per 6 months there will be no results available before 2033.

57.7.7.3. Others

As the DIAS, DEDAS, and DIAS-2 trials which use desmoteplase (DSPA) are MRI-based trials, these studies are described in the stroke MRI part of this chapter. Tenecteplase has been tested in a single pilot trial only (Haley et al., 2005). The rationale for this was the still considerable symptomatic intracranial bleeding rate in patients treated with rtPA of 6.4% (NINDS trial). Patients were treated with an intravenous bolus of TNK within 3 hours of stroke onset in an open-label, dose-escalation safety study. The primary endpoint was intracerebral hemorrhage within 36 hours. Eighty-eight patients were treated in four dosing tiers. In the first three dosing tiers (0.1, 0.2, 0.4 mg/kg) there was no intracerebral hemorrhage. The tier at 0.5 mg/kg was closed after 2 of 13 patients experienced symptomatic intracerebral hemorrhage and a high rate of asymptomatic intracerebral hemorrhage. Outcome according to the mRS was similar to historical controls treated with rtPA. Further studies of TNK are warranted but currently not underway.

A recent Taiwanese study of a new thrombolytic agent—human tissue urokinase type plasminogen activator (HTUPA)—in patients with acute ischemic stroke treated patients with a single bolus intravenous HTUPA under an open-label dose escalation design within 5 hours after symptom onset (Hu et al., 2006). Three doses of HTUPA (0.3 mg/kg, 0.35 mg/kg, and 0.4 mg/kg) were administered to 33 patients, with the majority of patients (n = 29) receiving 0.3 mg/kg. Two cases of fatal intracerebral hemorrhage occurred (1 each at 0.4 mg/kg and 0.3 mg/kg). At day 90 patients treated in the 5-hour time window had a NIHSS of 0 or 1 in 34%, when treated in under 3 hours, 86% reached this score. Further testing of this drug is warranted.

57.7.7.4. Glycoprotein IIb/IIIa antagonists

The use of glycoprotein IIb/IIIa antagonists such as tirofiban, abciximab, and eptifibatide may be a promising approach and result in increased vessel patency rates in accordance with cardiological studies (Abciximab Emergent Stroke Treatment Trial Investigators, 2005), however, the Abestt-2 trial recently had to be stopped because of increased bleeding rates. Combination of lower doses of rtPA with GP IIb/IIIa antagonists in selected patients may be a better approach.

These trials however are at present only phase I and II (Junghans et al., 2001, 2002; Seitz et al., 2003).

The ROSIE study (Reopro Retavase Reperfusion of Stroke Safety Study-Imaging Evaluation) is a clinical trial to determine an acceptable dose of reteplase in combination with a fixed dose of abciximab for the treatment of ischemic stroke 3–24 hours from onset (Dunn et al., 2004); however, as it is MRI based it will be reported at a later time in this chapter. The CLEAR (Combined Approach To Lysis Utilizing Eptifibatide And rtPA) study combines low-dose rtPA with eptifibatide (Pancioli, 2006). It is a multicenter, sequential, dose-escalation, double-blind, randomized safety study evaluating the risks and benefits of combining a glycoprotein IIb/IIIa antagonist, eptifibatide, with low-dose IV rtPA in 100 acute ischemic stroke patients treated within 3 hours of onset. The study's two dose tiers contain 40 (rtPA 0.3 mg/kg) and 60 patients (rtPA 0.45 mg/kg) respectively plus eptifibatide 75 μg/kg as bolus and 0.75 μg/kg/minute as 2 hour infusion. Patients are randomized 3:1 to the combination of IV eptifibatide plus low-dose rtPA, or standard-dose rtPA. The primary safety endpoint is the incidence of symptomatic intracerebral hemorrhage within 36 hours. Tier I is complete with 40 patients and tier II up to February 2006 had recruited 30 patients. Compared to similar NINDS-treated patients as historical controls, frequency of symptomatic intracerebral hemorrhage (3% versus 5.9%) and mortality (23.0% versus 17.3%) did not differ significantly; however, time to treatment was significantly longer in the combined treatment group (median 2.5 versus 1.5 hours). Depending on the results after completion of tier II, a randomized trial may be planned (Pancioli, 2006).

57.7.7.5. Ultrasound-facilitated thrombolysis

An interesting approach is the addition of ultrasound to facilitate thrombolysis. Ultrasound can induce reversible changes in the fibrin mesh of a thrombus thereby increasing microstreams of plasma (Alexandrov et al., 2004; Molina et al., 2006) through the thrombus and accelerating the transport and penetration of rtPA into the clot. This results in a faster and more complete dissolution of the clot. The CLOTBUST study published in 2004 showed in 126 patients (all rtPA, 63 each placebo or ultrasound) that continuous insonation with 2 MHz standard diagnostic ultrasound for 2 hours increases the rate of complete recanalization or dramatic clinical recovery (primary endpoint) within 2 hours after the administration of the rtPA bolus (49% versus 30%, $p = 0.03$). Symptomatic intracerebral hemorrhage occurred in 3 patients in each group, the rate of good outcomes at 3 months differed non-significantly (42% ultrasound versus 29% placebo; $p = 0.20$). The study was not powered, however, to detect a difference for a clinical endpoint.

Another study used high-energy low-frequency ultrasound (Daffertshofer et al., 2005). Potential advantages of low-frequency ultrasound include that it does not require complex positioning procedures, penetrates through the skull better, and has been demonstrated to accelerate thrombolysis with rtPA in animal experiments in wide cerebrovascular territories without hemorrhagic side-effects. Patients were (in contrast to CLOTBUST) included in a 6-hour time window, with an NIHSS score larger than 4. Stroke MRI was used to document vascular occlusion and to rule out cerebral hemorrhage. Follow-up included serial MRI directly thereafter and 24 hours later to confirm recanalization and tissue imaging. The study had to be terminated prematurely after 26 patients (70.4 +/−9.7 years) had entered the trial (12 rtPA, 14 rtPA plus ultrasound). The reason for this was that 5 of 12 patients from the rtPA-only group but 13 of 14 patients treated with the rtPA plus ultrasound showed signs of bleeding in MRI ($p < 0.01$). Within 3 days of treatment, 5 symptomatic intracerebral hemorrhages occurred within the rtPA plus ultrasound group, although this did not translate into significant differences with regard to morbidity or treatment-related mortality or recanalization rates, this study demonstrated bioeffects from low-frequency ultrasound that caused an increased rate of cerebral hemorrhages in patients concomitantly treated with intravenous rtPA. While low-frequency ultrasound appears to be damaging to the blood–brain barrier the main advantage in the study design compared to CLOTBUST is the stringent monitoring with MRI pre- and post-treatment.

Molina et al. (2006) in a first pilot study investigated whether microbubbles, which are normally used as an ultrasound contrast agent, could further aid the positive effect of the combination of rtPA and ultrasound demonstrated in the CLOTBUST trial. Microbubbles are air- or gas-filled microspheres that increase the reflection of ultrasound due to an impedance mismatch between fluid and tissue (Molina et al., 2006). This in theory could add to the mechanical effect of 2-MHz ultrasound on the fibrin mesh in the thrombus as shown in CLOTBUST (Alexandrov et al., 2004). One-hundred and eleven patients (median NIHSS score 18) with acute stroke attributable to middle cerebral artery occlusion were treated with rtPA. Thirty-eight patients were treated with tPA plus continuous 2-hour TCD monitoring plus 3 doses of 2.5 g (400 mg/ml) of galactose-based microbubbles given at 2, 20, and 40 minutes after tPA bolus, the other 73 received rtPA plus continuous 2-hour TCD ultrasound monitoring or rtPA plus placebo

(from the CLOTBUST trial). Thirty-eight patients (34%) received rtPA/ultrasound/microbubbles, 37 patients (33%) rtPA/ultrasound, and 36 (32%) rtPA alone. The groups did not differ with regard to baseline variables. Some recanalization at 2 hours was seen in 71% (rtPA/ultrasound/microbubbles), 68% (rtPA/ultrasound), and 39% (rtPA). The 2-hour complete recanalization rate was significantly ($p = 0.038$) higher in the rtPA/ultrasound/microbubbles group (54.5%) compared with rtPA/ultrasound (40.8%) and rtPA alone (23.9%) groups. Symptomatic intracerebral hemorrhage rate was low ($n = 2$ rtPA alone, $n = 1$ rtPA/ultrasound and rtPA/ultrasound/microbubbles each) and did not differ between groups. Also early improvement (NIHSS at 24 hours) and late outcome (mRS day 90) tended to be better with ultrasound and microbubbles (both $p < 0.075$) than in the other groups. The authors conclude that microbubbles do further accelerate time to recanalization, frequency of recanalization and also extent of recanalization all of which may lead to better clinical early and also late outcomes (Molina et al., 2006). In a further study, Rubiera and colleagues evaluated the impact of microbubbles on the success of recanalization among different stroke subtypes. 155 consecutive stroke patients were categorized by Molina into three groups (rtPA only, plus ultrasound, plus ultrasound and bubbles) (Molina et al., 2006). Stroke subtypes were assessed by the TOAST criteria. Strokes were categorized as cardio-embolic in 76 (49%), atherothrombotic in 37 (24%), undetermined in 35 (23%) patients, and others 4%. The 2-hour complete recanalization rates were significantly ($p = 0.039$) higher in the microbubbles group (52%) as compared to rtPA/US (40.2%) and rtPA only (24%) groups. This was mainly due to increased recanalization rates in patients with atherothrombotic etiology of the stroke and not cardio-embolic or unknown etiology ($p = 0.021$). This translated into outcome with atherothrombotic strokes having a significantly worse outcome in the two groups not receiving microbubbles ($p = 0.043$ and $p = 0.021$). This is probably explained by the different composition of atherothrombotic plaques that might be harder and more calcified than fresh cardiac emboli and therefore profit from an increased mechanic energy transfer by microbubbles in addition to ultrasound (Rubiera et al., 2006). A phase II safety and dose finding study of nanobubbles in addition to ultrasound and <3h thrombolysis with rt-PA was stopped due to increased bleeding rates in the 2nd dose tier (TUCSON study).

57.7.7.6. Neuroprotectants and thrombolysis

Neuroprotection is not a topic of this chapter. However, one concept for the implementation of neuroprotective drugs is the early, maybe even preclinical, administration of a drug that widens the time window for an effective reperfusion treatment. The benefits of arterial recanalization may be supplemented by neuronal protection, particularly when the two strategies are used simultaneously, and if they can be used very early following symptom onset. Until recently there were no successful neuroprotective trials in stroke. This was mainly due to poor methodology and poor trial design. Following and adhering to the STAIR (Stroke Therapy Academic Industry Roundtable) recommendations for neuroprotective trials, the SAINT I (Stroke Acute Ischemic NXY Treatment) study was designed and recently published (Lees et al., 2006). NXY-059 is a free-radical scavenger that was tested in 1,722 patients with acute stroke within 6 hours after symptom onset and measured disability at 90 days. The study was randomized, double-blind and placebo-controlled, patients need to have a NIHSS score of at least 6, the drug (or placebo) was infused over 72 hours. A priori patients, who received rtPA were defined as a subgroup, where the rates of asymptomatic and symptomatic intracerebral hemorrhage were to be determined in between groups. Approximately 30% of the patients received rtPA. The odds ratio for an improved outcome was 1.2 (CI 1.01–1.42; $p = 0.038$). Interestingly, asymptomatic (12.9% versus 20.9%) as well as symptomatic (2.4% versus 6.4%; $p = 0.036$) intracerebral hemorrhage was significantly less common in patients treated with rtPA and NXY-095 compared to rtPA and placebo, an effect not observed in the overall analysis, but only in thrombolyzed patients. This is the first evidence of efficacy for a neuroprotectant and for an increase of safety of thrombolytic therapy in the presence of a neuroprotectant. SAINT II aims to confirm these data in a planned set of 3,200 patients and started recruiting in early 2006.

57.8. Phase IV studies and registries for intravenous thrombolysis: cost aspects

After FDA approval of rtPA for intravenous thrombolytic therapy in June 1996, the rate of thrombolysis remained fairly constant until the end of 1998 (Hacke et al., 1999). At most centers where thrombolysis is performed, the NINDS protocol is used; many of these centers also use the ECASS-CT criteria of early infarction. Despite level I evidence in favor of thrombolysis, it is estimated that overall less than 2% of the time-eligible (3-hour window) are treated with rtPA, a rather low rate. This has several reasons such as persisting doubts, fear of hemorrhage, or inadequate reimbursement, although the latter has improved in several countries such as the USA and Germany. The reported

outcome and complication rates seem to be similar to the NINDS trial in most instances. A few examples shall be presented here.

57.8.1. Phase IV studies and registries

Two earlier phase IV studies showed divergent results: Albers et al. (2000) reported the STARS (Standard Treatment with Alteplase to Reverse Stroke) study results, a phase IV trial mandated by the FDA. STARS was a prospective, multicenter study of consecutive patients, who received intravenous rtPA according to NINDS criteria. Outcome measurement was the mRS at 30 days. Here, 389 patients received rtPA within 2 hours 44 minutes, and the median baseline NIHSS score was 13. The 30-day mortality rate was 13%, 35% of patients had very favorable outcomes (mRS $\leq$ 1), and 43% were functionally independent (mRS $\leq$ 2) at day 30. Another 3.3% of the patients experienced symptomatic intracerebral hemorrhage, which was fatal in seven cases. Asymptomatic intracerebral hemorrhage was seen in 8.2%. Protocol violations were reported for 32.6% of the patients and consisted mostly of treatment after 3 hours (13.4%) mainly due to a door-to-needle-time of 1 hour 36 minutes, treatment with anticoagulants within 24 hours of rtPA administration (9.3%), and rtPA administration despite systolic blood pressure exceeding 185 mmHg (6.7%). The authors concluded that favorable clinical outcomes and low rates of symptomatic intracerebral hemorrhage can be achieved using rtPA for stroke treatment, while the time effort for emergency evaluation may leave room for logistic improvement. The study by Katzan et al. (2000) yielded different results and was the reason for raised concerns with regard to the safety and efficacy of thrombolysis in real life. Twenty-nine hospitals in the metropolitan area of Cleveland, Ohio, prospectively assessed the rate of rtPA use, rate of intracerebral hemorrhage, and outcomes in 3,948 stroke patients. Seventy patients (1.8%) admitted with ischemic stroke received rtPA. Sixteen of these patients (22%) experienced intracerebral hemorrhage; 11 (15.7%) had a symptomatic intracerebral hemorrhage (of which 6 were fatal), and 50% had deviations from national treatment guidelines. In-hospital mortality was significantly higher ($p < 0.001$) among patients treated with rtPA (15.7%) than in patients not receiving rtPA (5.1%). The fact that blood pressure guidelines were followed in only 47.8% and that the baseline NIHSS was only documented in 40% of the patients illustrates that intravenous thrombolysis, though an effective therapy, should be performed at experienced centers only and may explain the substantially higher rate of mortality and intracerebral hemorrhage in this study compared to other investigators.

In Cologne, approximately 22% of the patients that arrive within 3 hours after symptom onset (5% of all ischemic stroke patients) receive thrombolysis (Grond et al., 1998b). This rate was achieved after cooperation between emergency caregivers, internists, and neurologists was initiated and the referral system optimized. The average door-to-needle-time in Cologne is 48 minutes. The rates of total, symptomatic, and fatal intracerebral hemorrhage were 11%, 5%, and 1%, respectively. Of all patients treated with rtPA, 53% recovered to a fully independent functional state. Recently, the same group published their data on long-term follow-up after thrombolytic therapy, where 150 patients treated within 3 hours were re-evaluated after 12 months (Schmulling et al., 2000). After 12 months, 41% of the patients had an mRS score of $\leq$1 and 52% of $\leq$2. The stroke recurrence rate (6.6%/year; TIA 3.3%/year) was consistent with that of population-based studies (Sacco et al., 1994) These results are nearly identical to the late follow-up outcome analysis published by Kwiatkowski et al. in 1999. In Houston, 30 patients were treated prospectively after the NINDS protocol (Chiu et al., 1998). Six percent of all patients hospitalized with ischemic stroke received intravenous tPA at the university hospital and 1.1% at the community hospitals. The rates of total, symptomatic, and fatal intracerebral hemorrhage were 10%, 7%, and 3%, and 37% of patients recovered to fully independent function. The average door-to-needle-time was 1 hour 40 minutes.

Two registries have been entering data for thrombolysis with rtPA into respective data banks and the results of one have been published recently (Hill and Buchan, 2005). The Canadian Alteplase for Stroke Effectiveness Study published in 2005 was a national prospective cohort study conducted to assess the effectiveness of rtPA for ischemic stroke in actual practice. In analogy to the SITS registry in Europe, this study was mandated by the federal government as a condition of licensure of rtPA for the treatment of stroke in Canada. Data collection was prospective, and follow-up was completed at 90 days after stroke. A total of 1,135 patients were enrolled, and an excellent clinical outcome was observed in 37% of the patients. Symptomatic intracerebral hemorrhage occurred in only 4.6% of the patients (95% CI 3.4–6.0%). An additional 1.3% (95% CI 0.7–2.2%) of patients had hemiorolingual angioedema. The authors concluded that stroke patients undergoing thrombolysis in Canada had similar outcomes and slightly lower bleeding rates compared to the results of clinical trials and therefore that thrombolysis with rtPA is safe and effective within 3 hours in a real-life setting.

Graham performed a meta-analysis of all open-label rtPA studies published up to April 2003 and included the preliminary data of the CASES study available in abstract form at that time (Graham, 2003). The analysis included 15 series with a total of 2,639 treated patients and a median baseline NIHSS score of 14. The rate of symptomatic intracerebral hemorrhage was 5.2% (95% confidence interval 4.3–6.0), slightly lower than the 6.4% rate in the treatment arm of the NINDS trial. The mean total mortality (13.4%) and proportion of subjects achieving a very favorable outcome (37.1%) were comparable to the NINDS trial results. Protocol deviations were reported in 19.8%. Comparing across studies showed that the mortality rate was correlated with the percentage of protocol violations ($r = 0.67$, $p = 0.018$), a fact that had already been observed in the ECASS I trial (Hacke et al., 1995) and in the stroke survey by Tanne et al. (1999). In the latter the incidence of symptomatic intracerebral hemorrhage was 11% among patients with protocol deviations as compared with 4% in patients who were treated according to the NINDS protocol guidelines.

The German Stroke Registers Study Group investigated predictors of in-hospital mortality and early outcome after intravenous thrombolysis with rtPA (Heuschmann et al., 2003, 2004) in community-based settings. The study was a prospective, observational cohort study conducted at 225 community and academic hospitals throughout Germany (Heuschmann et al., 2004). A substudy in 104 centers matched rtPA patients to patients not receiving tPA (Heuschmann et al., 2003) and analyzed the effect of hospital experience with safety of rtPA use. In the first study a total of 1,658 patients showed a mortality of 10% (166 patients), 67.5% of these deaths occurring within 7 days. Factors predicting in-hospital death after rtPA use were older age (OR 1.6; CI 1.3–1.9; for each 10-year increment in age) and altered level of consciousness (OR, 3.4; CI 2.4–4.7). The overall rate of symptomatic intracranial hemorrhage was 7.1% and increased with age. There was an inverse relation between the number of patients treated with rtPA in the respective hospital and the risk of in-hospital death (OR 0.97; CI 0.96–0.99; for each additional patient treated with rtPA per year) (Heuschmann et al., 2004). The substudy of 384 patients treated with rtPA also showed that in-hospital mortality was significantly higher for patients treated with rtPA compared with patients not receiving rtPA (11.7% versus 4.5%; $p < 0.0001$). After matching for propensity score, overall risk of inpatient death was still increased for patients treated with rtPA (OR, 1.7; 95% CI 1.0–2.8). Patients receiving rtPA in hospitals that administered ≤ 5 thrombolytic therapies had an increased risk of in-hospital mortality (OR 3.3; CI 1.1–9.9). This effect was not observed in hospitals administering >5 thrombolytic treatments per year (OR 1.3; CI 0.8–2.4). While there were several methodological weaknesses in both studies, the observation that lack of experience is associated with less successful results in thrombolysis seems valid and is consistent with preliminary results from the SITS registry.

In an analysis of the nationwide inpatient sample from 1999 to 2002, Bateman and colleagues assessed factors associated with inpatient mortality in rtPA treated stroke patients ($n = 2{,}594$) versus non-treated patients ($n = 246{,}370$). While information about baseline severity and long-term outcomes were not available, rtPA-treated patients had a higher in-hospital mortality rate compared with the non-thrombolysis patients (11.4% versus 6.8%) (Bateman et al., 2006). The rate of symptomatic intracerebral hemorrhage was 4.4% for the thrombolysis cohort and 0.4% for non-thrombolysis patients. Again, advanced age was an independent risk factor for inpatient mortality, however experience was not. This result is probably due to imbalances with regard to stroke severity. The fact that only 1% of stroke patients received rtPA again illustrates the need for improved acute stroke management to increase treatment numbers. Also it remains open whether old patients fare better when treated with rtPA compared to non-treated equally old patients.

With the conditional approval of rtPA by the European Medicine Evaluation Agency's (EMEAs) Committee for Proprietary Medicinal Products for use in selected patients with acute ischemic stroke, continuous quality control through clinical audit is needed as routine clinical use of alteplase in stroke becomes established. SITS-MOST (Safe Introduction of Thrombolysis in Stroke-Monitoring Study) is an observational safety monitoring study embedded within the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register (SITS-ISTR) and will analyze the outcome data in stroke patients treated in the EU (plus Iceland, Norway, and Switzerland). SITS is an Internet-based, international monitoring registry for auditing the safety and efficacy of routine therapeutic use of thrombolysis in acute ischemic stroke, through which SITS-MOST will be performed. The registry has been established by the ECASS investigators, is driven by independent collaborators and available to clinicians across Europe, and is located in Stockholm (SITS Study Group, Wahlgren, 2005). 6483 patients were recruited from 285 centres for SITS-MOST. Besides verifying if intravenous thrombolysis treatment is as safe and

efficacious in routine clinical practice it also aimed to provide immediately upgraded statistical reports to show how a centre's outcome compares with other centers. This should lead to improved efficacy and safety over time. As with SITS-ISTR, centers entered their data in the register over the internet by responding to specified questions. The data focused on time delays in management, baseline and demographic data, baseline stroke severity (NIHSS), baseline imaging studies, and follow-up NIHSS scores and imaging. There was an independent follow-up of ICH, evaluated by the Brain Imaging Committee. Mortality and independence were reported at 3 months by the participating centers. Symptomatic ICH (worsening NIHSS score of $>$or$=4$) within 24h occurred in 1.7% (107/6444; 95% Cl 1.4-2.0), for the Cochrane definition this was 7.3% compared with 8.6% in the randomized control trials (RCT). Mortality was 11.3% (701/6218; 10.5-12.1) compared with 17.3% in the RCT. The rate of patients with independent outcomes was also non-significantly better than in the RCT. The authors conclude that intravenous rt-PA is safe and effective in routine clinical use when used within 3 h of stroke onset. Overall the results are reassuring and encouraging. SITS allows centers to compare their characteristics with those of other centers, and there are dramatic differences. Median door-to-imaging times for centers vary from 9 minutes (best practice) to 90 minutes (worst practice), with a median of 28 minutes for all centers. Median door-to-needle times range from 20 minutes to 139 minutes with the median for all centers of 73 minutes. This is higher than the recommended door-to-needle time of less than 60 minutes. In fact, a well organized stroke service should achieve a median door-to-needle time of less than 30 minutes.

57.8.2. Costs

The costs associated with intravenous thrombolytic therapy will be a factor in determining the extent of its utilization. In 2004 the USA costs in terms of healthcare and loss of productivity after stroke were estimated at US$53.6 billion (American Heart Association, 2004). Fagan et al. (1998) analyzed data from the NINDS study and the medical literature were used to estimate the health and economic outcomes associated with using tPA in acute stroke patients. A Markov model was developed to compare the costs per 1,000 patients treated with tPA compared with the costs per 1,000 untreated patients. In the NINDS rtPA stroke trial, the average length of stay was significantly shorter in tPA-treated patients than in placebo-treated patients (10.9 versus 12.4 days; $p = 0.02$) and more rtPA patients were discharged to home than to in-patient rehabilitation or a nursing home (48% versus 36%; $p = 0.002$). The Markov model estimated an increase in hospitalization costs of US $1.7 million, a decrease in rehabilitation costs of US $1.4 million and nursing home costs of US$4.8 million per 1,000 treated patients with a greater than 90% probability of cost savings. The estimated impact on long-term health outcomes was 564 (CI 3–850) quality-adjusted life years saved over 30 years of the model per 1,000 patients, which makes a net cost saving to the healthcare system likely. With growing experience and better training of emergency medicine personnel, internists, and neurologists throughout all stroke services, the efficacy of intravenous thrombolytic therapy with rtPA may even further improve and the time window may be routinely extended if ECASS III is positive.

Mar et al. (2005) presented a European cost-effectiveness analysis based on a probabilistic model of the use of thrombolytic therapy in stroke treatment. Patients, who had had a stroke during their hospital stay were surveyed and examined again 1 year after release from the hospital to obtain data on costs and natural history. Using a Markov model as per Fagan et al. (1998), utility weights using the European Quality of Life Questionnaire were calculated. The incremental cost-effectiveness ratio obtained by means of the parameters was €19,000 per quality-adjusted life year, reflecting a saving of €6,000 and a health benefit for patients. The cost-effectiveness plane showed that thrombolysis was a dominant variable in 96.1% of simulations (Mar et al., 2005). The authors deduced that thrombolytic therapy is a useful intervention because it is inexpensive and cost-effective. The key factor was a decreased rate of disability resulting in a better quality of life of the patient and lower costs.

Overall, thrombolytic therapy of acute stroke patients within 3 hours after CT-based exclusion of intracerebral hemorrhage appears to be safe and effective resulting in a significant reduction of death and dependence. Despite this, the use of rtPA is disappointingly low. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy within the 3-hour time window but also about its potential benefit and thus the risk of not being treated.

57.9. Guidelines

Several national and international societies presented guidelines for the acute treatment of stroke. Here, two of them shall be briefly presented: (1) the European Stroke Initiative (EUSI) guidelines (www.eusi-stroke.com); and (2) the American College of Chest Physicians (ACCP) guidelines (www.chestnet.org) (The European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Albers et al., 2004).

57.9.1. European Stroke Initiative guidelines

1. Intravenous rtPA (0.9 mg/kg, maximum 90 mg), with 10% of the dose given as a bolus followed by an infusion lasting 60 minutes, is the recommended treatment within 3 hours of onset of ischemic stroke (level I).
2. The benefit from the use of intravenous rtPA for acute ischemic stroke beyond 3 hours after onset of the symptoms is smaller, but present up to 4.5 hours (level I).
3. Intravenous rtPA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes persons whose strokes are recognized upon awakening (level IV).
4. Intravenous administration of streptokinase is dangerous and not indicated for the management of persons with ischemic stroke (level I).
5. Data on the efficacy and safety of any other intravenously administered thrombolytic drugs are not available to provide a recommendation.

57.9.2. American College of Chest Physicians guidelines

Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices

1. For patients with acute ischemic stroke, administration of i.v. rtPA is recommended, if treatment is initiated within 3 hours of clearly defined symptom onset (grade 1A).
2. For patients with extensive and clearly identifiable hypodensity on CT, we recommend against thrombolytic therapy (grade 1B).
3. For unselected patients with acute ischemic stroke of >3 hours but <6 hours, we suggest clinicians not use i.v. rtPA (grade 2A).
4. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, we suggest intra-arterial thrombolysis with rtPA (grade 2C).
5. For patients with acute ischemic stroke, we suggest clinicians do not use full-dose anticoagulation with i.v., subcutaneous, or low-molecular-weight heparins or heparinoids (grade 2B).
6. For patients with ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy, 160–325 mg/day (grade 1A).
7. For acute stroke patients with restricted mobility we recommend prophylactic low-dose subcutaneous heparin or low molecular weight heparins or heparinoids (grade 1A).
8. For patients who have contraindications to anticoagulants, we recommend that clinicians use intermittent pneumatic compression devices or elastic stockings (grade 1C).
9. For patients with acute ischemic stroke, we recommend against streptokinase (grade 1A).
10. For patients with angiographically demonstrated middle cerebral artery occlusion and no signs of major early infarction on the baseline CT scan, who can be treated within 6 hours of symptom onset, we suggest intra-arterial thrombolytic therapy with rtPA (grade 2C).

57.10. Intravenous thrombolysis based on advanced magnetic resonance imaging

Three CT-based trials assessed the efficacy of rtPA beyond the 3-hour time window but yielded negative results (Hacke et al., 1995, 1998; Clark et al., 1999). While the NINDS trial applied CT only for the purpose of intracerebral hemorrhage exclusion, the later trials for the first time established criteria for the diagnosis of early ischemic stroke in CT (Von Kummer et al., 1995). Despite the poor sensitivity of noncontrast CT within the therapeutic time window—at best 45–65% among specialists (Von Kummer et al., 1996)—and the fact that meta-analyses suggest a therapeutic effect of rtPA beyond the 3-hour time window up to 4.5 hours and up to 6 hours in some patients (Wardlaw et al., 2002; Hacke et al., 2004) it is surprising that modern techniques such as CT angiography (Knauth et al., 1997) or MRI have not had a role in acute stroke imaging until recently (Mohr et al., 1995).

Although Nobel prizes seem to be awarded to developers of imaging techniques (1979 Hounsfield for CT, 2003 Lauterbur and Mansfield for MRI), the last but most important step for a new technology is its establishment in clinical practice. The evolution from tentative reports and early research activity to the definition of possible clinical benefits and acceptance into practice (Jackson, 2001) is often protracted in complex technologies such as MR imaging. Lauterbur published his landmark article about the derivation of position-dependent information by nuclear magnetic resonance and magnetic gradients in the early 1970s (Lauterbur, 1973). Despite the work that followed by Sir Peter Mansfield (Mansfield and Maudsley, 1976, 1977) and other groups, the first clinical MRI system was not available until 1984 and the first paramagnetic MRI contrast agent until 1987. The past 20 years has seen several advances in computer technology and software development, and these changes have continuously improved the accessibility and quality of

MR imaging. The earliest scans—T2-weighted, T1-weighted and PD-weighted sequence without contrast—took literally hours to complete. Today, multiparametric protocols can assess within 15 minutes the most complex pathophysiological processes, which has allowed a dramatic shift in the evaluation and treatment of neurological illness. As the clinical discipline of neurology has evolved from a diagnostic to a therapeutic specialty, MRI has been and is being transformed into a clinical tool that impacts on neurology at the bedside. It is exciting that with an increasing number of clinical therapeutic trials being designed, MRI may not only function as a diagnostic tool but also have prognostic strength and thus serve as a selection tool and a surrogate end-point for the development of new therapies (Warach, 2001b).

57.11. Pathophysiological concepts transferred to magnetic resonance imaging in acute ischemic stroke

The brain is exquisitely sensitive to ischemia, with irreversible damage occurring within minutes of complete ischemia. Collateral flow sources through the circle of Willis and leptomeningeal circulation provide some redundancy in arterial supply and can potentially help protect against tissue death. As a result, focal arterial occlusions can produce regionally varying gradients in hypoperfusion. Electrophysiological, biochemical, and histological data, primarily from animal models, suggest the presence of ischemic thresholds for cellular functions such as protein synthesis, electrical excitability, and immediate or delayed cell death. Such thresholds are also influenced by ischemic duration (Hossman, 1994), since this also contributes to tissue fate. Available information concerning ischemic thresholds in mammalian brain pertains almost exclusively to gray matter.

In the 1970s the term "ischemic penumbra" was coined to describe the volume of brain that is dysfunctional due to ischemic injury but is above the threshold for cell death (Astrup et al., 1981; Belayev et al., 2003). This concept was first described in relation to a baboon model of middle cerebral artery occlusion (Branston et al., 1977). In this model, a cortical region of extreme hypoperfusion around insular cortex represented the ischemic "core" with cerebral blood flow values below 10 ml/100 g/minute. A surrounding "penumbral" region showed cerebral blood flow values below 20 ml/g/minute but above 10 ml/g/minute—this region may still be salvaged if blood flow is restored. In rodent models of middle cerebral artery occlusion, the lenticulostriate distribution represents the ischemic core that is irreversible after about 1 hour, while the cortical distribution has greater reversibility due to leptomeningeal collaterals, which reduce the extent of ischemia (Memezawa et al., 1992). This differential sensitivity of cortical and deep middle cerebral artery distributions also helps explain the propensity for basal ganglia hemorrhage into regions of ischemic necrosis following reperfusion of middle cerebral artery strokes in humans. This region is also the first and at times the only region to be reperfused.

The target for most therapeutic interventions for focal ischemia should be ischemic tissue that can respond to treatment and is not irreversibly injured (i.e., the penumbra). Until recently only PET and SPECT imaging could approximately define ischemia and penumbra thresholds. However, application of these methods in the clinical setting of acute stroke is not practical or feasible. Until recently only limited diagnosis has been possible for the degree of ischemia and potential reversibility in terms of sensitivity and specificity. Newer imaging techniques such as novel MR pulse sequences, perfusion techniques, and other improvements of imaging software and hardware have provided the opportunity to improve the diagnostic yield.

Non-contrast CT is the current diagnostic standard for acute stroke. Its status is mainly due to its wide availability and its near 100% sensitivity for acute intracerebral hemorrhage, the most important differential diagnosis to ischemic stroke (Larrue et al., 2001). For infarction, a number of early signs have been described (Grond et al., 1997) and formalized CT scores have been developed (Barber et al., 2000). The sensitivity of these findings varies widely, ranging from a low of 12% to a high of 92%, depending on the imaging features of infarction, exam time from clinical onset of stroke, the study population, and other study variables (Von Kummer et al., 1995). A post hoc analysis of the NINDS CT data yielded a 31% sensitivity for early infarct signs and a mild correlation with concurrent clinical severity assessed by the National Institutes of Health Stroke Scale (NIHSS), albeit only in the 3-hour time window from onset of clinical signs (Patel et al., 2001). Use of the ASPECTS score on the NINDS CT data set (Demchuk et al., 2005) resulted in the following conclusion: "There was no evidence of treatment effect modification by the baseline ASPECTS value in the NINDS rtPA Stroke Study. Therefore, exclusion of patients for thrombolysis within 3 hours of symptom onset based on EIC is not supported by our data." Overall, the sensitivity of CT for acute ischemic stroke in the 6-hour time window can be estimated to be around 40–60%, which is substantially increased in the further hours after stroke onset (Von Kummer et al., 1995). Although CT

accuracy in acute stroke has never been established by a formal assessment of the evidence, it has become the de facto diagnostic standard for acute stroke with its general acceptance into clinical practice as such.

Two MRI techniques that have received much attention in the past 15 years are diffusion- and perfusion-weighted imaging (DWI and PWI) (Moseley et al., 1991; Warach et al., 1992; Ostergaard et al., 1996; Heiland et al., 1997). The phenomenon of indirectly measuring Brownian molecular motion of water with DWI was first described in 1965 (Stejskal and Tanner, 1965). The measurement of water diffusion renders pathophysiological tissue information especially in ischemic, inflammatory, and neoplastic disease that cannot be obtained with standard MRI sequences (Le Bihan et al., 1986, 1992). In addition to the qualitative measurements of diffusion, the apparent diffusion coefficient can be quantified from measurements at different b-values (Tanner and Stejskal, 1968) on a per pixel basis, within a region of interest, or to generate apparent diffusion coefficient parameter maps. For structures such as nerve fibers or tracts, which have a predominant direction in space, the apparent diffusion coefficient depends on the direction of the diffusion gradient. While water diffusion is only mildly impaired in the longitudinal direction, water diffusion in a perpendicular direction to the main axis is decreased (Basser and Pierpaoli, 1996). This is referred to as anisotropy. In the brain, anisotropy is most pronounced in the white matter, especially in densely packed fiber structures such as the corpus callosum and the corona radiata. The effects of anisotropy can be used to obtain information of the regional fascicular or fiber tract anatomy, which may be helpful for neurosurgical procedures. The expansion of these principles has led to the development of diffusion tensor imaging, which has been used to characterize myelination and demyelination (Ono et al., 1995; Pierpaoli et al., 1996; Neil et al., 1998; Le Bihan et al., 2001). Now that more patients have been evaluated with stroke MRI and at earlier time points, partial reversal of the initial DWI lesion has been reported. These findings suggest that the DWI lesion might be included in the therapeutic target, not as the definite infarct core (Kidwell et al., 2000; Fiehler et al., 2002, 2003; Kidwell et al., 2003). However, DWI lesion reversal seems also to be associated to ultra-early and permanent reperfusion. Therefore, in most instances and especially in later time windows the DWI lesion may adequately reflect permanently damaged brain tissue.

PWI utilizes a dynamic bolus (paramagnetic contrast) tracking technique to derive concentration time curves, allowing the qualitative assessment of various hemodynamic parameters relative to areas of normal parenchyma (Villringer et al., 1988; Rosen et al., 1989, 1990). Typical parameters are mean transit time, cerebral blood volume, cerebral blood flow, and time to peak, which can be deconvoluted with an arterial input function to get semiquantitative data. The actual quantification of hemodynamic information has been limited by post-processing capabilities and methods of calculating the arterial input function. Nevertheless, areas of relative hypoperfusion can be reliably demonstrated by current methods; of special relevance in ischemic stroke (Schlaug et al., 1999). Other applications, such as functional imaging with the BOLD (blood-oxygen-level dependence) technique and spectroscopic imaging exceed the scope of this chapter. The idea that quantitative perfusion imaging is required for stroke assessment is derived from concepts of ischemic thresholds and ischemic penumbra, the premise being that if cerebral blood flow could be accurately quantified then the tissue could be characterized as normal, reversibly ischemic, or irreversibly damaged. Unfortunately, a variety of factors noted above make this unlikely to be the case in human patients. First, the duration as well as extent of ischemia must be known, and such information is not available from a single study acquired at the time of presentation. Second, human stroke typically involves both gray and white matter, whereas threshold data applies primarily to gray matter. Third, while some human strokes such as those caused by thromboembolism in atrial fibrillation consist of a solitary middle cerebral artery occlusion, many human strokes are multifocal or are caused by partial occlusions and in these cases a complex topological relationship is likely to occur between “core” and “penumbra” including variations between cortical laminae. Fourth, mathematical approaches to account for bolus delay and dispersion are complex (Weisskoff et al., 1993). Finally, it is now recognized that delayed cell death occurs as a result of ischemia (apoptosis) and also that recurrent sub-lethal ischemia can make the brain less sensitive to subsequent ischemic events (ischemic conditioning) (Wegener et al., 2004).

Most authors, however, agree that time-based parameters such as mean transit time or time to peak give the best prognostic information (Baird et al., 2000; Schellinger et al., 2001a) for patients with acute ischemic stroke. Further PWI research is aimed at differentiating oligemia from critical ischemia (Kidwell et al., 2003) with the goal of better guiding clinical management. It has been shown that a time thresholding on mean transit time or time to peak maps may increase accuracy. Neumann-Haefelin and colleagues found a threshold of 4 seconds on time to peak maps

to indicate moderately severe and beyond 6 seconds to indicate severe ischemia (Neumann-Haefelin et al., 1999). Sobesky and colleagues compared PWI to H_2O^{15} PET imaging and also showed that a threshold of 4 seconds gains the best sensitivity and specificity for critical (i.e., penumbral) hypoperfusion (Sobesky et al., 2004, 2005). Thus, while hypoperfusion remains a key pathophysiological mechanism in stroke it is no longer clear that absolute quantification of cerebral blood flow at any one moment in time is sufficient or even necessary for predicting tissue outcome. More practically, the "ischemic penumbra" may be operationally defined as those brain regions which are at risk of infarction but remain salvageable based on any criteria, namely the target of stroke therapy (Schlaug et al., 1999).

The volume difference of DWI and PWI—also termed PWI/DWI mismatch—gives an approximate measure of this tissue at risk of infarction (Warach, 2001a). While its non-quantitative approach in part suffers from inaccurate PWI measurements and the fact that DWI abnormalities may reverse (Kidwell et al., 2003) they serve their purpose of easy clinical application. In fact, most experts agree that from a practical standpoint this simple model of PWI/DWI mismatch is sufficiently accurate in most acute stroke patients, and furthermore stroke MRI findings are consistent with our understanding of the pathophysiology of acute ischemia (Schellinger et al., 2001a, 2003). According to unpublished data (S. Warach, pers. comm.) partial or complete DWI lesion reversal is an independent predictor of an improved outcome. However, DWI reversal is associated to early and rapid reperfusion and this per se is a far stronger predictor of clinical and imaging outcome (Chalela et al., 2004). Applying the mismatch concept may identify the individual time window for the patient and thus allow therapeutic decision making based on an individual vascular and hemodynamic situation, rather than the elapsed time. Additional MR findings not captured by CT, such as early blood–brain barrier disruption (Latour et al., 2004) and old microbleeds (Kidwell et al., 2002; Nighoghossian et al., 2002) may predict a poor outcome after thrombolysis and therefore can be used to improve patient selection although this has been contradicted (Derex et al., 2004). It is established that microbleeds are associated with a higher risk of hemorrhagic and ischemic stroke in general (Tsushima et al., 2003), however, whether the one-time-risk of intracerebral hemorrhage after treatment with rtPA is increased at present is unknown (Viswanathan and Chabriat, 2006). Preliminary data of more than 800 patients (Fiehler et al., 2006) indicate that microbleeds do not in fact increase the risk for symptomatic intracerebral hemorrhage after thrombolysis. Therefore the presence of microbleeds currently should not influence our treatment practice, but in the face of doubt may be used as an exclusion criterion in reperfusion studies to increase safety.

57.12. Comprehensively diagnosing stroke with magnetic resonance imaging

The advent of new MRI techniques such as PWI and DWI in the early 1990s added another dimension to diagnostic imaging in stroke (Fisher and Albers, 1999; Hacke and Warach, 2000; Schellinger et al., 2003; Warach, 2003; Warach and Schellinger, 2003). Several investigators found a significant correlation of DWI and PWI changes with follow-up imaging as well as with neurological outcome (Sorensen et al., 1996; Warach et al., 1996, 1997; Lovblad et al., 1997; Barber et al., 1998; Tong et al., 1998). Some authors concluded that different infarct patterns can be identified by means of DWI and PWI in hyperacute stroke, which may allow a more rational selection of therapeutic strategies based on the presence or absence of tissue at risk (Jansen et al., 1999; Schlaug et al., 1999; Kidwell et al., 2003; Schellinger et al., 2003).

The supposed lack of feasibility and practicality of MR as a diagnostic tool in hyperacutely ill patients (Powers and Zivin, 1998; Powers, 2000; Zivin and Holloway, 2000) has been consistently disproven. Many centers have demonstrated that logistical obstacles can be overcome (Schellinger et al., 2000; Buckley et al., 2003). Despite this, substantial doubts remain regarding the feasibility and practicality as well as the validity of stroke MRI in the clinical setting (Powers and Zivin, 1998; Powers, 2000; Zivin and Holloway, 2000). This criticism is mainly based on a supposed lack of studies that assess sensitivity and specificity of these new imaging methods in a randomized, blinded, and controlled fashion. Also, the over-extensive use of the term "imaging gold standard" has added to the controversy, as there remains no such thing as an imaging gold standard for acute ischemic stroke due to the current lack of correlations of any neuroimaging method with neuropathological findings (Von Kummer, 2002a,b). Therefore, as a quasi gold standard the diagnosis of ischemic stroke in most studies is established at follow-up with proof of a lesion on either CT or conventional MR images consistent with a clinical syndrome and a comprehensive diagnostic workup.

Several studies addressed the diagnostic power of stroke MRI for ischemic as well as hemorrhagic stroke, and the most important are summarized in the following paragraph. One study comparing MRI and

CT across a broad sample of patients has been published in preliminary form for the findings of ischemic stroke (Chalela et al., 2003a,b). The authors assessed the relative accuracy of MRI versus CT in a representative sample of patients ($n = 356$) who consecutively presented to a hospital emergency department over an 18-month period and in whom the emergency physician diagnosed possible acute stroke, thus including a representative proportion of patients with not only ischemic strokes, but also non-ischemic strokes and stroke mimics. Patients with the suspected diagnosis of acute stroke were imaged at a median of 33 minutes earlier by MRI than by CT. In the subset of 221 patients scanned within 12 hours from onset, four reviewers (two neuroradiologists and two stroke neurologists) interpreted all scans in a blinded and independent fashion. Acute ischemic stroke as confirmed by the final dismissal diagnosis was diagnosed by MRI significantly more often than by CT (90 versus 20, $p < 0.0001$). Fiebach et al. prospectively evaluated a total of 50 patients with ischemic stroke and 4 patients with transient ischemic attacks (Fiebach et al., 2002). To avoid any bias in favor for the neuroimaging strategy, the patients were randomized to the sequence of imaging modalities (either stroke MRI or CT first followed by the other). Patients were excluded, when the delay from symptom onset to one of the imaging modalities exceeded 6 hours or the delay between the two modalities exceeded 90 minutes. The correct diagnosis of stroke was established by the clinical course and follow-up CT or MRI examination. Follow-up examinations served as reference for validation analysis. Five stroke experts and four residents independently judged stroke signs and lesion size on the images. Inter-rater variability was assessed with unweighted kappa-values for blinded interpretation of CT and DWI for both rating groups. The reviewers were blinded to the symptoms and signs the patients had presented with but they knew that the cohort was an ischemic stroke population. Of the 50 patients, 55% were examined with DWI first. The mean delay from symptom onset until CT was 180 minutes; and from symptom onset until DWI was 189 minutes. The mean delay between DWI and CT was 30 minutes. In the following, the number in parentheses denote the range of the reviewers' results.

Expert readers yielded with DWI a sensitivity of 91% (88–94%), specificity of 95% (75–100%), accuracy of 91% (89–94%), positive predictive value of 100% (98–100%) and negative predictive value of 47% (38–57%). With CT the experts reached a sensitivity of 61% (52–70%), specificity of 65% (50–100%), accuracy of 61% (56–70%), positive predictive value of 96% (94–100%) and negative predictive value of 12% (9–17%).

The novices yielded on DWI a sensitivity of 81% (78–86%), specificity of 100% (100%), accuracy of 82% (80–87%), positive predictive value of 100% (100%) and negative predictive value of 30% (27–36%). On CT the novices reached a sensitivity of 46% (32–64%), specificity of 56% (25–75%), accuracy of 46% (35–61%), positive predictive value of 93% (90–96%) and negative predictive value of 7% (5–11%).

Inter-rater variability of lesion detection was also significantly better for DWI (CT/DWI, $\kappa = 0.51/0.84$). The assessment of lesion extent was less homogeneous on CT (CT/DWI, $\kappa = 0.38/0.62$). The differences between the two modalities were more apparent in the residents' ratings (CT/DWI: sensitivity, 46/81%; $\kappa = 0.38/0.76$). The inter-rater variability of stroke detection on DWI decreased with the delay from symptom onset.

With regard to hemorrhage, Fiebach et al. (2004) performed a multicenter trial with 62 prospectively acquired patients with intracerebral hemorrhage and with ischemic stroke, who were assessed within 6 hours (mean 3 hours 23 minutes) with DWI, T2-DWI and T2*-DWI. Baseline CT, follow-up imaging, and clinical course were used to establish the correct diagnosis of intracerebral hemorrhage and ischemic stroke, respectively. Patients were not matched for age, time since onset, and baseline stroke severity. Randomization numbers were assigned to all scans. Three raters blinded and independently rated all scans. All ischemic strokes and intracerebral hemorrhage were correctly identified by all three raters yielding a sensitivity of 100% (95% CI 97.1–100%), specificity, positive and negative predictive values, and accuracy were 100%. It has to be stressed, however, that the main aim of this study was to prove that stroke MRI can differentiate ischemic stroke from intracerebral hemorrhage within the first 6 hours and therefore the spectrum of patients and controls is narrow. Kidwell et al. (2004) recently published their study in 200 patients within 6 hours. They compared the accuracy of MRI and CT in a prospective, blinded multicenter design. For the diagnosis of any hemorrhage, MRI was positive in 71 patients with CT positive in 29 ($p < 0.001$). For the diagnosis of acute hemorrhage, MRI and CT were equivalent (96% concordance). Acute hemorrhage was diagnosed in 25 patients on both MRI and CT. In four other patients, acute hemorrhage was present on MRI but not on the corresponding CT. In 49 patients, chronic hemorrhage, most often microbleeds, was visualized on MRI but not on CT.

57.13. Guiding therapy with stroke MRI

Despite its potential, only 1–2% of all stroke patients receive rtPA (Kaste, 2003). Among the major problems are that relatively few candidates present within the time window, and meet the clinical criteria. Educating the general public to regard stroke as a treatable emergency and training emergency caregivers in the use of thrombolysis can decrease these problems but demands a continuous effort. Healthcare institutions should be made aware of the potential in long-term cost savings, once stroke management is optimized and thrombolytic therapy is more widely available. Stroke physicians are frequently confronted with stroke patients who awaken with a deficit (Fink et al., 2002) or are unable to provide the required information due to aphasia or disorientation. At present, such patients are excluded from thrombolytic therapy, even if a CT scan is normal or has only minor ischemic changes. In these patients, who might profit from rapid recanalization, thrombolysis is often withheld.

It has been proposed that a more rational selection of therapeutic strategies based on the presence or absence of a tissue at risk, as identified by means of DWI and PWI patterns would improve patient outcome. Open pilot trials have used stroke MRI and the PWI/DWI mismatch for treatment decisions with regard to thrombolytic therapy. MRI is presently used in most of the major stroke centers worldwide for the management of acute stroke beyond the NINDS time criteria, with thrombolysis rates ranging from 10% to 25% of all stroke patients in these centers. In due time, MRI may become not only the most powerful but also the most widely and potentially uniformly used tool to guide therapy based on individual pathophysiology rather than a surrogate parameter such as elapsed time.

57.13.1. Prospective studies

A prospective, open-label, non-randomized multicenter trial examined the MRI baseline characteristics of 139 patients who presented with acute ischemic stroke within 6 hours of symptom onset, and studied the influence of intravenous rtPA on MR parameters and functional outcome (Röther et al., 2002). There was a significantly higher occurrence of independent outcome after treatment with rtPA (76 patients versus 63 controls) despite the significantly worse baseline NIHSS score and the larger volume of tissue at risk in these patients. Another study treated patients according to the NINDS protocol within the first 3 hours ($n = 115$) and according to stroke MRI findings in the 3–6 hour time window ($n = 48$). Baseline NIHSS scores and the rate of symptomatic intracerebral hemorrhage did not differ in between groups, but mortality did trend in favor of the patients receiving late rtPA (3–6 hours) according to stroke MRI criteria (16.5% versus 6.3%, $p = 0.08$). Interestingly, the outcome—independent versus dependent or dead (mRS 0–2 versus 3–6)—of the stroke MRI group was (non-significantly) better than in the group who received early intervention (47% versus 62.5%, OR 0.54, CI 0.27–1.06) based on CT and NINDS criteria. These numbers suggest that with a selection tool such as stroke MRI, the time window for treating stroke with thrombolytic therapy may be substantially expanded, with improved results as compared to historical studies.

Thomalla et al. (2006) compared outcome and symptomatic bleeding complications of intravenous rtPA within 6 hours of symptom onset in MRI-selected patients with acute MCA infarction with the pooled data of the large stroke rtPA trials (Thomalla et al., 2006). From 174 MRI-selected tPA patients, 62% ($n = 108$) were treated within 3 hours and 38% ($n = 66$) after 3–6 hours. Favorable outcome was more frequent in MRI-selected tPA patients (48%; CI 39–54) compared with pooled placebo (33%; CI 31–36; $p < 0.001$) and pooled tPA patients (40%; CI 37–42; $p = 0.046$). Odds ratios for favorable outcome in the MRI-selected tPA group were 1.82 (1.32–2.51) compared with the pooled placebo and 1.39 (1.01–1.92) compared with the pooled tPA group. The rate of symptomatic intracerebral hemorrhage in MRI-selected tPA patients (3%; CI 0–5) was lower than in the pooled tPA group (8%; CI 7–10; $p = 0.012$) and comparable to the pooled placebo group (2%; CI 1–3; $p = 0.392$). This study supports that it is safe and effective to expand the time window for IV-tPA up to 6 hours in patients with tissue at risk as defined by MRI.

Another study by Köhrmann and colleagues (2006) compared in a single center study patients who were treated with rtPA based on CT findings within 3 hours with patients treated based on MRI within and beyond 3 hours. Clinical outcome and occurrence of symptomatic intracerebral hemorrhage were prospectively assessed in 382 consecutive patients. Patients were divided into three groups: (1) CT-based <3 hours ($n = 209$ patients); (2) MRI-based <3 hours ($n = 103$ patients); and (3) MRI-based >3 hours ($n = 70$ patients). Median age was 71, median NIHSS in all groups 13. The rate of independent outcomes in groups 1–3 was 47.8%, 50.5%, and 55.7%. Mortality was trendwise reduced (21.0%, 12.6%, and 11.4%, $p = 0.068$), and symptomatic intracerebral hemorrhage (9.1%, 1.0%, and 5.7%, $p = 0.021$) was significantly reduced in the MRI-based groups. MRI selected patients

overall had a significantly lower risk for symptomatic intracerebral hemorrhage (2.9% versus 9.1% CT-based; $p = 0.013$) and mortality (12.1% versus 21%; $p = 0.021$). The bleeding rate in patients over 80 was higher ($\leq$80 years: 7.7%; >80 years: 15%) in CT-based patients. In multivariate analysis only age (OR 1.050, CI 1.003–1.099, $p = 0.036$) and treating MRI-based (OR 0.343, CI 0.124–0.952, $p = 0.04$) were significant predictors of symptomatic intracerebral hemorrhage, whereas for independent outcome and mortality age, NIHSS score and symptomatic intracerebral hemorrhage were predictive. Time to treatment proved to be irrelevant for all outcomes in univariate and multivariate analyses. These data suggest that patient selection is more important than time to treatment beyond and maybe even within 3 hours. MRI-based thrombolysis within and beyond 3 hours is at least as safe as and maybe more effective than standard CT-based treatment (Köhrmann et al., 2006).

Two prospective trials, Diffusion/Perfusion-weighted Imaging Evaluation For Understanding Stroke Evolution (DEFUSE, USA) and Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET, Australia) (Parsons et al., 2002; Davis et al., 2008) are other MRI-based open studies, which perform therapy with rtPA in the 3–6-hour time window. Both, DEFUSE and EPITHET recruited patients in the 3-6h time window with non-contrast CT and performed MRI thereafter. MRI findings were not taken into account for treatment decisions. The major difference between both studies was that EPITHET randomized to rt-PA versus placebo and DEFUSE did not.

EPITHET is a multicenter trial, aimed at determining whether MRI can be used to select patients for thrombolytic therapy based on identification of potentially salvageable tissue in the ischemic penumbra. The primary hypothesis is that patients with a PWI/DWI mismatch will exhibit reduced infarct growth with tPA (Davis and Donnan, 2006). The study is a double-blind, randomized (1:1), and controlled trial of rtPA versus placebo in patients with hemispheric ischemic stroke, 3–6 hours after stroke onset. The primary endpoint was geometric mean of infarct growth, which did not differ significantly in between placebo and rt-PA, secondary measures of volume expansion did, however, in favour of rt-PA. Reperfusion was more common with rt-PA and was associated with less infarct growth ($p = 0.001$), better neurological outcome ($p < 0.0001$), and better functional outcome ($p = 0.010$) than was no reperfusion.

Results of the DEFUSE trial had first been presented at the International Stroke Conference 2006 in Orlando but are not published yet (Albers et al., 2006; Lansberg et al., 2006; Marks et al., 2006). DEFUSE was a seven-center trial (5 USA, 1 Canada, 1 Belgium), which recruited 74 patients (NIHSS $\geq$6) treated with rtPA within 3–6 hours after symptom onset based on CT findings. An MRI was obtained immediately prior to, and 4–8 hours (median 4.25 hours) after rtPA. PWI/DWI mismatch was defined as a PWI volume 20% larger than the baseline DWI volume. Early reperfusion required a $\geq$30% and $\geq$10 ml reduction on the 4–8 hour post-treatment PWI compared to the baseline PWI. Median NIHSS score was 12, median age 71 years, median time to treatment 5 hours 24 minutes, and median door-to- needle time was 2 hours, which was fairly long. Vessel status according to MRA was defined as normal, partially occluded, completely occluded, or technically not usable. Complete recanalization was defined as a normal, early follow-up MRA after partial or complete occlusion at baseline, partial recanalization as partial occlusion after baseline complete occlusion according to MRA (Marks et al., 2006). Sixty-eight of 74 patients had an interpretable MRA, 44 with a lesion and a successful follow-up MRA. Nineteen patients (43%) experienced early recanalization, 12 (27%) of these complete and 7 (16%) only partial. Patients with proximal middle cerebral artery occlusions only recanalized in 36%. PWI lesion volumes were twice as large in complete as compared to partial occlusions. Patients with recanalization had a 74% volume reduction of PWI, non-recanalizers a 16% PWI volume increase. However, recanalization and outcome were poorly correlated in all patients. Recanalization in patients with mismatch led to a favorable outcome in 47% but only 8% of patients without a mismatch (Marks et al., 2006).

A malignant MRI pattern (MP) was defined as a baseline DWI $\geq$105 ml or severe PWI lesion ($\geq$8 seconds delay on T_{max}) of $\geq$100 ml and seen in six patients. Three out of these six patients had early reperfusion, all of them with fatal symptomatic intracerebral hemorrhage, while one of these patients (17%) only experienced an independent outcome (mRS 0–2). In a multivariate analysis including clinical (age, NIHSS, glucose) and MRI variables, DWI lesion volume was the only independent predictor of symptomatic intracerebral hemorrhage ($p = 0.002$; OR 1.41; CI 1.07–1.87) (Lansberg et al., 2006). The group with a target mismatch excluded patients with the malignant MRI pattern. Early reperfusion was associated with a favorable clinical response in mismatch patients, particularly those with a target mismatch (57% versus 19% mRS 0–2, OR 8.7, $p = 0.011$). Adjusted for age and NIHSS differences this was even more pronounced. If malignant MRI patterns were included, these results were still significant. Patients without mismatch did not benefit

from early reperfusion, but in fact did worse than those without mismatch and without reperfusion. Patients with small baseline lesions had favorable outcomes (74%) regardless of reperfusion (Albers et al., 2006).

In conclusion the preliminary results of DEFUSE show that early recanalization on MRA is associated with early reperfusion on PWI, both events being not as frequent with rtPA as might be expected. Only PWI/DWI mismatch and not the matched patients have a benefit from early reperfusion, especially if DWI and PWI lesions do not show a malignant pattern; that is, large lesion volumes with extensive perfusion reduction and that patients with small lesions have a good outcome. Symptomatic intracerebral hemorrhage rate is associated with lesion size and reperfusion in patients with a malignant MRI pattern.

Two parallel phase II trials (DIAS, DEDAS) with a 3–9-hour time window for another thrombolytic drug (desmoteplase) have been completed, and the results of DIAS have been published (Hacke et al., 2005). The principle underlying DIAS and DEDAS was the same. Both trials use a thrombolytic in a prolonged time window coped for by a better imaging selection process. The Desmoteplase In Acute Ischemic Stroke trial (DIAS) was a placebo-controlled, double-blind, randomized, dose-finding phase II trial designed to evaluate the safety and efficacy of intravenous desmoteplase in the 3–9-hour time window. Patients needed to present with a PWI/DWI-mismatch on MRI. After a fixed dose applied in part 1 (47 patients; 25 mg, 37.5 mg, or 50 mg) led to an excessive rate of symptomatic intracerebral hemorrhage, lower weight-adjusted doses escalating through 62.5 μg/kg, 90 μg/kg, and 125 μg/kg were subsequently investigated in 57 patients (part 2). The safety end-point was the rate of symptomatic intracerebral hemorrhage. Efficacy endpoints were the rate of reperfusion on MRI after 4–8 hours and clinical outcome as assessed by NIHSS, modified Rankin scale, and Barthel index at 90 days. After part 1 was terminated prematurely because of high rates of symptomatic intracerebral hemorrhage with desmoteplase (26.7%), part 2 had a symptomatic intracerebral hemorrhage rate of 2.2%. No symptomatic intracerebral hemorrhage occurred with placebo in either part. Reperfusion rates up to 71.4% ($p = 0.0012$) were observed with desmoteplase (125 μg/kg) compared with 19.2% with placebo. Favorable 90-day clinical outcome was found in 22.2% of placebo-treated patients and between 13.3% (62.5 μg/kg; $p = 0.757$) and 60.0% (125 μg/kg; $p = 0.009$) of desmoteplase-treated patients. Early reperfusion correlated favorably with clinical outcome ($p = 0.0028$). Favorable outcome occurred in 52.5% of patients experiencing reperfusion versus 24.6% of patients without reperfusion.

The DEDAS study yielded confirmatory results (W. Hacke, pers. comm.) but has not been published yet. In total, 37 patients were included in DEDAS into three tiers (placebo, 90 μg/kg and 125 μg/kg). There were no symptomatic intracerebral hemorrhages, mortality was lower in active arms (12.5% versus 7.1% and 6.7%). Several protocol violations (no PWI/DWI mismatch) accumulated in the 90 μg dose arm rendering the results useless. The 125 μg dose arm showed a good clinical outcome in 60% of patients versus 25% in the placebo arm. The most important results of both trials together are that high doses of desmoteplase cause excessive bleeding, whereas body-weight-adapted doses led to an increase of early reperfusion as measured with MRI and clinical improvement. Interestingly, imaging parameters parallel the clinical outcome proving that the MRI parameters function as adequate surrogate parameters. Also, within 3–9 hours it does not matter when the therapy is given. If a mismatch is present, time from symptom onset was not a treatment effect-modifying factor. DIAS-2 is currently recruiting in two dosage arms (90 μg/kg, and 125 μg/kg) versus placebo. As of February 2006, 40 patients have been included. In contrast to DIAS and DEDAS there are centers that instead of MRI can use stroke CT (CT, CT angiography, and perfusion CT) to screen for patients. DIAS-2 has been completed, the data have not been published yet. The presented results showed no significant benefit of desmoteplase over placebo.

The combination of rtPA with glycoprotein IIb/IIIa antagonists may be a promising approach and results in increased vessel patency rates in accordance with cardiological studies. These trials currently are only phase II, but will include patients in late time windows up to 24 hours after stroke onset, using stroke MR findings as inclusion criteria (tirofiban plus rtPA—SATIS (M. Siebler pers. comm.); abciximab plus reteplase—ROSIE; eptifibatide plus aspirin, low-molecular-weight heparin, rtPA—ROSIE 2 (S. Warach, pers. comm).

In the ROSIE trials, patients are selected by criteria to minimize likelihood of toxicity and maximize likelihood of response (age, NIHSS $\leq$16, lesion volume on DWI less than one-third middle cerebral artery territory, PWI/DWI mismatch, no microbleeds). ROSIE is an open-label, dose escalation, safety and proof-of-principle study of the combination of intravenous abciximab and rPA with a fixed standard dose of abciximab for 12 hours and five dosing groups for the reteplase dose (0 U, 2.5 U, 5.0 U, 7.5 U, and 10.0 U). Doses are assigned according to a Bayesian approach (Thall and Cook, 2004) based on the trinary

outcome response (1), toxicity (2), or neither (3). Thresholds for dose acceptability were a maximum rate of 10% for toxicity and minimum rate of 50% for response.

The study has recruited 34 of the planned 72 patients and interim results were recently presented (Warach et al., 2006). Two toxicities (one non-fatal symptomatic intracerebral hemorrhage, one fatal GI hemorrhage) were observed (6%), both in the 7.5 U reteplase dose tier. Overall response rate at 24 hours was 29% (10 patients). Confidence intervals for toxicity in all tiers extend to less than 10% and extend to over 50% for all tiers except abciximab monotherapy. The doses of reteplase straddling both thresholds range from 5 to 10 U, the dose of 7.5 U having a projected response rate of 48% and toxicity of 11% (5 U: 45%/9%; 10 U: 50%/12%). The authors conclude that abciximab monotherapy is safe but unlikely to give acceptable reperfusion rates without a fibrinolytic. ROSIE will continue to randomize (Warach et al., 2006).

57.13.2. Stroke upon awakening

Time of stroke onset is uncertain for patients who wake from sleep with stroke. Usually these patients are excluded from studies as well as reperfusion therapies just based on the unclear time window from symptom onset. Only trials such as the ROSIE study with time windows of up to 24 hours are suited to include these patients. However, imaging constellations as described above may also be helpful to offer effective strategies to these patients, especially when the stroke occurred upon awakening rather than upon going to bed. Fink and colleagues compared stroke MRI findings in patients with uncertain stroke onset with those with known onset time (Fink et al., 2002). A total of 364 patients were identified, of whom 100 (27%) woke from sleep with stroke. The groups did not differ in baseline demographic variables and stroke severity except of time from onset defined as latest time the patient was seen neurologically intact (mean 6.0 versus 13.3 hours). DWI and PWI lesion volumes were similar in both groups, as was the rate of mismatch (82% versus 73%). The authors concluded that despite the unknown time windows, stroke upon awakening has similar clinical and imaging features as in those patients with known onset time and therefore might profit from therapy based on imaging findings rather than time windows (Fink et al., 2002).

Cho et al. (2006) tested whether safety and outcome of MRI-based thrombolysis in patients with unclear onset time is inferior compared to patients with clear onset time. Two-hundred and thirteen acute ischemic stroke patients within 6 hours of stroke awareness were considered for thrombolysis. Patients within 6 hours from last known normal time ($n = 182$) were considered for conventional CT or MRI-based thrombolytic therapy. For patients with unclear onset time and more than 6 hours from last known normal time ($n = 31$), stroke MRI criteria (mismatch, no major T2 changes) were applied. Of these 213 patients screened for thrombolysis, 70 (38.5%) with clear onset time and 10 (32.3%) without received thrombolysis. Demographics, baseline stroke severity, stroke subtypes, and door-to-needle times were comparable between the groups. Early neurologic improvement (30% in group A versus 40% in group B), symptomatic intracerebral hemorrhage (5.8% versus 0%), 3-month outcomes (mRS 0–1, 26% versus 20%; mRS 0–2, 42% versus 40%; mortality, 24.6% versus 10%) did not differ between two groups, but tended to be better overall (Cho et al., 2006). This may be due to the fact that even stricter MRI criteria were applied in wake-up strokes and therefore safety and efficacy might be improved, which needs to be tested in a larger sample however.

57.14. Intravenous thrombolysis based on advanced computed tomography imaging

Non-contrast CT imaging is currently the most widely used diagnostic tool for stroke imaging (Schellinger et al., 2003) mainly due to its close to 100% high sensitivity for intracerebral hemorrhage, the most important differential diagnosis to ischemic stroke (Von Kummer et al., 1995). The utility of stroke MRI has been discussed with controversy (Schellinger and Fiebach, 2005; Zivin, 2005). The overall availability of higher-generation CT scanners with CT angiography and CT perfusion protocols offers an attractive alternative to stroke MRI. Modern CT scanners of the third, fourth, or even fifth generation (volume scanners) are less expensive and available in most centers even in smaller community hospitals, where they are mostly used for extracranial scanning. Acute stroke is not only treated at specialized academic medical centers; indeed, the majority of patients present first in local general hospitals that have no MRI facilities (Handschu et al., 2001).

57.14.1. Non-contrast computed tomography

Improvements of non-contrast CT ratings have been achieved with a more formalized approach with the ASPECTS score (Barber et al., 2000; Pexman et al., 2001), which however does not apply to the standard 3-hour time window (Demchuk et al., 2005). The ASPECTS score divides the middle cerebral artery

territory into 10 regions of interest as seen on two standardized axial CT slices (basal ganglia and lateral ventricles). The whole middle cerebral artery territory is allotted 10 points (one for each area) and a single point is subtracted for each of the defined regions if ischemic lesions are seen. A sharp increase in dependence and death occurs with an ASPECTS score of 7 or less in patients beyond the 3-hour time window. While the ASPECTS score may be superior to the ECASS one-third middle cerebral artery rule, it is rather a refinement of that rule than a completely new development.

Another simple method to improve the diagnostic accuracy of non-contrast CT is the use of non-standard, variable window width, and level review settings (Lev et al., 1999). With standard viewing parameters, sensitivity and specificity for stroke detection were 57% and 100%, with narrow window and variable settings sensitivity significantly increased to 71% without loss of specificity ($p = 0.03$). In conclusion, the sensitivity of non-contrast CT for intracerebral hemorrhage is high. While clearly defined, the diagnostic impact of early infarct signs is debatable as these signs often may be subtle and require a high level of experience for detection and interpretation. A large area of manifest hypodensity exceeding one-third of the middle cerebral artery territory, however, should be regarded as a contraindication for thrombolytic therapy.

57.14.2. CT angiography/CT angiography source images

Today, CT-angiography (CTA) by using spiral CT is a widely available tool used to evaluate the circle of Willis. In acute ischemic stroke patients this technique can provide accurate information on stenoses or occlusions in the basal arteries of the brain (Knauth et al., 1997; Shrier et al., 1997). The method is non-invasive, safe, and independent from the grade of experience of the investigator (in contrast to Doppler ultrasound (DU)). In experimental studies (Doerfler et al., 1998) as well as larger series of stroke patients there were no immediate adverse reactions after administration of the intravenous non-ionic iodinated contrast material (Shrier et al., 1997). Newer generations of CT scanners allow for lower contrast doses. A recent study addressed the frequency of contrast-induced nephropathy in acute stroke imaging (Krol et al., 2006). Of 526 patients receiving CTA, DSA, or both, none developed acute renal failure needing dialysis. Out of these, 494 had a baseline creatinine result, mean 83.9 mmol/l and 215 patients received a follow up creatinine result, mean 80.4 mmol/l. Creatinine increases ranging from 17 to 41 mmol/l as a sign of mild radiocontrast nephropathy were observed in 7 patients (3.3%). Acute CTA alone or combined with DSA appears to be safe in acute stroke patients. If urgent CTA is critical for acute stroke decision making, this study supports proceeding without knowledge of baseline creatinine level (Krol et al., 2006).

In addition to the assessment of a major vessel occlusion, CTA has the potential to deliver information about the quality of the collateral circulation. In patients with good leptomeningeal collaterals contrast enhancement in arterial branches beyond the occlusion occurs. This degree of enhancement can be taken as an estimate of the collateral blood flow (Knauth et al., 1997; Wildermuth et al., 1998). Analysis of CTA source images must be clearly differentiated from perfusion CT, where in analogy to perfusion MRI a contrast bolus tracking method is applied and hemodynamic parameters may be assessed (Koenig et al., 1998). CTA source image analysis is a stronger predictor of clinical outcome than the initial NIHSS score and may predict final infarct volume and clinical outcome. Schramm et al. (2002) investigated whether CTA source images allow the detection of ischemic brain lesions in patients with acute ischemic stroke, whether their sensitivity is comparable to that of DWI, whether the hypoperfused brain area seen on CTA source images correlates with the final infarct, and whether the qualitatively assessed collateral status reflects the risk of infarct growth. Of 20 consecutive stroke patients imaged within 6 hours after stroke onset with both imaging modalities, 16 had a vessel occlusion seen on both CTA and MRA. Five of these patients showed good collaterals, and 11 showed poor collaterals surrounding the lesion site. While CTA stroke image volumes did not differ from DWI volumes at baseline regardless of the collateral status, at day 5 there was a significant increase of infarct volume on T2-WI in patients with poor collateral vessel status ($p = 0.006$), whereas in patients with good collaterals no significant difference was found. Similar to the PWI/DWI mismatch concept, a poor collateral status predicted a significantly worse clinical outcome without recanalization. CTA source images may indeed provide information similar to that of the PWI/DWI mismatch concept. The volume of the affected brain area that has inadequate blood supply can be estimated by the difference between the CTA source image lesion volumes and the brain area supplied by the occluded artery, taking the qualitative assessment of the collateral status into account. The patients with poor collaterals seem to represent those that may have a PWI/DWI mismatch in analogy to stroke MRI and the patients with good collaterals those patients without tissue at risk.

57.14.3. Dynamic perfusion CT

Perfusion CT allows the generation of functional maps of cerebral blood volume, cerebral blood flow, or time-to-peak enhancement calculated from a contrast bolus time curve in analogy to PWI (Hamberg et al., 1996). Perfusion CT within 6 hours of symptom onset compared to SPECT in 32 patients with acute stroke showed a good correspondence in 81% of the patients (Koenig et al., 1998). In perfusion CT scans of 45 acute stroke patients, the extent of cerebral ischemia on cerebral blood volume, cerebral blood flow, and time-to-peak maps compared favorably with non-contrast CT (Koenig et al., 2000). Twenty-nine of 45 patients showed early signs of ischemia on conventional CT only, whereas perfusion CT revealed cerebral ischemia in all patients. Measurements of the relative cerebral blood flow, relative cerebral blood volume, and relative time-to-peak may be used to differentiate areas undergoing infarction from reversible ischemic tissue (Koenig et al., 2001). However, calculated thresholds for cerebral blood volume, cerebral blood flow, and time-to-peak differ between various scanners, perfusion post-processing techniques, and other variables. However, pathological findings on perfusion CT are predictive of lesions at follow-up (Röther et al., 2000). In some patients, ischemia is located outside the scanning level of perfusion CT, which at present covers 2 cm at the most with one assessment. Some authors therefore recommend two perfusion CT acquisitions with a gap of 1 cm to obtain 5 cm brain coverage. This may be limited by cumulative contrast and radiation exposure on the other hand. New and already available developments in CT technology, including dynamic scanning with multisection data acquisition (multislice CT), may further increase the value of this technique and provide information about the three-dimensional extent of cerebral ischemia. Another problem of perfusion CT is that, as with PWI, it only renders semiquantitative information about cerebral blood flow as opposed to PET and SPECT, even if this has been advertised differently. In clinical practice the need for quantification of hemodynamic parameters is probably negligible.

Schramm and colleagues assessed the diagnostic value of perfusion CT and CTA including CTA source images in comparison with PWI and DWI in 22 acute stroke patients within 6 hours (Schramm et al., 2004). Hypoperfusion volumes on perfusion CT time-to-peak maps did not differ from PWI-time-to-peak ($p = 0.686$), nor did perfusion CT cerebral blood volume differ from PWI-cerebral blood volume ($p = 0.893$). CTA source image volumes did not differ from DWI volumes ($p = 0.465$). Also, lesion volumes measured in perfusion CT maps significantly correlated with lesion volumes on PWI (all $r > 0.9$, all $p < 0.005$) and perfusion CT-cerebral blood volume lesion volumes significantly correlated with follow-up CT lesion volumes ($r > 0.8$, $p < 0.005$). Wintermark and colleagues also compared stroke MRI and perfusion CT/CTA in 42 acute stroke patients in the 3–9 hour time window. Agreement between perfusion CT/CTA and MRI was excellent regarding infarct size and the penumbra/infarct ratio. Agreement for treatment decisions based on algorithms was also excellent. Only one patient would have been treated based on MRI, and not treated based on CT. Therefore, if stroke MRI is not available, advanced CT imaging appears to be a viable alternative imaging option rendering comparable results (Schramm et al., 2004; Wintermark et al., 2006).

57.14.4. Suggested treatment algorithm

The following treatment algorithm is based on an institutional protocol and not primarily on international guidelines. However, a recent publication presents algorithms from several of the leading groups of MRI-based management of stroke and these algorithms are fairly consistent (Hjort et al., 2005). Whenever possible, explicit informed consent should be obtained and the next of kin if available should be informed about the individual treatment character of these recommendations. It acknowledges the fact that at present approval of thrombolysis is based on CT diagnosis within the 3-hour time window (Fig. 57.1) and therefore states this latter procedure as the highest priority. Generating evidence by participating in randomized trials is the second priority. The open use of stroke MRI as pictured in this review is priority 3 (Fig. 57.1 and Table 57.1). The 3–9 hour time window was chosen in parallel to the DIAS trial (Table 57.2). Patients with unknown time window are included, if strict MRI criteria are met (Fink et al., 2002; Cho et al., 2006). Patients with a PWI/DWI mismatch represent an absolute, and with a PWI/DWI match a relative indication for thrombolysis based on potential reversibility of DWI lesions. However, with the results of DEFUSE this should be changed. A fourth priority is based on stroke CT criteria (CT, CT angiography, perfusion CT). This technique has been far less validated in stroke studies and not at all in treatment studies. Nevertheless, preliminary data and common sense dictate that stroke CT can be used in a similar fashion as stroke MRI, however, with less diagnostic strength. Finally, based on the combined analysis (Hacke et al., 2004), if neither a study, stroke MRI or stroke CT is available, there is sufficient evidence for expanding the time window to 4.5 hours with non-contrast CT only.

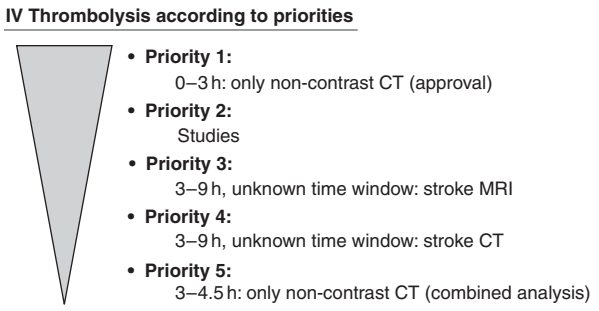

Fig. 57.1. Thrombolysis according to priorities.

Table 57.1 **Thrombolysis according to priorities—Priority III specified**

Priority III: 3–9 hours + unknown
Stroke MRI algorithm
All patients no matter what age
NIHSS score >4
NIHSS score ≤4 and disabling neurological deficit
MRI indication for rtPA
PWI > DWI (mismatch) including leukoaraiosis, lacune, old microbleeds
MRI contraindication for rtPA
Intracerebral hemorrhage
DWI > 33%, FLAIR/T2 clearly hyperintense
PWI negative or << DWI (negative match)

Table 57.2 **Thrombolysis according to priorities—Priority IV specified**

Priority IV: 3–9 hours + unknown
Stroke CT (CT, CTA, PCT)
All patients no matter which age with:
NIHSS score >4
NIHSS score ≤4 and disabling neurological deficit
Stroke CT indication for rtPA
TTP > maximal extent on CTA source image, cerebral blood volume, and NC-CT
Middle cerebral artery occlusion on CTA
Stroke CT contraindication for rtPA
Normal NC-CT exlusion criteria as in 0–3 hours (priority I)
Intracerebral
CTA source image or NC-CT or cerebral blood volume > 33% middle cerebral artery
TTP and CTA negative

57.15. Intra-arterial thrombolysis

The delivery of thrombolytic agents locally, at or within the occluding thrombus, has the advantage of providing a higher concentration of the particular thrombolytic agent where it is needed while minimizing the concentration systemically. Hence, local intra-arterial thrombolysis has the potential for greater efficacy with regard to arterial recanalization rates and greater safety with regard to lower risk of hemorrhage. The technique involves performing a cerebral arteriogram, localizing the occluding clot, navigating a microcatheter to the site of the clot, and administering the lytic agent at or inside the clot with or without mechanical dissolution of the thrombus. Grade of vessel occlusion is usually assessed with the Thrombolysis in Myocardial Infarction (TIMI) score, where TIMI 0 is complete occlusion, TIMI 1 minimal perfusion, TIMI 2 partial flow (recanalization), and TIMI 3 complete flow (recanalization) (TIMI Study Group, 1985). The agents most commonly used or which are under investigation are urokinase, rtPA, and pro-urokinase, all of which are usually administered at a lower dose than used in the intravenous treatment of acute ischemic stroke.

57.15.1. Early trials of intra-arterial thrombolysis for acute ischemic stroke

Results of several case series on local thrombolysis in the carotid artery territory have been promising, although not convincing (Schellinger et al., 2001b). For rtPA, doses ranged between 10 and 80 mg; for urokinase, doses usually ranged up to 1.5 million units. Time from symptom onset to treatment in the smaller series has been for the most part within 6 hours, but not within 3 hours or even 4 hours of symptom onset. The reported complete or partial recanalization rates vary substantially between less than 50% (Mori et al., 1988) and more than 90% (Zeumer et al., 1993). When combining the results of these case series, complete clot lysis is reported for approximately 40% and partial clot lysis for another 35%. The combined partial or complete recanalization rate therefore is higher than that demonstrated in angiography-based intravenous studies (approximately 55%). Each of these intra-arterial case series differs from all of the others with regard to thrombolytic agent, baseline neurological deficit, angiographic anatomy, time-to-treatment, outcome, and method of neurological evaluation at follow-up. Accordingly, conclusions regarding efficacy are not possible. The most feared complication of local intra-arterial therapy for stroke, as for intravenous thrombolytic therapy, is symptomatic intracerebral hemorrhage which is lower than that reported for many intravenous

thrombolysis series (4%). However, this rate is also lower than that reported in the PROACT I and II trials, in which 24-hour CT scans were performed on all patients. Other complications of intra-arterial thrombolysis include arterial intracranial embolization, subarachnoid hemorrhage, arterial perforation, secondary embolization, hemorrhagic infarction, groin hematoma, and retro-peritoneal hematoma. These complications occur infrequently, certainly in less than 5% for all the series. One drawback of intra-arterial in contrast to intravenous thrombolysis is the considerable time delay to angiography, and from initiation of angiography to clot lysis (Zeumer et al., 1993).

57.15.1.1. PROACT I

PROACT I was a randomized phase II trial of recombinant pro-urokinase (rpro-UK) versus placebo in patients with angiographically documented proximal middle cerebral artery occlusion (Del Zoppo et al., 1998). Angiography was performed after exclusion of intracerebral hemorrhage by CT. Patients displaying TIMI grade 0 or 1 occlusion of the M1 or M2 middle cerebral artery were randomized 2:1 to receive rpro-UK (6 mg) or placebo over 120 minutes into the proximal thrombus face. Recanalization efficacy was assessed at the end of the 2-hour infusion and symptomatic intracerebral hemorrhage at 24 hours. A total of 105 patients underwent angiography; 65 of these ($n = 25$: no occlusion, $n = 36$: no M1 or M2 occlusion, $n = 2$: time interval >6 hours, $n = 2$: complications) were excluded from randomization. Among the 40 treated patients, 26 received rpro-UK and 14 placebo at a median of 5.5 hours from symptom onset. Recanalization was significantly associated with rpro-UK ($p = 0.0085$) and TIMI 3 recanalization was achieved in 5 rpro-UK patients, as opposed to none of the placebo patients. Intracerebral hemorrhage occurred in 15.4% of the rpro-UK-treated patients and 7.1% of the placebo-treated patients (non-significant); all patients with rpro-UK *and* early CT signs of more than 33% suffered intracerebral hemorrhage. In patients who received high-dose adjuvant heparin the recanalization rate was 81.8%; in the low-dose heparin group (dose was lowered for reasons of safety by the safety committee) it was 40% ($p = 0.0255$). Mortality was lower in the rpro-UK group, albeit not significantly.

57.15.1.2. PROACT II

PROACT II, a randomized, controlled, multicenter, open-label clinical trial with blinded follow-up, aimed to determine the clinical efficacy and safety of intra-arterial rpro-UK in patients with acute stroke of less than 6 hours' duration caused by middle cerebral artery occlusion (Furlan et al., 1999). Eligible patients had new focal neurological signs attributable to the middle cerebral artery territory, allowing initiation of treatment within 6 hours after symptom onset, a minimum NIHSS score of 4 points, and exclusion of intracerebral hemorrhage on CT. Patients with these criteria underwent angiography and were randomized (2:1) to either treatment with 9 mg rpro-UK/2 hours plus the PROACT I lower dose of heparin (2000 IU bolus, 500 IU/hour continuous infusion) or heparin alone. Mechanical disruption of the clot was not permitted. After 1 hour (4.5 mg rpro-UK) a control angiogram was performed and if the clot had partially or even completely dissolved, the rest of the rpro-UK dose was administered. The primary outcome was the rate of patients with an mRS of ≤2 at 90 days. Secondary outcomes included middle cererbral artery recanalization (TIMI 2 and 3), the frequency of symptomatic intracerebral hemorrhage, and mortality. Of 12,323 patients screened in 54 centers, only 474 (4%) underwent angiography at a median of 4.5 hours after stroke onset, 294 of which demonstrated angiographic exclusion criteria, leaving 121 rpro-UK and 59 control patients with a median baseline NIHSS of 17 points for intention-to-treat analysis. Further, 40% of rpro-UK patients and 25% of control patients had an mRS of 2 or less (absolute benefit 15%, relative benefit 58%, number needed to treat = 7; $p = 0.04$). Mortality was 25% for the rpro-UK group and 27% for the control group ($p = 0.8$.) The recanalization rate was 66% for the rpro-UK group and 18% for the control group ($p < 0.001$); TIMI 3 recanalization rates were 19% and 2%, respectively ($p < 0.003$). All other secondary outcomes were non-significant. Early intracerebral hemorrhage occurred in 35% versus 13% of patients ($p = 0.003$); at 10 days the rates were 68% and 57% ($p = 0.23$). Early symptomatic intracerebral hemorrhage occurred only in patients with NIHSS scores >11 within 24 hours in 10.2% of rpro-UK patients and 2% of control patients (number needed to harm = 12; $p = 0.06$).

The higher rate of symptomatic intracerebral hemorrhage (10.2% in PROACT II versus 8.8% in ECASS II, 6.4% in NINDS and 7.2% in ATLANTIS) is very well explained by the far larger baseline severity of stroke in PROACT II (NIHSS of 17 in PROACT II versus 11 in ECASS II and ATLANTIS, and 14 in NINDS). According to the Cochrane meta-analysis, combining PROACT I and II data (Wardlaw et al., 2002), there is a 0.55 OR (CI 0.31–1.00) for death or disability, an OR of 2.39 (CI 0.88–6.47) for early symptomatic intracerebral hemorrhage (7–10 days), and an OR of 0.75 (CI 0.4–1.42) for death from all causes at follow-up. Although recanalization rates may be superior with intra-arterial (66%) than with intravenous (≈55%) thrombolysis and may even

be increased by careful mechanical disruption of a thrombus, in addition to the lytic effect of the drug, a limited availability of centers with round-the-clock interventional neuroradiology service may restrict the use of this therapy. On the other hand, the clinically more severe strokes may benefit even more from an intra-arterial than an intravenous approach. Furthermore, the time to eventual recanalization may be substantially shorter with intra-arterial thrombolysis. The results of PROACT II did not suffice for FDA approval. Another study (PROACT III) of intra-arterial pro-urokinase for acute stroke within 6 hours had been intended but currently is not planned due to lack of funding.

57.16. Combined intravenous/intra-arterial thrombolysis

Several groups assessed the combination of IV and IA thrombolysis—the so-called "bridging concept." The advantage of this concept lies in compensating for the time loss to start of IA lysis with a reduced rate of IV lysis started early after intracerebral hemorrhage exclusion. In a double-blind, randomized, and placebo-controlled phase I Emergency Management of Stroke (EMS) study, Lewandowski et al. (1999) tested the IV/IA approach with rtPA in 35 patients (17 IV/IA, 18 placebo/IA). Recanalization was better ($p = 0.03$) in the IV/IA group with TIMI 3 flow in 6 of 11 IV/IA patients versus 1 of 10 placebo/IA patients and correlated to the total dose of rtPA ($p = 0.05$). Symptomatic intracerebral hemorrhage within 24 hours occurred in 1 placebo/IA patient only. Beyond 24 hours, symptomatic intracerebral hemorrhage occurred in 2 IV/IA patients only, mortality was slightly higher in the combined arm. This pilot study demonstrated feasibility and better recanalization rates of the combined IV/IA treatment approach, however no effect on outcome.

57.16.1. Interventional management of stroke (IMS) studies

In a first study, the IMS group investigated the safety of a combined IV/IA approach to recanalization in patients with ischemic stroke. Patients aged 18 to 80 with an NIHSS $\geq$10 at baseline had IV rtPA started (0.6 mg/kg, 60 mg maximum over 30 minutes) within 3 hours of onset. Additional rtPA was then administered via microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until thrombolysis (IMS Study Investigators, 2004). Primary comparisons were made with historical controls (rtPA-treated subjects from the NINDS rtPA stroke trial). Eighty patients with a median baseline NIHSS score of 18 were included in a median time to initiation of IV rtPA of 140 minutes. The 3-month mortality in IMS patients (16%) was non-significantly lower than the mortality of placebo (24%) and rtPA-treated subjects (21%) in the NINDS rtPA stroke trial. The rate of symptomatic intracerebral hemorrhage (6.3%) in IMS subjects was similar to that of rtPA-treated subjects (6.4%) but higher than the rate in placebo-treated subjects (1.0%, $p = 0.018$) in the NINDS rtPA stroke trial. Despite the higher baseline severity, IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures (IMS Study Investigators, 2004). Symptomatic intracerebral hemorrhage may be related to occlusion location (carotid artery versus middle cerebral artery) and presence of atrial fibrillation, although this has to be confirmed (IMS Study Investigators, 2006).

The IMS-2 study used the same protocol as in the IMS study, however, the use of the EKOS ultrasound device was permitted compared to standard IV rtPA (IMS 2 Investigators, 2006). Here, the catheter tip emanates low-frequency ultrasound waves that aid in thrombus fragmentation. Intravenous rtPA had to be initiated within 3 hours and the minimum baseline NIHSS score had to be 10. Seventy-three patients were included, 22 received IV rtPA, 51 received IV/IA rtPA. Of these 51 patients, 18 received normal IA with a standard microcatheter, 33 received treatment with the EKOS catheter, in 30 of whom ultrasound was actually used, and 3 received IA rtPA only. The median NIHSS was 19, a TIMI 2–3 recanalization was achieved in 57.7%, mortality was 16%, symptomatic intracerebral hemorrhage rate was 11%, favorable and independent outcomes were seen in 33% (mRS 0–1) and 45% (mRS 0–2), respectively. Comparison of the subgroups was not yet presented (IMS 2 Investigators, 2006). A randomized, open label phase III trial in 900 patients within 3 hours, with a baseline NIHSS $\geq$10 and a primary outcome endpoint (mRS 0–2) at 3 months is planned. Randomization will be 2:1 IV/IA (0.6 mg/kg over 40 minutes, 10% bolus of the 0.9 mg/kg dose) versus IV (0.9 mg/kg) followed by angiography in the IV/IA arm. If an occlusion is seen then the patient will be randomized to one of three treatments: (1) rtPA up to 22 mg with EKOS ultrasound; (2) MERCI retriever; or (3) rtPA 22 mg only.

57.16.2. Thrombolytic therapy for vertebrobasilar infarction

While vertebral artery occlusion resulting in PICA-infarcts is not necessarily associated with poor

outcomes, basilar artery occlusion is. Basilar artery thrombosis is a rare, but the most severe subtype of ischemic stroke often presenting with progressive or hyperacute brainstem symptoms, tetraplegia and loss of consciousness ranging from somnolence to frank coma. It is associated with a mortality between 50% and 90% in patients treated conventionally (antiplatelets and/or heparin) or not at all (Hacke et al., 1988; Schonewille et al., 2005). Different patterns include caudal vertebrobasilar, mid-basilar and top-of-the-basilar thrombosis, the former mostly being of atherothrombotic; and the latter of embolic origin (Brandt et al., 2000).

Vertebrobasilar distribution cerebral infarction has been of particular interest to centers experienced with local intra-arterial thrombolysis. Multiple case series mostly addressing intra-arterial (Schellinger et al., 2001b) and less frequently intravenous (Lindsberg et al., 2004) thrombolytic therapy for basilar artery thrombosis have been published in the last 20 years, the first report by Zeumer et al. dating back to 1982 (Zeumer et al., 1982; Schellinger et al., 2001b). Most studies suffered from small numbers (<10 patients) with only a few in the range of 40–50 patients (Hacke et al., 1988; Brandt et al., 1996; Arnold et al., 2004). All had an open, retrospective or partly prospective design with differing treatment regimens mostly intra-arterial thrombolytic drugs formally rendering level III evidence at best. The great majority of the more than 120 patients treated were administered intra-arterial urokinase locally; a few patients were given rtPA. Treatment was almost always delayed such that no patients were reported in these series as having been treated within 3 hours of symptom onset. The median time from the beginning of treatment to the time of recanalization was reported to be 120 minutes (Zeumer et al., 1982). For the total group the complete or partial recanalization rate approximates 70%; in reality the rate probably is somewhat lower. While some studies only used presence or absence of recanalization induced by a thrombolytic as a surrogate outcome, in all but one series it was shown that overall survival and an independent outcome depended on successful partial or complete recanalization of the occluded basilar artery (Hacke et al., 1988; Brandt et al., 1996; Arnold et al., 2004). Successful recanalization was associated with a survival rate of 55–75%, as opposed to 0–10% in persistent or untreated basilar artery occlusion (Hacke et al., 1988; Brandt et al., 2000). Two-thirds of the survivors after recanalization had a favorable outcome; all survivors in the untreated group were moderately disabled.

Grond et al. (1998a) reported one small case series of 12 consecutive patients in whom they investigated whether early intravenous thrombolysis could also effectively be applied in acute vertebrobasilar ischemic stroke. Patients with clinically diagnosed moderate-to-severe vertebrobasilar ischemic stroke with clearly determined symptom onset were treated with intravenous rtPA within 3 hours after symptom onset, following a protocol similar to that of the NINDS study. On admission, seven patients exhibited moderate-to-severe brainstem symptoms without impairment of consciousness and five patients had impairment of consciousness, of whom two were comatose. Of 12 patients, 10 had a favorable outcome after 3 months. Unfortunately, basilar artery occlusion was not demonstrated with any means such as Doppler ultrasound, CT or MR angiography, or digital subtraction angiography. The utility of Doppler ultrasound and CTA in the diagnosis of vertebrobasilar occlusion, however, has been studied and demonstrated by Brandt et al (1999), who showed a greater than 90% sensitivity and specificity for CTA but only 30% for Doppler ultrasound. Lindsberg et al. (2004) recently published outcomes for 50 consecutive patients with angiographically (MRA or DSA) proven basilar artery occlusion treated with intravenous thrombolytic therapy. Recanalization was studied in 43 patients and verified in 26 (52%) of all patients. By 3 months, 20 patients (40%) had died while 11 had good outcomes (mRS 0–2). In the long term (median follow-up 2.8 years), 15 patients (30%) reached good outcomes while 23 (46%) died. An advantage of IV thrombolysis with rtPA for basilar artery occlusion is that it is fast, approved for therapy within 3 hours and has a large database (for anterior circulation strokes). IV thrombolysis is probably as effective as IA thrombolysis without further intervention.

An Australian group ventured to perform a randomized trial (Australasian Urokinase Stroke study) (Macleod et al., 2005) following a pilot trial (Australasian Urokinase Stroke Trial, AUST) published in 1997 (Mitchell et al., 1997). The pilot study included 15 patients within 31 hours (mean 18 hours) in an uncontrolled observational design. Eleven of 15 patients recanalized, and 10 of these survived (only one of four non-recanalizers). The AUST study was designed as an open-label, multicenter, randomized controlled trial with a blinded endpoint assessment and launched in 1996 (Macleod et al., 2005). Inclusion criteria were an acute posterior circulation stroke syndrome <24 hours time from symptom onset, age 18–85, and no hemorrhage on CT. Patients underwent DSA and—if a lysable lesion was identified—were randomized to either heparin (unfractionated, PTT 60–80 seconds, 5000 IU bolus) or heparin plus intra-arterial urokinase (increments of 100,000 IU up to a maximum of

1,000,000 IU) followed by warfarin (INR 1.5–2.5) for 6 months. Clinical outcomes (mRS, NIHSS, BI) were independently assessed by a nurse or neurologist blinded for treatment. The study was terminated due to low recruitment (20 patients screened, 16 randomized). There were only four deaths in each group, seven of eight in the placebo group were disabled or dead, and only four in the treatment group (i.e., all survivors had an independent outcome). The early termination is disappointing, because the total sample size would have been 65 patients (absolute effect size of 35%, two-sided alpha, power 0.8) to answer this question once and for all with IA thrombolysis for vertebrobasilar stroke becoming a level A recommendation.

A meta-analysis by Lindsberg analyzed systematically published case series of $\geq$10 patients reporting the outcome of basilar artery occlusion after IA or IV thrombolysis within 12 hours (Lindsberg and Mattle, 2006). In 420 basilar artery occlusion patients treated with IV thrombolysis ($n = 76$) and IA thrombolysis (344), death or dependency were equally common: 78% (59 of 76) and 76% (260 of 344), respectively ($p = 0.82$). Recanalization was achieved more frequently with IA thrombolysis (225 of 344; 65%) than with IV thrombolysis (40 of 76; 53%; $p = 0.05$), but survival rates after IV thrombolysis (38 of 76; 50%) and IA thrombolysis (154 of 344; 45%) were similar ($p = 0.48$). A total of 24% of patients treated with IA thrombolysis and 22% treated with IV thrombolysis reached good outcomes ($p = 0.82$). Without at least partial recanalization, the likelihood of a good outcome was close to zero (2% versus 38%).

Another approach is the bridging concept in analogy to the anterior circulation (IMS 2 Investigators, 2006) using GP IIb/IIIa antagonists such as abciximab. Eckert et al. (2005) performed a study using a combined therapy of local rtPA fibrinolysis and intravenous abciximab platelet inhibition with additional percutaneous transluminal angioplasty and/or stenting. Compared with a retrospective cohort treated by intra-arterial rtPA monotherapy (median dosage: 40 mg, $n = 41$) symptomatic intracerebral hemorrhage rates did not differ (13% versus 12%) but complete TIMI 3 recanalization rate was higher under the combined therapy (45% versus 22%). Also, the rate of favorable outcomes appeared to be better under the combined therapy (34% versus 17%) with a significantly lower mortality (38% versus 68%; $p = 0.006$). These results were consistent for embolic and atherothrombotic occlusions (Eckert et al., 2005).

In summary, the natural disease course of vertebrobasilar occlusion has a grim prognosis. Neuroradiological intervention with intra-arterial or intravenous thrombolysis to date is the only life-saving therapy that has demonstrated benefit with regard to mortality and outcome, albeit not in a randomized trial. However, sufficient data are available to justify thrombolytic therapy in the light of mortality and disability in these patients. The time window for thrombolysis in the posterior circulation has not been established but most experts limit it to 12 hours. Presence or absence of vertebrobasilar vessel occlusion can be safely, non-invasively, and rapidly established by CT (or MR) angiography before IV thrombolysis or a neuroradiological intervention is initiated. Although improved therapy forms for basilar artery occlusion are necessary, hospitals without a neuro-interventionalist should set up IV thrombolysis protocols as intravenous thrombolysis represents probably the best treatment that can be offered to victims of acute basilar artery occlusion in such hospitals.

57.17. Conclusion

At present thrombolytic therapy is still underutilized. Among the major problems are that relatively few patients meet the clinical and time criteria. Educating the general public to regard stroke as a treatable emergency and training emergency caregivers in the use of thrombolysis can decrease these problems but demands a continuous effort. Healthcare institutions should be made aware of the potential in long-term cost savings, once stroke management is optimized and thrombolysis is more widely available. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy but also about its potential benefit and thus the risk of not being treated. Positive results from studies currently underway may encourage more centers to offer this therapy to an overall increasing number of stroke patients in Europe after the approval of the European Agency for the Evaluation of Medicinal Products (EMEA) and thereby reduce the considerable socioeconomic burden of stroke. Improvements in early diagnostic evaluation of patients, particularly in MRI techniques, allow a better patient selection and possibly a qualification of the presently rigid therapeutic time frame.

Intra-arterial thrombolysis with or without devices and/or combination therapies such as GP IIb/IIIa inhibitors is under further investigation in the anterior circulation. For basilar artery occlusions, intra-arterial thrombolysis, although not yet proven in randomized trials, may dramatically reduce mortality and disability, and therefore is the therapy of choice eventually up to 12 hours after symptom onset. In centers without interventional neuroradiologists intravenous thrombolysis is probably as effective as intra-arterial therapy and therefore a viable alternative for these patients.

The adjunctive use (and also the optimal time-point of use) of antithrombotic agents and/ or PTA with stenting is still controvers ial and under investigation.

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Chapter 58

Acute stroke units and teams

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58.1. 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 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 USA, 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 lies on 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 from possible symptoms of transient ischemic attacks or stroke are (Helsingborg Conference, 1995; Aboderin and Venables, 1996; Warlow et al., 2001):

1. prompt and accurate diagnosis of the stroke and the underlying etiology;
2. specific medical and surgical treatment;
3. assessment of patients' stroke-related medical problems in the acute phase and providing adequate care;
4. terminal care for patients that are unlikely to survive;
5. comprehensive rehabilitation;
6. continuing long-term care for severely disabled patients;
7. hospital discharge and placement;
8. adequate secondary prevention of further vascular events including surgery or interventional radiology, where appropriate;
9. educational and research program;
10. established guidelines.

58.2. 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:

1. geographic location of stroke treatment, such as emergency ward, intensive care unit, specialized ward, general ward;
2. consistency of the diagnostic and treatment process;
3. expertise of the treating physicians and involved staff members;
4. availability of diagnostic facilities and general infrastructure;
5. focus of activities; for example, emergency treatment only, rehabilitation only, comprehensive treatment covering all needs;
6. 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; that is, treatment covering the whole period from the acute phase to the end of rehabilitation (Kaste et al., 2000). The minimal, but not necessarily the least, is the community-based home treatment (Bhalla et al., 2001).

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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 pathways (Stroke Unit Trialists' Collaboration, 1998, 2001). So-called dedicated stroke units can be distinguished as follows.

58.2.1. 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; that is, 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 (Bath et al., 1996).

58.2.2. 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 USA (Alberts et al., 1998) and in some hospitals in the UK (Kalra et al., 2000). 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.

58.2.3. Stroke rehabilitation units

Stroke rehabilitation units only accept patients after the acute phase of the disease; that is, 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.

58.2.4. Comprehensive stroke units

Comprehensive stroke units combine acute and rehabilitation stroke care. Here, patients may also be treated for a prolonged time (Stroke Unit Trialists' Collaboration, 1998, 2001). Furthermore, comprehensive stroke units have to be able to deliver the wide variety of specialized care needed by patients with serious cerebrovascular disease comprising health care personnel with specific expertise in a number of disciplines, advanced neuroimaging capabilities, cerebral angiography, endovascular techniques, carotid endarterectomy, intra-arterial thrombolytic therapy, and other specific infrastructure and programmatic elements; for example, intensive care unit as well as a stroke registry. An improvement of patients outcome is likely to be dependent on the integration of these elements into a coordinated hospital-based program or system (Stroke Unit Trialists' Collaboration, 1998; Alberts et al., 2005).

58.3. 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 patient evaluation, any diagnostic workup, treatment, rehabilitation procedures, as well as staff responsibilities and duties.

58.3.1. Responsible physician

A responsible physician with specialized knowledge has to be appointed to lead the stroke unit. This raises the question about mandatory qualification. This person should implement the stroke unit, adopt and develop the concept to local needs, select and supervise the staff and be 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 strong interest in neurology might be regarded as particularly suitable if they acquired specialized knowledge (Helsingborg Conference, 1995). Warlow et al. (2001) do not specify what kind of physician is most apt 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 neurological impairment. Moreover, a neurologist may be more aware of stroke in the posterior fossa than untrained physicians (Stroke Unit Trialists' Collaboration, 1998; Lyrer et al., 1999). Recent reports suggest that treatment by neurologists in the acute phase may be more expensive, but outcome is better overall (Alberts et al., 1998; Smith et al., 1999). As stroke patients suffer from a broad range of symptoms, their care requires input from several disciplines.

58.3.2. Type of organization

Different types of stroke unit organization can be identified. Several models have been described, but

few have been evaluated. Stroke units are far from being homogeneous. There are on the one hand acute stroke units (Levine, 1989) or intensive care units (Langhorne, 1995; Langhorne and Dennis, 1998) 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 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 hospitals 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 (Langhorne, 1995; Langhorne and Dennis, 1998):

1. a comprehensive assessment of the patient's illness and disability;
2. development, and implementation of a collaborative policy for stroke management;
3. identification and awareness of objectives of rehabilitation;
4. close multidisciplinary collaboration;
5. focus on the education and research activity.

An easy access to a stroke service for patients has to be aimed at. Furthermore, a reduction of in-hospital delays of stroke treatment by adequate measures; for example, by establishing a phone call system, is regarded as essential (Gomez et al., 1994).

58.3.3. Infrastructure and facilities to run a stroke unit

As strokes occur at any time of the day and are considered medical emergencies, an emergency room should be accessible on a 24-hour basis. The assessment of patients and close monitoring has to be warranted. A minimal amount of diagnostic tools should be available on site, namely 24-hour cranial computer tomography (CCT) scan facility, a 24-hour neurosonology examination on request, routine laboratory tests, cerebral angiography, and intensive care unit. Emergency CCT diagnosis is mandatory in order to diagnose intracerebral hemorrhage and is 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 in order to avoid early systemic complications and to closely monitor impairment as well as cardiovascular functions. Rapid access to neurosurgical operation procedures is also mandatory (Kaste et al., 2000).

A recent expert survey divided the current available facilities providing stroke care for acute stroke patients into the following three types: comprehensive stroke centers, primary stroke centers, and any hospital ward admitting acute stroke patients in an emergency, as a matter of routine (Leys et al., 2007). "Comprehensive stroke centers" were defined as centers with the necessary staffing, infrastructure, expertise and programs to provide appropriate diagnosis and treatment for stroke patients who require a high intensity of medical and surgical care, specialized tests or interventional therapies: (1) to act as referral center for other hospitals in their area; and (2) to be an educational resource for health care professionals (Alberts et al., 2005). "Primary stroke centers" were defined as centers with the necessary staffing, infrastructure, expertise, and programs to provide appropriate diagnosis and treatment for most stroke patients (Alberts et al., 2000). Although primary stroke centers provide high-quality care, some patients with rare disorders, complex strokes, or multi-organ diseases may need more specialized care and resources not available in these centers (Alberts et al., 2000). "Any hospital wards" were defined as any hospital where general acute care is provided, and where more than 50 acute stroke patients are admitted per year, even if there is no stroke unit or even if patients are subsequently transferred to a primary or to a comprehensive stroke center. Eight components were considered mandatory by more than 75% of the experts for both comprehensive stroke centers as well as for primary stroke centers: multidisciplinary team, stroke-trained nurses, 24/7 brain CT scan, CT priority for stroke patients, extracranial Doppler sonography, automated ECG monitoring, 24/7 intravenous rtPA protocols, and in-house emergency department (Leys et al., 2007).

58.4. Evidence of efficacy

58.4.1. Specifically established pathways for stroke care

With the aim of establishing a meta-analysis for stroke care, the Stroke Unit Trialists' Collaboration identified

the following stroke pathways that provided information by randomized controlled trials.

58.4.1.1. Dedicated stroke unit

This 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: (a) acute (intensive) stroke units which accept patients acutely but discharge early (usually within 7 days); (b) rehabilitation stroke units which accept patients after a delay of usually 7 days or more and focus on rehabilitation; and (c) 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 as well as the comprehensive unit offer prolonged periods of rehabilitation.

58.4.1.2. Controlled randomized trials

Several controlled randomized trials aimed to show the efficacy of different types of stroke unit care. By itself 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 (Stroke Unit Trialists' Collaboration, 1998, 2001).

58.4.1.3. 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 intervention was compared with the contemporary conventional care (alternative services). Case fatality recorded at final review (median follow-up 12 months; range 6 weeks–12 months) was lower in the organized (stroke unit) care in 15 of the 20 trials. The overall estimate gives an odds ratio of 0.86 (95% confidence interval 0.71–0.94, $p = 0.005$). The odds ratio 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.

58.4.1.4. Effect on death or institutional care

The second outcome examined was the odds ratio 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 (0.80, CI 0.71–0.90; $p = 0.0002$), but some heterogeneity existed between trials attributable to five analyzed trials that had a very short or variable period of follow-up. Trials with a fixed prolonged period of follow-up showed a significant reduction in death or institutionalization with less heterogeneity.

58.4.1.5. 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 odds ratio for being dead or dependent if receiving organized (stroke unit) care rather than conventional care was 0.78 (0.68–0.89; $p = 0.0003$), 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 (stroke unit) care organized was compared to conventional care provided in a general medical ward. The conclusions were not altered by the exclusion of trials with a variable follow-up 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.

58.4.1.6. 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 very significantly depend on the clinical syndrome, priority should be given to patients with certain specific syndromes. There is no clear evidence so far whether any clinical neurological syndrome should be excluded from treatment in stroke units. Patients with lacunar syndromes are likely to be less disabled compared to patients with cortical syndromes, even though exceptions to this do exist. 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 odds ratio (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 more elderly; that is, over 75 years, of 0.71 (0.57–0.90).

58.4.1.7. 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, which is measurable until 10 years later (Indredavik et al., 1999).

58.4.1.8. 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 (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 base line outcome rates vary considerably.

Data from large randomized trials are missing so far. Yet, a recent retrospective blinded analysis showed that stroke unit care within wards with specifically dedicated beds and staff admitting stroke patients within 48 hours are superior to a conventional ward. The probability of being disabled or dead at the end of follow-up after 20 months had an odds ratio of 0.81 (95% CI 0.72–0.91) in favor of stroke wards. The sample size was large enough to be significant (11,572 patients) (Candelise et al., 2007).

58.4.1.9. Patient satisfaction and quality of life

Two trials (Indredavik et al., 1991; Berman et al., 1994) 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 (Indredavik et al., 1991). There was no information on any systematically gathered information on patients' preferences.

58.4.1.10. Length of stay

Length of stay data was 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 in one place from entry until 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 (Stroke Unit Trialists' Collaboration, 1998, 2001).

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 benefit nor of cost effectiveness (Early Supported Discharge Trialists, 2005). So far, these models need further evaluation and cannot be propagated at the present stage.

Appropriately resourced early supported discharge (ESD) services provided for a selected group of stroke patients can reduce both long term dependency and admission to institutional care as well as length of hospital stay. No adverse impact was observed on the mood or subjective health status of patients or carers (Early Supported Discharge Trialists, 2005).

58.4.1.11. 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 (Helsingborg Conference, 1995). 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, which are able to treat acute stroke patients.

58.4.1.12. Avoiding hospitalization after stroke

Another systematic Cochrane review deals with the need of hospitalization of stroke patients (Langhorne et al., 1999). In the UK, it has become increasingly fashionable to develop alternatives to hospital-based

care for a number of conditions including stroke, which are often called "hospital-at-home." In a recent UK survey, over 100 schemes of this type were planned or underway (Shepperd and Iliffe, 1996). The underlying rationale bases on the facts that these services not only provide equivalent or better patients' outcome at lower cost, but are also preferred by patients and care-givers. 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; for example, 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 care-givers' outcomes. Furthermore, 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 (Langhorne et al., 1999). 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 (Stroke Unit Trialists' Collaboration, 1998, 2001). Any future trials should compare home care services to the best available in-patient 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 improved patients' outcomes nor reduced cost (Langhorne and Dennis, 1998). 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 (Kalra et al., 2000). 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.

58.4.1.13. 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 in-patient rehabilitation, it is important to prepare the patient for this next step, to choose the adequate institution, and to warrant information on follow-up information as well as on final outcome. It is not the aim of this chapter to describe rehabilitation-related procedures.

58.4.1.14. Effect of organization

One recent study assessed the effect of different type of stroke care organization: (a) acute stroke unit care (patients admitted within 36 hours of stroke onset and remaining for up to 2 weeks; $n = 5$), (b) units combining acute and rehabilitative care (combined; $n = 4$), and (c) rehabilitation units where patients were transferred onto the service approximately 2 weeks following stroke (post-acute; $n = 5$). Overall on one hand, specialized stroke services were associated with significant reduction in mortality, death and dependency, and length of hospital stay, yet the different types of care yielded unequal benefit (Foley et al., 2007). On the other hand, a former meta-analysis of the effect of different pathways for stroke care, did not show a statistically significant effect of different forms of hospital organizations (Kwan and Sandercock, 2004)

58.5. Economic issues

Stroke units appear to improve outcomes, but at what cost? No detailed cost–benefit analysis of stroke units has been carried out to date (Gladman, 1992), 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 (Warlow et al., 2001) 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 (Major and Walker, 1998), 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 (Bowen and Yaste, 1994).

In-patient costs vary depending on the type of stroke. In a recent estimate on stroke cost, patients with subarachnoid hemorrhage had the most cost-intensive treatment, followed by patients with intracerebral hemorrhage (Shelby et al., 2001). The least expensive were those with ischemic stroke and transient ischemic attacks. The average cost amounted to US$23,777 for subarachnoid hemorrhage, US$10,241 for intracerebral hemorrhage, US$5,837 for ischemic stroke and US$3350 for transient ischemic attack, respectively. It has to be taken into account that this estimate was issued in the USA, and that costs vary among institutions; for example, the costs were higher in teaching hospitals than in non-teaching hospitals. These data provide a judgement of hospital cost, but it will be much more difficult to estimate the personal cost as well as those of relatives and society cost. 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 hospital costs in the first days of occurrence are determined by several predictors such as length of stay, stroke severity, atrial fibrillation, ischemic cardiac disease, male sex, and the use of heparin (Diringer et al., 1999).

Overall the cost for stroke treatment varies a great deal 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 cost for one stroke within 3 months after onset vary from less than US$1,000 in Eastern Europe to approximately US$8,000–9,000 in London or Copenhagen. At present, it is not clear what kind of stroke care is the most cost-effective (Grieve et al., 2001). 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 (Alberts et al., 1998).

Modeling costs for a stroke unit gives estimates that the 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 (Laaser et al., 1999). Overall, there would be a savings in hospital as well as in community resources as patients are better off after a shorter hospital stay.

58.6. Establishing guidelines and education

Institutional guidelines are mandatory to any clinic that treats stroke patients. They must be compatible to published stroke unit pathways. Guidelines have to implement specifically local habits and 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 (Langhorne, 1995; Langhorne and Dennis, 1998). These arguments created a series of different recommendations for stroke unit care in different countries; for example, the USA, in the European Community, or Switzerland, which are adapted to each medical system (Alberts et al., 2000, 2005; European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Engelter and Lyrer, 2004).

58.7. Continuous evaluation process

Once a stroke unit care pathway is established, quality control of the care given is mandatory. The availability of data draws the attention to possible failures and enables changes where required. Quality improvement proceeds most effectively if all elements of the quality triad, such as structures, processes, and outcomes are used in the assessment, provided that the structures and processes chosen have demonstrated to be associated with the desired outcome of care (Hammermeister et al., 1995). One of the most suitable tools is the use of a stroke database that catches the predefined and relevant items on processes and outcomes.

58.8. Conclusions

It can be stated that patients receiving organized in-patient (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) is much more statistically robust and warrants the institutionalization of stroke unit care. The requirement for long-term care is a useful surrogate for disability and is likely to show good inter-observer agreement. However, the absolute rates of institutionalization will be influenced by a variety of national and cultural factors (Stroke Unit Trialists' Collaboration, 1998, 2001). This is also true for the cost.

Methodological limitations may also have had an influence on the analysis of descriptive information about service organization (Stroke Unit Trialists' Collaboration, 1997, 1998; Stroke Unit Trialists' Collaboration, 2001). Service descriptions are collated retrospectively. The above-mentioned findings may therefore be biased in regard to the expectations of the authors, who ran an 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. Three approaches to stroke unit care (comprehensive units, rehabilitation stroke units, and rehabilitation units) exist. All of them tend to be more effective than conventional care in a general medical ward. 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 patients who receive organized inpatient care in a stroke unit are more likely to be alive, independent, and living after the stroke. From the available data, it seems that the benefits are most apparent in units based in a discrete ward.

Stroke units appear to improve outcomes, but at what cost? No detailed cost–benefit analysis of stroke units has been carried out (Gladman, 1992). Available information on detailed cost analyses showed a heterogeneous picture with huge differences in stroke case cost within Europe. There is no 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 (Warlow et al., 2001) 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 (Major and Walker, 1998), 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.

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Chapter 59

Approaches to neuroprotective and reperfusion injury therapy

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59.1. Introduction

The concept of neuroprotection was first documented in Ancient Greece (Jones, 1923). Greek physicians used hypothermia as a medical treatment by applying ice or snow. However, their knowledge for the etiology of cerebral damage was markedly different compared with current literature. For example, according to Hippocrates, stroke was a result of an imbalance in the four fluids comprising the human body: the blood, the phlegm, the black bile, and the yellow bile. Since then, our knowledge about cerebral damage and stroke has increased exponentially, but this has not been accompanied by a concomitant increase in our ability to confer neuroprotection.

In order to develop neuroprotective agents against ischemia, the mechanisms responsible for ischemic damage have been extensively studied (all reviewed by Lipton, 1999). From a physiological viewpoint, cerebral ischemia is classified either as focal or global. Focal ischemia occurs when an artery is occluded, leading to reduced cerebral blood flow in a particular brain region. This type of ischemia is representative of ischemic stroke. Global ischemia results from severe, transient oligemia, whereby blood flow is blocked to the entire forebrain. Global ischemia can be a result of cardiac arrest, near drowning, or massive hemorrhage.

Neuroprotective studies have been carried out using in vitro and in vivo models of cerebral ischemia (Lipton, 1999). These studies have provided insights into the molecular pathways that cause ischemic cell death. In summary, lack of oxygen supply to the brain is pivotal to ischemic damage. Lack of oxygen results in inhibition of oxidative phosphorylation, leading to free-radical production by the mitochondrial respiratory chain, decreased adenosine triphosphate (ATP) synthesis, increased intracellular sodium, and membrane depolarization. Ultimately, all these events lead to unregulated influx of calcium, which results in calcium excitotoxicity. Other pathways that are induced by cerebral ischemia are inflammation, free-radical production, and astrocytic cell death.

In addition to cell death initiated by ischemia, reperfusion also leads to cell damage (Lipton, 1999). Upon reperfusion the blood–brain barrier breaks down resulting in leukocyte infiltration and cerebral edema. Moreover, the oversupply of oxygen in the previously ischemic brain causes the production of free radicals. Consequently, cell death is manifested through apoptosis, necrosis, or autophagocytosis.

Neuroprotective strategies, aimed at rescuing the ischemic tissue, have been developed to prevent all these processes. The therapeutic approaches to neuroprotection can be divided into two broad categories. The first aims at reperfusing the ischemic tissue by thrombolysis. The second attempts to prevent cellular events that lead to instantaneous or delayed ischemic cell death.

Currently, the only method that confers long-term neuroprotection is hypothermia. Other promising interventions act simultaneously to several pathways induced by ischemia. Examples of this approach are erythropoietin (EPO) and statins. However, most neuroprotective interventions have tried to inhibit distinctly either calcium excitotoxicity, inflammation, or astrocytic cell death. Although these agents have demonstrated neuroprotective action in preclinical

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studies, they have failed to translate to clinical practice (Hoyte et al., 2004). This was mainly due to the inappropriate design of preclinical and clinical studies. Therefore, to optimize the clinical potential of future studies, particular design criteria should be considered and are discussed in this chapter.

This chapter will focus on the aforementioned advances of neuroprotection related to cerebral ischemia/reperfusion injury. Particular emphasis will be given to the unsuccessful pursuit of pharmacological protection. This will highlight the importance of controlling the physiological parameters (i.e., blood flow, body temperature, and glucose levels) when carrying out experiments for neuroprotection. Finally, the need for imaging surrogates of ischemia to visualize and therefore confirm the therapeutic action of putative neuroprotective agents will be presented.

59.2. Models of ischemia

To examine the mechanisms underlying ischemic cell death, both in vitro and in vivo models have been developed. These models mimic experimentally the damage induced by ischemic stroke (Table 59.1). The in vitro models involve hippocampal brain slices (Pond et al., 2004) or primary neuronal cultures subjected to both oxygen and glucose deprivation (Iijima et al., 2003). A representative in vitro model uses organotypic hippocampal tissue cultures exposed to oxygen and glucose deprivation in a medium that has the same ionic composition as the cerebrospinal fluid during ischemia (Rytter et al., 2003). This model has the advantage of exhibiting the selective and delayed vulnerability of hippocampal CA1 neurons (Rytter et al., 2005). In addition, the effects of hypothermia and hyperglycemia on ischemic cell damage are replicated. All these characteristics of ischemia are also observed in the in vivo models of global ischemia and will be discussed below.

For the in vivo studies, different animal models have been devised for global or focal ischemia. The most widely used animal model for global ischemia is the four-vessel occlusion carried out in rats, which causes transient forebrain ischemia (Pulsinelli et al., 1982; Pulsinelli and Buchan, 1988). The carotid and vertebral arteries are occluded bilaterally, resulting in lack of blood flow in the striatum, hippocampus, and cortex. Delayed, selective cell death is observed, which is very sensitive to temperature. Also, the extent of damage is dependent on the duration of both the ischemic insult and the reperfusion (Colbourne et al., 1999a). Certain neuronal populations are more vulnerable than others to global ischemia. In particular, pyramidal cells of the CA1 region of the hippocampus are most prone to cell death.

Focal ischemia can be achieved by occluding both the distal middle cerebral artery, using a mini-clip, and a bilateral common carotid artery, followed by a period of reperfusion, leading to a cortical infarct (Buchan et al., 1992a). The infarct is defined as a

Table 59.1

Summary of the models used to mimic ischemia experimentally

Type	Model	Methodology	Duration of ischemia	Duration for damage maturation	Profile of damage
In vitro	Hippocampal slices	Oxygen/glucose deprivation	10–20 minutes	1–3 days	Selective and delayed CA1 cell death
	Primary neuronal culture		30–90 minutes	3–24 hours	Neuronal disintegration
In vivo	Focal	Distal middle cerebral artery occlusion with mini-clip	1–2 hours (transient) 1 day (permanent)	6 hours–3 days	Cortical damage
		Proximal middle cerebral artery occlusion with intraluminal suture	1–2 hours (transient) 1 day (permanent)		Striatal damage
	Global	Four-vessel occlusion	2–20 minutes	1–7 days	Selective and delayed CA1 cell death
				12 hours–7 days	Cortical damage
				3–24 hours	Striatal damage

volume of brain tissue that exhibits neuronal, glial, and endothelial cell death. In an alternative focal model, the proximal middle cerebral artery is blocked by an intraluminal suture (Hata et al., 2000). Proximal middle cerebral artery occlusion causes severe striatal ischemia, with milder cortical ischemia.

Furthermore, focal ischemia can be either permanent or transient. In permanent focal ischemia the middle cerebral artery is occluded for 1 day. In this case, the middle cerebral artery occlusion is not followed by reperfusion. However, in transient focal ischemia the middle cerebral artery is occluded for 1–2 hours, followed by reperfusion. The permanent model results in more severe blood–brain barrier disruption and larger infarct volumes compared with the transient model (Mao et al., 1999).

The successful outcome of the focal model depends on the reduction of blood flow at the site of occlusion to at least 15% of baseline value. Successful focal ischemia results in the formation of two characteristic regions: the core region, which is the tissue with irreversible cellular damage; and the penumbra, which is defined as the dynamic area in the process of cell death. The penumbra, however, can be potentially salvaged by reperfusion or by intervention with a neuroprotective agent (Fig. 59.1).

Animal models for ischemia have been developed for rats, mice, gerbils, cats, dogs, and primates. However, the mice models have a significant advantage versus other animal models. The reason is the availability of transgenic mice. This provides a potent tool to study the involvement of particular gene products in the pathophysiology of ischemia. This ability to manipulate genes is a very powerful platform for investigating molecular events. Nevertheless, it is harder to control murine physiology compared with managing adequate physiological homeostasis in rats (Barber et al., 2004a). This is critical because the physiological details, such as temperature and blood flow, are detrimental for the experimental outcome.

59.3. Thrombolytics

The reason for ischemic cell damage is the lack of blood supply caused by a blocked artery. The quanta of injury are dependent on the severity of the blood flow reduction, the duration of the insult, and the underlying susceptibility of the parenchyma. Therefore, the best neuroprotectant will always be to restore blood flow, recovering normal oxygen/glucose levels as early as possible.

Compounds that restore blood flow have been developed and it is not surprising that they are efficacious, constituting the first approved drug for acute stroke therapy. Hitherto, the thromobolytic agent that is effective in reperfusing the blocked artery and is approved by the Food And Drug Administration (FDA) is tissue plasminogen activator (tPA) (Adams et al., 1996). New thrombolytics currently being tested include desmoteplase (Hacke et al., 2005) pro-urokinase (Furlan et al., 1999) and tenecteplase (Haley et al., 2005).

The efficacy of all these drugs depends on the time of administration following stroke onset; the therapeutic

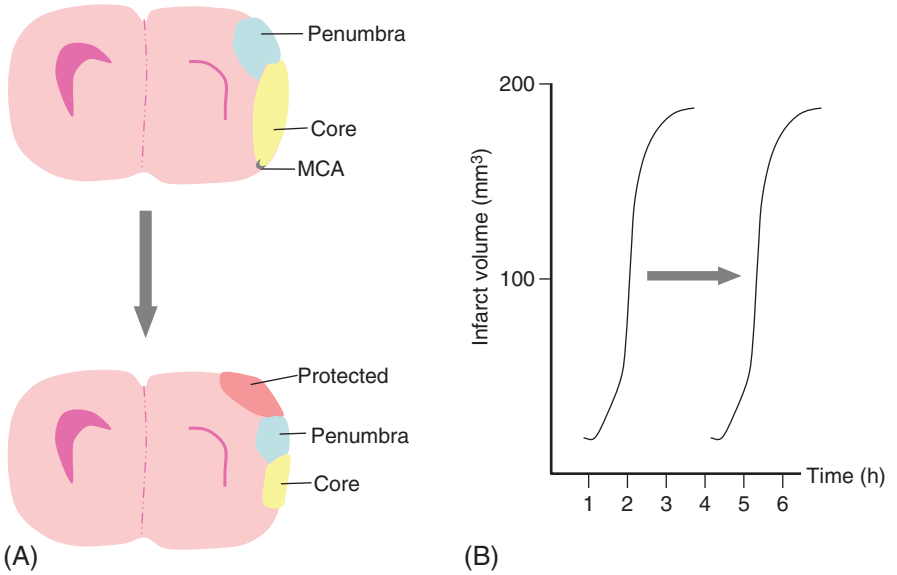

Fig. 59.1. Administration of a neuroprotective compound should result in decreased infarct volume of the core region (A). This can be achieved by protecting the penumbra, which is the area that exhibits reversible ischemic damage. Alternatively, neuroprotection can be conferred by extending the time window of intervention for a given infarct volume (B).

window for tPA is 3 hours. Nevertheless, there is variation in reperfusion efficacy. In more detail, reperfusion following: carotid occlusion carries a 10% efficacy, middle cerebral artery occlusion 40% efficacy, M2 occlusion 50–60% efficacy. Since only a maximum of 60% of the occluded vessels open by thrombolysis, the treatment is unable to confer complete recovery.

In addition, there is variance in the susceptibility to ischemic injury; some patients may display a lot of damage on computed tomography (CT) scan and despite getting the occluded vessel open, will not benefit. These patients have early ischemic change, which precludes the utility of thrombolytic intervention. In such cases, even opening up blocked vessels through intra-arterial approaches, similar to the PROACT trial, fails to rescue tissue despite restoring reperfusion (Hill et al., 2003).

Thrombolysis is conferred from tPA by dissolving clots. In more detail, tPA is a protease, converting the zymogen, plasminogen, to its active form, plasmin, which dissolves fibrin clots. However, tPA has pleiotropic actions on the brain, some of which raise concerns about the safety of the drug. The NINDS tPA Stroke Study Group showed that tPA treatment is associated with a 6% increase in the absolute risk of symptomatic intracerebral hemorrhage (National Institute of Neurological Disorders and Stroke, 1995).

In addition to its effects on the vasculature, tPA crosses the blood–brain barrier to exhibit neurotoxic properties to the neuronal parenchyma. The toxic action of tPA to the neurovascular unit is mediated by a family of endopeptidases, termed matrix metalloproteinases (MMPs). MMPs are activated by both tPA and fibrin, cleaving extracellular matrix proteins like elastin, fibronectin, collagen, and gelatin. Thus, the risk of hemorrhage in stroke patients that have received tPA treatment is increased (reviewed by Wang et al., 2004a).

Employing neuroprotectants in combination with tPA could offset the risk of the thrombolytic therapy. It would therefore be required to develop neuroprotectants that reduce the risk of both the neurotoxicity and hemorrhage induced by tPA, while increasing the therapeutic time window for thrombolytic intervention. Thus, the clinical applicability of thrombolytics would be improved (Kaur et al., 2004).

As previously mentioned, although thrombolytic strategies salvage the ischemic tissue by reperfusion, they do not completely prevent the cellular damage taking place during and after ischemia. Ongoing research has provided information on the biochemical pathways that result in ischemic and ischemia/reperfusion-induced cell death. Therefore, neuroprotective agents that prevent these deleterious cellular events have also been developed. To appreciate the putative action of these compounds, the signaling mechanisms that result in ischemic cell death must first be discussed.

59.4. L-glutamate as a neurotoxin

A critical breakthrough in the research of cerebral ischemia was the establishment of a close link between cellular damage induced by ischemia and the toxicity of L-glutamate. Monosodium glutamate was first identified as a neurotoxin by Lucas and Newhouse (1957). Their experiments showed that subcutaneous injections of L-glutamate in mice results in the degeneration of the ganglion layer of the inner retina. Similar studies by Olney (1969) demonstrated that monosodium glutamate causes degenerative lesions in the developing mice hypothalamus.

L-glutamate induces an increased neuronal uptake of calcium. This is a catalytic factor for its cytotoxic action (Retz and Coyle, 1984; Choi, 1985). The importance of calcium to the excitotoxic action of L-glutamate was demonstrated by in vitro experiments (Choi, 1985; Garthwaite et al., 1986). Removing calcium from the medium of rat cerebellar slices or cortical cell cultures, prior to excitotoxic stimulation, led to cell survival, whereas increasing extracellular calcium concentration intensified the toxic effect of L-glutamate.

Cell death by L-glutamate is manifested by an acute phase of swelling and increased granularity of the cell body, followed by a late phase of extensive neuronal disintegration (Choi, 1987). The acute phase is obliterated by substituting extracellular sodium with choline and is therefore sodium dependent, whereas the late phase is mediated by calcium (Choi, 1987).

59.5. The role of L-glutamate in ischemia

The pathophysiology of ischemia is closely related to the toxicity of L-glutamate. This was revealed when the accumulation of L-glutamate in the extracellular space, during transient cerebral ischemia, was established (Benveniste et al., 1984). In addition, experiments in cultured cerebellar granule cells, subjected to anoxia and hypoglycemia, showed that replacing calcium with cobalt reduced the concentration of extracellular L-glutamate (Drejer et al., 1985). The absence of calcium inhibited exocytosis in the presynaptic terminal, thereby demonstrating that synaptic activity was a requisite for L-glutamate release.

Synaptic activity is not only implicated in ischemic damage, but also in hypoxic and anoxic cell death.

Experiments with hippocampal cultures from fetal rats showed that immature cultures were resistant to hypoxic/anoxic conditions (Rothman, 1983). However, in cultures older than 2 weeks the same conditions caused extensive cell death. In the same mature cultures, hypoxic/anoxic cell death was prevented by magnesium. Since functional synapses are present only in mature cultures, reduced synaptic activity in immature cultures was responsible for their resistance to hypoxia/anoxia (Clark and Rothman, 1987). Collectively, these studies established the paramount importance of L-glutamate in mediating ischemic cell death.

However, the significance of the results derived from these in vitro experiments should be carefully scrutinized. The demonstrated implication of the sodium, calcium, and L-glutamate in culture is far from the clinical paradigm. Nevertheless, as discussed below, these results lead to the development of a series of glutamate receptor antagonists resulting in a plethora of clinical trials.

59.6. NMDA receptor antagonists prevent ischemic cell death

The recognition of L-glutamate as an excitatory neurotransmitter (Mayer and Westbrook, 1987) fueled studies to identify the receptor subtypes and gain insights into their mechanism of toxicity. Ionotropic glutamate receptors, according to agonist binding, are subdivided into three types: kainate, α-amino-3-hydroxy-5-methyl-5-isoxazole-4-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors.

As previously mentioned, the toxicity of L-glutamate is calcium-dependent. The development of selective NMDA receptor antagonists was an invaluable tool to investigate the importance of NMDA receptors in L-glutamate-induced calcium excitotoxicity.

Pharmacological studies demonstrated that NMDA receptors, based on their high permeability to calcium ions, are the main mediators of calcium excitotoxicity (Choi et al., 1989). Aminophosphonovalerate (APV), a selective NMDA receptor antagonist, prevented the excitotoxic action of L-glutamate on cortical neurons. In addition, in rat global models of ischemia, injection of the NMDA receptor blocker, 2-amino-7-phosphonoheptanoic acid (APH), into one hippocampus reduced significantly the percentage of ischemic cell death in the ipsilateral side compared with the contralateral side (Simon et al., 1984). Similar protective effects were observed when the competitive NMDA antagonist, cis-4-(phosphonomethyl)-20-piperidine-carboxylic acid (CGS-19755; Seflotel) was administered in animal models of global ischemia (Boast et al., 1988).

The NMDA receptor-mediated calcium influx was also prevented by using the non-competitive NMDA receptor antagonist, MK801. Preliminary animal studies indicated that MK801 exhibited a neuroprotective effect, following either transient forebrain or focal ischemia (Gill et al., 1987; Rod and Auer, 1989; Swan and Meldrum, 1990).

However, attempts in clinical trials to confer neuroprotection post-ischemia, by blocking the NMDA receptor channel, have failed (Davis et al., 1997). The reason for the unsuccessful action of MK801 was revealed by studies that monitored various physiological variables, such as temperature, blood flow and blood glucose levels (Buchan and Pulsinelli, 1990, 1991b; Buchan et al., 1992b). These investigations showed that the protective effect of MK801 was facilitated by making the animal hypothermic and increasing blood flow, rather than by blocking the NMDA receptor channel. Thus, the neuroprotective effect of MK801 was physiological and not pharmacological.

The distribution of NMDA receptors is another reason for the inability of NMDA receptor antagonists to confer clinical neuroprotection. The regional profile of NMDA receptors does not correlate closely to the areas that are sensitive to global ischemia. For instance, although NMDA receptors are expressed in the vulnerable CA1 hippocampal pyramidal cells, the sensitive CA4 neurons lack NMDA receptor expression. Contrary, granule neurons in the dentate gyrus, which are relatively resistant to global ischemia, contain a high concentration of NMDA receptors (Monaghan and Cotman, 1985). Finally, a determinant factor for the termination of the clinical trials for all NMDA receptor antagonists was their significant side-effects, including acute psychomimetic effects and disruption of synaptic plasticity.

59.7. Excitotoxicity via activation of PSD-95

Apart from increasing intracellular calcium levels, overactivation of NMDA receptors is also cytotoxic by facilitating the synthesis of nitric oxide (NO). NO synthesis is mediated via the indirect interaction of NMDA receptors with neuronal nitric oxide synthase (nNOS) (Dawson et al., 1991). The accessory protein post-synaptic density-95 (PSD-95) couples NMDA receptors to nNOS. Under ischemic conditions, NO is produced at low micromolar levels, which are cytotoxic. Subsequently, NO acts as inhibitor of oxidative phosphorylation by binding to complex IV of the mitochondrial respiratory chain (Fig. 59.2). The cytotoxic effects of NO are also manifested via its reaction with superoxide, which is increased during and after ischemia, to form the oxidant peroxynitrite (reviewed by Keynes and Garthwaite, 2004).

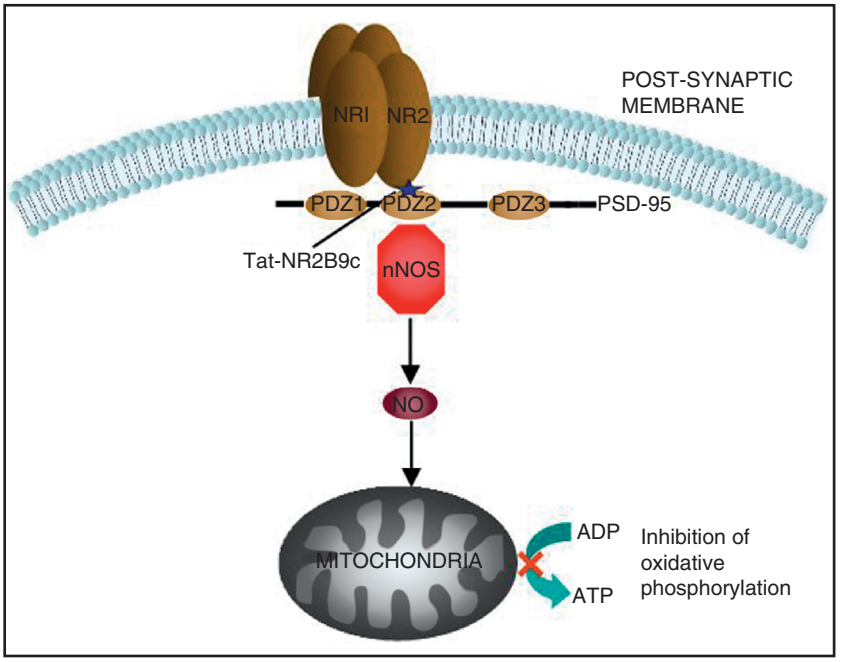

Fig. 59.2. NO cytotoxicity pathway during ischemia. Activation of NMDA receptors during ischemia results in the synthesis of NO by nNOS. NO disrupts oxidative phosphorylation in the mitochondria by binding to complex IV of the respiratory chain. nNOS is activated by PSD-95, which associates with the NR2 subunit of the NMDA receptor via the PDZ2 domain of PSD-95. Disrupting the association of PSD-95 with the NR2 subunit, using the synthetic peptide, Tat-NR2B9c, has been recently employed as a novel strategy for neuroprotection (Aarts et al., 2002).

A recent study attempted to reduce the excitotoxicity caused by ischemia, by disrupting the NMDA receptor/PSD-95 interaction, thereby uncoupling NO synthesis from the activation of NMDA receptors (Aarts et al., 2002). To dissociate the interaction between the NMDA receptor and PSD-95, the authors introduced a peptide, named Tat-NR2B9c. This peptide was composed of the carboxyl-terminal amino acids of the NMDA receptor subunit, which contains the motif that mediates the association with PSD-95. This approach showed promising neuroprotection in rats, expressed as a reduction of infarct volume and improved neurological function, following transient middle cerebral artery occlusion (Aarts et al., 2002).

Perturbing the NMDA receptor/PSD-95 interaction to treat stroke does not inhibit completely the activity of NMDA receptors. This is therapeutically advantageous, because the intervention has been designed to produce fewer side-effects as compared with the NMDA-receptor antagonists.

59.8. AMPA receptor antagonists prevent ischemic cell death

Two reasons result in the build-up of extracellular L-glutamate during ischemia. First, there is reduced glutamate reuptake due to the energy-dependence of the process. Second, the glutamate content of dead cells is released into the synaptic area. L-glutamate does not activate NMDA receptors only, but also AMPA receptors. This leads to further unregulated influx of calcium ions.

AMPA receptors are heteromeric or homomeric assemblies comprised of subunits, termed GluR1–4 (reviewed by Hollmann and Heinemann, 1994). According to the type of subunits composing the AMPA receptor, a wide range of ion selectivity is exhibited. In particular, AMPA receptors are permeable to calcium ions, but can limit calcium entry if they contain the GluR2 subunit in their assembly (Gorter et al., 1997).

Compounds that antagonize AMPA receptors have been employed, in an attempt to block calcium excitotoxicity through the receptor channel, after ischemia. In addition, their clinical relevance has been determined. The selective AMPA receptor antagonists 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX) and 1-[2-aminophenyl]-4-methyl-7, 8-methylene-dioxy-5H-2,3-benzodiazepine hydrochloride (GYKI 52466) proved to be powerful neuroprotectants in both focal and global models of cerebral ischemia in rats and gerbils (Sheardown et al., 1990; Buchan et al., 1991a; Le Peillet et al., 1992; Smith and Meldrum, 1992). Unfortunately, it was revealed that these compounds

were nephrotoxic, hence not appropriate to use in clinical trials (Xue et al., 1994).

In addition to neurons, oligodendrocytes also contain AMPA receptors composed of GluR3 and GluR4, but not GluR2 subunits, making them especially sensitive to excitotoxic injury. It is therefore of great interest to determine the cytoprotective capacity of AMPA receptor antagonists to block calcium-induced cell death in oligodendrocytes. Studies in primary oligodendrocyte mouse cultures showed that oxygen and glucose deprivation results in cell death that could be prevented by NBQX (McDonald et al., 1998).

59.9. Mechanisms of calcium excitotoxicity

During ischemia, calcium entry can also take place through voltage-gated calcium channels, reverse operation of sodium/calcium exchanger (NCX) or leak conductances activated by cell swelling. As previously discussed, all these modes of calcium overload lead to excitotoxic cell death.

Although calcium excitotoxicity was established in the mid-1980s, the mechanisms responsible are still being explored (reviewed by Arundine and Tymianski, 2003). Currently identified pathways include the activation of the calcium-activated hydrolytic protease, calpain, and activation of phospholipase A_2, which results in the release of arachidonic acid (Nicotera et al., 1986). Arachidonic acid, following its enzymatic conversion to prostanoids, generates free radicals that lead to lipid peroxidation and breakdown of cellular membranes (Fig. 59.3).

Another neurotoxic pathway that is activated by calcium is the uncoupling of mitochondrial electron transport chain from ATP synthesis, leading to the production of free radicals and mitochondrial dysfunction. Mitochondria sequester excess calcium by dissipating their proton gradient, which is generated by the electron transport chain (Gunter and Pfeiffer, 1990). Subsequently the ATP production of mitochondria is reduced.

The increased production of free radicals during ischemia and especially during reperfusion is not accompanied by an increase in the levels of antioxidants enzymes (e.g., glutathione peroxidase and superoxide dismutase), resulting in oxidative stress.

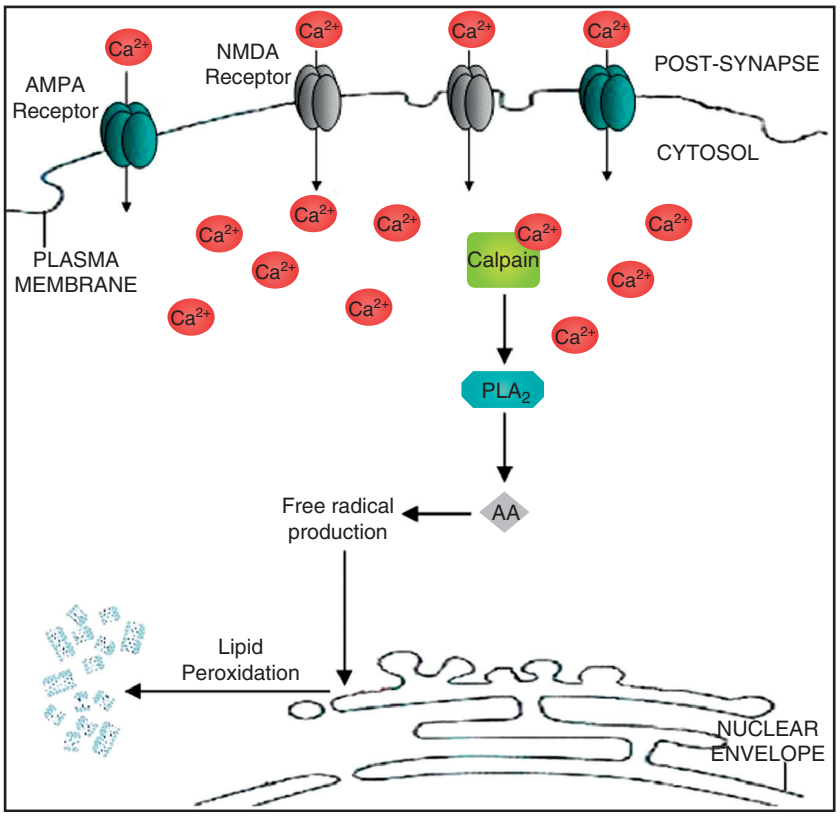

Fig. 59.3. Glutamate receptor-mediated calcium excitotoxicity during ischemia. The accumulation of L-glutamate during an ischemic insult results in overactivation of NMDA and AMPA receptors. Unregulated calcium influx activates calpain which stimulates phospholipase A_2 (PLA_2), leading to the release of arachidonic acid. Arachidonic acid mediates the generation of free radicals that cause lipid peroxidation and ultimately disintegration of membranes.

Importantly, employing antioxidants such as Ebselen to prevent ischemic injury has shown prominent results in salvaging both white and gray matter in mouse models of focal ischemia (Imai et al., 2001).

Various attempts to confer neuroprotection by preventing calcium influx via voltage-gated calcium channels have been unsuccessful. A characteristic example is the L-type calcium channel antagonist, nimodipine. Based on preliminary experimental data from animal focal models, numerous clinical studies have been carried out using nimodipine to treat ischemic stroke patients (all reviewed by Horn et al., 2001). However, there was no definitive consensus among the conclusions of those studies. Furthermore, the clinical benefits of nimodipine remain highly debatable.

An exciting development was the introduction of calcium chelators, aimed at increasing the buffering capacity of neurons to calcium. This approach demonstrated efficacy by preventing intracellular calcium accumulation and looked extremely promising in the laboratory. A variety of agents were developed, for example, analogs of the calcium buffer 1,2-bis-[2-aminophenoxyl] ethane-N,N,N′,N′-tetraacetic acid acetoxymethyl ester (BAPTA-AM). Administrating BAPTA-AM to rats resulted in decreased infarct volumes following focal ischemia (Tymianski et al., 1993). However, these compounds were never successfully developed in clinical trials.

Recent studies in cultured cortical neurons proposed an explanation for the failure of glutamate receptor and calcium channel antagonists to completely prevent calcium-mediated neurotoxicity (Aarts et al., 2003). Under oxygen and glucose deprivation for more than 1.5 hours, a calcium conductance was detected, which was attributed to the voltage-gated ion channels, named transient receptor potential (TRP) channels. Electrophysiological experiments demonstrated the importance of TRP-mediated calcium influx in amplifying the deleterious effect of free radicals by promoting their formation (Aarts et al., 2003). In addition, the same study showed that blocking TRP channels with Gd^{3+} prevented anoxic cell death. These results suggested a central role of TRP channels in excitotoxic cell death.

The massive influx of calcium during ischemia would have been sustained if the extrusion mechanisms were sufficient. Neurons export calcium through the low-capacity plasma membrane calcium pump and through the NCX. However, the NCX is cleaved during ischemia by the calcium-depended activation of calpains, as shown by experiments carried out with mice models of focal ischemia (Bano et al., 2005). This mechanism accounts for the delayed calcium accumulation, which is detrimental to ischemic cell death. In conclusion, despite the failures to develop a direct clinical manipulation of intracellular calcium from a mechanistic standpoint, calcium remains at center stage (reviewed by Choi, 1995).

59.10. Astrocytic ischemia

The excitotoxic pathways induced by calcium are similar to neurons as well as glial cells. Therefore, the neuroprotective strategies that prevent calcium excitotoxicity (Table 59.2) have an advantage, since most of the approaches aimed at treating ischemic stroke are unfortunately focused on rescuing mainly neuronal elements. For humans in particular, salvaging white matter and specifically astrocytes is of equal importance to saving gray matter. This is because astrocytes are pivotal mediators for maintaining neuronal viability.

Astrocytes are involved in the uptake and removal of synaptically released neurotransmitters and regulate the extracellular concentration of ions such as calcium and sodium. Furthermore, they participate in neuronal sustainability by releasing growth factors and cytokines; for example, brain-derived neurotrophic factor (BDNF) (Bruno et al., 2001), nerve growth factor (NGF) (Bruno et al., 2001), and interleukine-6 (IL-6) (Eskes et al., 2002). Significantly, astrocytes contain glycogen stores and therefore control the energy metabolism of the brain by converting glycogen to lactate and providing it to neighboring cells (Dringen et al., 1993).

Table 59.2

Neuroprotective agents to prevent the cytotoxic effect of calcium excitotoxicity during ischemia

Compound	Pharmacological property
APV	Competitive NMDA receptor antagonist
Selfotel	Competitive NMDA receptor antagonist
MK801	Non-competitive NMDA receptor antagonist
NBQX	AMPA receptor antagonist
GYKI 52466	AMPA receptor antagonist
Nimodipine	L-type calcium channel antagonist
BAPTA-AM	Calcium chelator
Gd^{3+}	TRP channel blocker
Tat-NR2B9c	Disruption of NR2B/PSD-95 interaction
Ebselen	Antioxidant
NXY-059	Free-radical spin trap
SAE0400	NCX blocker
IL-1RA	IL-1R antagonist
MLN519	Proteosomal inhibitor

The importance of astrocytes in neuroprotection can be highlighted by their responsibility to remove glutamate from the extracellular space. GLT-1 is the main glutamate transporter present in astrocytes, thus limiting glutamate excitotoxicity in neurons during ischemia (Bruhn et al., 2000). Astrocytes also contain high concentrations of antioxidants, such as glutathione. Experiments in co-cultured astroglial and neuronal cells showed that glutathione is released by astrocytes and taken up by neurons, thereby supporting the neuronal free radical scavenging defense (Drukarch et al., 1997).

Studies in cultured rat astrocytes revealed that calcium overloading and consequently free-radical production, similar to that observed after ischemia/reperfusion, induced apoptosis in astrocytes (Matsuda et al., 1996). Calcium overloading is mediated by reverse operation of the NCX and could be blocked pharmacologically with 2-[-4-[2,5-difluorophenyl) methoxy]phenoxy]-5-ethoxyaniline (SEA0400). This intervention prevented the subsequent free-radical production and apoptotic cell death in cultured astrocytes (Matsuda et al., 1996, 2001).

59.11. Mitochondrial dysfunction and apoptosis in ischemia

As previously discussed, calcium excitotoxicity during ischemia results from mitochondrial dysfunction. In addition, the absence of oxygen is critical because dioxygen is the ultimate elector acceptor of the mitochondrial electron transport. As a result, respiration in the mitochondria is disrupted because the electron transport chain is reduced. Cytochrome C is released from the mitochondria to the cytoplasm, irreversibly damaging the mitochondrial components, leading to apoptotic cell death (Fujimura et al., 1998; Ouyang et al., 1999).

Therefore, another approach to prevent ischemic cell damage is to inhibit the biochemical signaling pathways that lead to apoptosis. The apoptotic cascade is similar in neurons and astrocytes and is widely observed following ischemia (Fig. 59.4). Since apoptotic cell death is programmed, it can be clinically prevented. This would be beneficial because except for rescuing neuronal cells, astrocytes would also be spared. Consequently, exacerbated neuronal injury

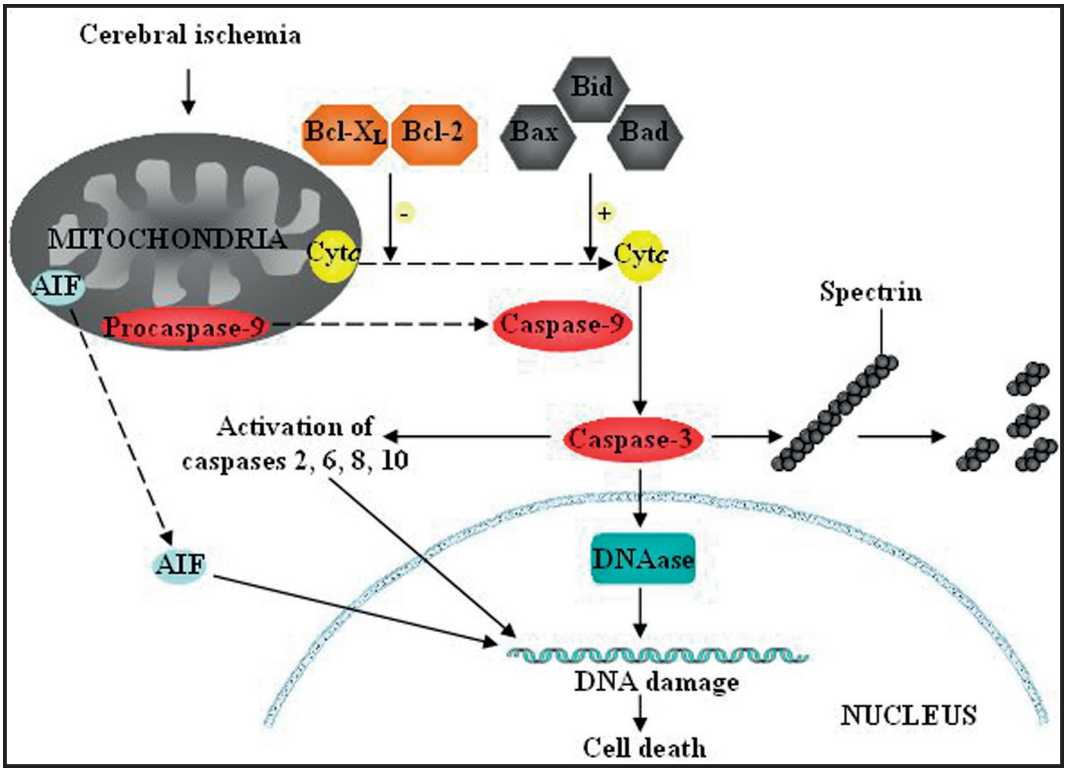

Fig. 59.4. Apoptotic pathways induced during ischemia. Reduction of the electron transport chain due to the absence of oxygen during ischemia, results in the release of proapoptotic factors: cytochrome C, AIF and procaspase-9. Procaspase-9 is converted to caspase-9, leading to the activation of caspases 2, 3, 6, 8, 10. Caspase-3 cleaves spectrin and activates DNAase. Together with the action of AIF and the rest of the caspases, DNA damage is induced, causing cellular disintegration and cell death.

caused by astrocytic dysfunction would be limited (reviewed by Takuma et al., 2004).

A key event during apoptosis is the release of cytochrome C from the mitochondria, regulated by the Bcl-2 family of proteins (reviewed by Ouyang and Giffard, 2004). The anti-apoptotic Bcl-2 members, Bcl-2 and Bcl-X_L, prevent cytochrome C release from the mitochondria. Conversely, the pro-apoptotic proteins of the Bcl-2 family, Bax, Bad and Bid, promote the release of cytochrome C to the cytosol.

The release of the apoptotic proteins such as cytochrome C, apoptosis-inducing factor and procaspase-9, from the mitochondria is facilitated by the formation of the mitochondrial permeability transition pore. This is a channel spanning both the inner and outer mitochondrial membranes. Its formation is promoted and inhibited by the pro- and anti-apoptotic proteins respectively and is facilitated by various factors such as free radicals and calcium (Crompton, 1999). Upon gating, permeability transition pore allows the influx of inorganic ions, causing swelling and rupture of the outer mitochondrial membrane. Alternatively, apoptogenic factors can directly exit the mitochondria through a pore composed of Bax molecules (De Giorgi et al., 2002). Cytochrome C release is followed by a cascade of signaling events that result in the activation of caspases (Shi, 2001). Caspases are cysteine proteinases that are critical effectors in cellular breakdown. In particular, caspase-3 cleaves spectrin and activates DNAase, which facilitates DNA injury.

Ischemic cells can be rescued from apoptosis by the activation of pathways that inhibit the action of pro-apoptotic proteins (reviewed by Chan, 2004). Specifically, the kinase Akt phosphorylates Bad, thus preventing release of cytochrome C. Activation of Akt also inhibits the proteolytic action of caspase-9, which is an initiator of the caspase cascade. Therefore, the Akt pathway constitutes a novel candidate for neuroprotection, by preventing apoptosis of ischemic cells.

59.12. Inflammation

The processes discussed above are vital for normal cellular function. Nevertheless, as previously discussed, attempts have been made to confer neuroprotection by interrupting those physiological processes. As a result, it is not surprising that the outcome of these neuroprotective strategies was unsuccessful. A process that is induced solely in response to injury and participates significantly in ischemic injury is inflammation. Therefore, interventions in the inflammatory pathways would be clinically advantageous, because they would limit the side-effects commonly induced by other neuroprotective approaches.

The ischemic brain releases inflammatory mediators including the platelet activating factor (PAF), tumor necrosis factor α (TNFα) and interlukin-1β (IL-1β). The inflammatory molecule that has attracted attention as a means for neuroprotection is the cytokine IL-1 (reviewed by Allan et al., 2005). IL-1 is a family of inflammatory cytokines composed by two ligands, IL-1α and IL-1β, which bind to the membrane-bound receptors, IL-1R. Activation of IL-1R results in the activation of various intracellular signaling pathways that are detrimental to cell survival or death (e.g., the activation of the transcription factor, nuclear factor-κB [NF-κB]). The mechanism responsible for ischemic cell death involves the exacerbation of leukocyte infiltration, activation of microglial cells, and promotion of neuronal excitability. IL-1 and its receptors are expressed in all cell types of the neurovascular unit (i.e., neurons, glia, endothelia cells, and invading leukocytes).

The involvement of IL-1 in ischemic injury can be inferred from studies of IL-1 knock-out mice, which exhibit significant reduction of up to ~80% in infarct volume following focal ischemia (Boutin et al., 2001). This effect was partially mimicked in wild-type rats, using the endogenous IL-1R antagonist, IL-1RA, a competitive inhibitor of the IL-1R response (Relton and Rothwell, 1992). In these experiments, intracerebroventricular administration of IL-1RA reduced ischemic injury by 50%.

A randomized, double-blinded placebo-controlled Phase II trial, using IL-1RA as a neuroprotective agent, indicated that IL-1RA administration was safe in acute stroke (Emsley et al., 2005). More importantly, the patients treated with IL-1RA had a better recovery and clinical outcome, as assessed by the Barthel index and the modified Rankin Scale. However, a major concern about the neuroprotective properties of IL-1RA is the hyperthermic action of IL-1. IL-1 is a known pyrogen, thus inhibiting its action would prevent a temperature increase. This is of great importance because a temperature rise augments the effect of the ischemic insult. In this case, the protective effect of IL-1RA would be physiological rather than pharmacological.

Inflammatory injury following ischemic insult can also be prevented by inhibiting the transcription of pro-inflammatory genes regulated by NF-κB. Inactive NF-κB is in a complex with another molecule, named I-κB. During ischemia the proteasome degrades I-κB, allowing the translocation of "activated" NF-κB onto the nucleus. This results in the transcription of various cytokines and cell adhesion molecules, triggering the immune response (reviewed by Elliott et al., 2003). Therefore, anti-inflammatory action can be conferred by proteosomal inhibitors. Indeed, the proteosomal

inhibitor, MLN519 showed efficacy in temporary middle cerebral artery occlusion rat models (Berti et al., 2003) and in phase I studies (Di Napoli and Papa, 2003).

59.13. EPO and statins

Current efforts to induce neuroprotection have focused on EPO. EPO is an endogenous growth factor that is synthesized in the kidneys and stimulates hematopoiesis (Jelkmann, 1994). Neurons also express EPO, which binds to EPO receptors inducing the activation of signaling pathways important for cell survival (Table 59.3). These pathways are anti-apoptotic, anti-inflammatory, antioxidant, angiogenic, neurogenic, and neurotrophic (reviewed by Siren and Ehrenreich, 2001). The ability of EPO to act as a potential novel neurotherapeutic agent was indicated by the increased expression of EPO receptor, following permanent middle cerebral artery occlusion in mice (Sadamoto et al., 1998). In vivo experiments in mice demonstrated that administration of recombinant human EPO significantly reduces infarct volume (Cerami et al., 2001). Moreover, recent phase I trials showed that EPO could be safely administered to stroke patients up to 8 hours after symptom onset (Ehrenreich et al., 2002).

Another neuroprotective agent with pleiotropic properties is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, commonly known as statin. Statins inhibit cholesterol biosynthesis in the liver by preventing the catalytic action of the HMG-CoA reductase in the mevalonate pathway, ultimately resulting in a reduction of cholesterol levels in the serum.

Pretreatment (Laufs et al., 2000; Amin-Hanjani et al., 2001) or post-treatment (Sironi et al., 2003) with statins results in a ~30% reduction of infarct volume following focal ischemia, by middle cerebral artery occlusion in mice. Beneficial results are obtained for a range of statins such as atrovastatin (Laufs et al., 2000) and mevastatin (Amin-Hanjani et al., 2001). In models of global ischemia, pretreatment with the statins pitavastatin (Kumagai et al., 2004) or pravastatin (Daimon et al, 2004) reduced significantly cell death in the CA1 area of the hippocampus.

The action of statins is mediated by a compilation of neuroprotective effects (all reviewed by Endres, 2005; Table 59.3), which are not directly linked to lower cholesterol levels. In more detail, the vascular endothelial NOS (eNOS) expression is increased and thereby cerebral blood flow is improved. In addition, both the activation of platelets and the formation of thrombus are prevented. Furthermore, angiogenesis is promoted by stimulating the production of endothelial progenitor cells. Importantly, the inflammatory response is limited by reducing the expression of various cytokines and the formation of free radicals is inhibited. Finally, the synthesis of particular MMPs is inhibited. MMPs are synthesized by macrophages and are able to disrupt an atherosclerotic plaque, which can potentially lead to embolus production.

There is a paradoxical lack of an epidemiological link between hypercholesterolemia and stroke risk (Prospective Studies Collaboration, 1995). However, the effects of statins described above explain why several small-scale clinical studies have demonstrated a beneficial outcome of statin administration to stroke patients (Greisenegger et al., 2004; Kennedy et al., 2005).

It is clear from cardiac studies that early use of statins in acute coronary syndromes has maximal benefit (Schwartz and Olsson, 2005). In order to achieve similar clinical benefits for cerebral ischemia, patients have to be pre-treated with statins. Alternatively, intravenous preparations of statins must be developed so that they can be given to stroke patients to achieve neuroprotection.

Table 59.3

Pleiotropic actions of EPO and statins in relation to neuroprotection

Compound	Neuroprotective effect	
EPO	Anti-inflammatory	Neurogenic
	Antioxidant	Neurotrophic
	Anti-apoptotic	Angiogenic
Statins	Increase cerebral blood flow	Inhibit synthesis of MMPs
	Angiogenic	Anti-oxidant
	Anti-inflammatory	Anti-thrombotic

59.14. Neurogenesis

A different approach to prevent the injury resulting from ischemia is to protect newly born neurons. Neurogenesis is a relatively unexplored, endogenous method of neuroprotection that has the potential to be utilized clinically. It takes place in the subventricular zone and the subgranular zone of the adult brain (Gage, 2000). Recent reports showed that transient global ischemia induces production of new neurons in the degenerated zone of the CA1 (Nakatomi et al., 2002; Schmidt and Reymann, 2002). Immunofluorescence studies, following either focal (Takasawa et al., 2002) or global (Sharp et al., 2002) ischemia demonstrated that neurogenesis increases

significantly ~7–9 days post-ischemia and the majority of these cells are differentiated to neurons.

Neurogenesis is further enhanced by treating rats with recombinant human EPO, following middle cerebral artery occlusion (Wang et al., 2004b). However, it is not yet clear whether EPO promotes neurogenesis by inducing the formation of new stem cells or by preventing them from ischemic degeneration.

A neuroprotective strategy that protects nascent stem cells, in addition to neurons and glia, would ultimately contribute to the recovery from the insult. A major concern to consider when the neurogenesis approach is translated to clinical studies is the functional competence of the neuroblasts. The formation of new neurons does not guarantee the functional substitution of the degenerated neurons. Subsequently, the electrophysiological and the synaptic profile of the new cells should be determined and compared with healthy, mature neuronal cells.

59.15. Hypothermia

The only confirmed method for long-term neuroprotection, discovered in ancient Greece and handed down the years, has been hypothermia (reviewed by Hachimi-Idrissi and Huyghens, 2004). The protective effects of hypothermia were demonstrated by Bigelow et al. (1950), in an attempt to reduce the need of cardiac circulation during open-heart surgery. The mechanisms governing the neuroprotective action of hypothermia, however, are not entirely understood. Nevertheless, the last 50 years have taught us how powerful hypothermia is as a way of protecting the brain in a variety of situations.

Drops in temperature protect against cell death in focal ischemia (Colbourne et al., 1999b, 2000). Reductions in infarct volume in animal models have been associated with improvement in neurological outcome (Colbourne et al., 2000). Critically, cell death following global ischemia in CA1 can be prevented with delayed hypothermia 6 hours after ischemia and this is accompanied with good behavioral recovery (Colbourne et al., 1999b). This satisfies the requirement for neuroprotective agents that there should be cytoprotection as well as organ protection.

Hypothermia has been translated to clinical neuroprotection in two studies (Bernard et al., 2002; Hypothermia After Cardiac Arrest Study Group, 2002). The effects of dropping body temperature to ~32°C for 12 hours (Bernard et al., 2002) or 24 hours (Hypothermia After Cardiac Arrest Study Group, 2002) have been shown following successful resuscitation from cardiac arrest. The outcome of these studies was significant improvement of both neurological function and survival rates. This was the first demonstration of neuroprotection in man, albeit using histological protection. However, hypothermia is very difficult to orchestrate in focal ischemia because the patients are awake and mobile. Hypothermia works best in situations of cardiac arrest or trauma during surgery for aneurysms, where patients can be maintained on ventilators and kept cool in an intensive care setting. Nevertheless, further trials to use hypothermia in stroke should not be carried out without adequate phase II data. The advantage of such clinical studies will be the capability to monitor the effect of the intervention using temperature as a surrogate.

59.16. Lost in translation

The failure of many putative neuroprotective agents to translate from animal studies to human clinical trials is attributed to multiple factors. The unsuccessful outcome of the NMDA receptor antagonists in the clinical trials highlighted some of those reasons (reviewed by Hoyte et al., 2004).

As discussed in section 59.6, the animal studies carried out with NMDA receptor antagonists failed to control physiological parameters such as temperature, blood pressure, glucose, and hemoglobin. This demonstrated the paramount importance of monitoring and regulating the animal physiology following the infusion of the drug.

Moreover, the protection by NMDA receptor antagonism would act mainly on neuronal cells, leaving glia cells prone to ischemic cell death. This would not have a significant effect in rats and mice because they are lissencephalic species, meaning that they have less white matter compared with humans who are gyroencephalic. This anatomical difference between animal and human brains is crucial since many human strokes are within white matter structures or lacunar. In addition, the time frame for evaluating the neuroprotection of a drug is different for animals and humans. In animal studies long-term neuroprotection is assessed after 28 days, while in human trials after 3 months. As a result, the neuroprotection observed in some animal trials may be a postponement of the ischemic injury. Another factor that differs in animal and human studies is the time window used for administration of the neuroprotective agent. This is frequently extended for human trials, probably negating the neuroprotective action of the compound. It must also be taken into account that the animal models do not mimic exactly human strokes. The age of the animals used is a factor that can be crucial for the efficacy of a compound when it is used in humans. The protective action of an agent

demonstrated in young animals might not be extrapolated to unhealthy humans of an old age.

Furthermore, the analysis of the data from the animal studies is more cohesively interpreted than the results of the human trials. The rodent studies are carried out to a genetically homogeneous population that is subjected to a particular type of stroke. In contrast, human trials are conducted using genetically heterogeneous subjects that have different types of stroke. Close examination of the results of phase II trial of selfotel demonstrated this inconsistency (Grotta et al., 1995). Selfotel is an NMDA receptor antagonist that acts in the glutamate binding site and can therefore prevent glutamate-induced excitotoxicity. Although the phase II trial showed positive results to groups of patients receiving higher doses, it was revealed that the severity of strokes in these patients was milder, compared with the lower-dose groups (Grotta et al., 1995). Finally, the excitement of positive results from preliminary studies in animal models is sometimes directly followed by clinical trials, prior to the confirmation and validation of the experimental data. This rushed approach increases the failure probability of these trials, as demonstrated in the nimodipine studies (Horn et al., 2001).

59.17. Preclinical stair criteria

To optimize the outcome of the neuroprotective studies, the design of the preclinical experimental strategy should include particular criteria (Stroke Therapy Academic Industry Roundtable, 1999; Table 59.4). The Stroke Therapy Academic Industry Roundtable (STAIR) recommendations were made based on functional measures. Briefly, they include efficacy of the neuroprotective compound on both histology and long-term outcomes, which implies behavioral recovery. They also include transcendence in species and a realistic therapeutic window; that is, the patient can be treated 2–3 hours into the insult.

Up until now, the successful outcome of most of the in vitro work has been based on protecting cells and nearly all of the in vivo work has been based on reductions in infarct volume. The translational step of demonstrating cell protection in a global model has been made very infrequently. This is a significant caveat for a neuroprotective agent because the apparent efficacy of a compound solely in models of focal ischemia can be misleading. Protection in focal ischemia implies protection, but this can be due to reduction of organotypic injury rather than an overall cytoprotective effect. For instance, there may be reductions in areas of infarction, but a considerable amount of cell loss in the cortex may still be present. As a result, a neuropathological improvement in terms of infarct volume may not necessarily be correlated with improvement in behavior.

Consequently, models of global ischemia should be initially employed. In essence, the neuroprotective agent should prevent the selective vulnerability of CA1 neurons of the hippocampus in order to be a strong candidate for cytoprotection. Collectively, the ideal neuroprotectant must protect cells in the global model, reduce focal infarction by volume in both permanent and transient focal ischemia, and improve behavior in at least two rodent species.

Before a compound undergoes clinical trials, it must also show promising action in cats and then primates. Importantly, the experiments must be randomized and blinded. A full and adequate dose–response curve should be constructed for different animal models and the corresponding toxicity should be carefully assessed. The therapeutic window must be determined and this must be compatible with the clinical setting. The protection offered by the drug must be investigated both during the acute phase (i.e., 1–3 days after the ischemic insult, and [long-term] 7–30 days post-ischemia). Finally, the results should be replicated by two independent laboratories and published in peer-reviewed journals.

The only compound to date that is claimed to meet all the STAIR criteria is 2,4-disulfophenyl-*N*-tert-butylnitrone (NXY-059) (Lees et al., 2001). NXY-059 is a free-radical spin trap that causes a nitro group to abduct the free radical and scavenge it by trapping it, thus forming a spin adduct (reviewed by Green et al., 2003). The product is stable and therefore unable to induce the deleterious effects of the free radicals, generated during ischemia and reperfusion.

Studies on rats subjected to transient middle cerebral artery occlusion showed that the mechanism of action of NXY-059 is also mediated by indirectly

Table 59.4

STAIR considerations for designing preclinical studies aimed at ischemic neuroprotection

Protection of CA1 neurons in global models
Reduction of infarct volume in focal models
Improvement of behavior
Assessment of toxicity
Construction of dose-response curves
Demonstration of neuroprotection in rats, cats, and primates
Determination of therapeutic window
Replication of results by independent laboratories
Publication in peer-reviewed journal

inhibiting the release of cytochrome C from the mitochondria (Yoshimoto et al., 2002). Significantly, the agent is neuroprotective in permanent and transient ischemia models of mice and rats (Kuroda et al., 1999; Sydserff et al., 2002) and in a rat model of hemorrhage (Peeling et al., 2001). Following focal ischemia in rats, infarct volume reductions of ~60%, at the mid-range dose, were recorded in the cortex (Sydserff et al., 2002). In addition, NXY-059 has a therapeutic time window of 3–6 hours following reperfusion, making it clinically applicable (Kuroda et al., 1999). Also, further studies in primates showed that protection by NXY-059 is conferred, using doses similar to what can be given to humans (Marshall et al., 2003).

To assess the efficacy of NXY-059, the phase III Stroke-Acute Ischemic NXY Treatment (SAINT-I) trial was carried out (Lees et al., 2006). This trial demonstrated a small but statistically significant improvement of the primary outcome by NXY-059 treatment. Reduced disability was observed at 90 days, as assessed by a shift in the modified Rankin Scale. Patients were treated within 4 hours of stroke onset, with doses of NXY-059 comparable with the neuroprotective effects seen in some animal models.

To confirm the efficacy of NXY-059, the larger-scale phase III SAINT-II trial was performed (Shuaib et al., 2007). Unfortunately, SAINT-II showed that NXY-059 is unsuccessful for the treatment of acute ischemic stroke. A probable reason for the failure of NXY-059 to successfully translate to clinical trials was that in the animal and phase I studies it was never proven that its efficacy was induced by the purported mechanism of free-radical scavenging at the penumbra, and not by an indirect physiological effect like an increase in blood flow. Therefore, for future neuroprotectants, before they enter phase II trials, a proof of principle must be established by employing imaging modalities like magnetic resonance imaging (MRI) and positron emission tomography (PET), together with surrogates of ischemia that directly demonstrate the ability of the compound to carry out its putative action at its therapeutic target, the penumbra (Papadakis and Buchan, 2006).

59.18. Designing a neuroprotective trial

After meeting successfully the preclinical STAIR criteria (Stroke Therapy Academic Industry Roundtable, 1999), a neuroprotective compound will go through clinical trials I, II, III and the outcome is highly dependent on the elaborate design of each trial (Stroke Therapy Academic Industry Roundtable, 2001). The key elements that lead to an accurate and efficient clinical trial are: clear primary objectives, careful selection of patients, appropriate data collection, and unbiased statistical analysis (Lees et al., 2003).

Establishing clear primary objectives is the first step in designing a trial, since this determines the variables to be measured as well as the methodology that should be employed. Both the hypothesis and the objectives of the trial depend upon the reliability of the preclinical studies. This is a crucial factor and has contributed to the failure of most neuroprotective trials because, as previously discussed, inappropriately controlled preclinical studies, albeit demonstrating efficacy in animal models, fail to translate to the clinical setting.

The selection of patients should be defined by rigid inclusion and exclusion criteria. Consequently, the results would show less variability between different centers carrying out the same trial, therefore facilitating their interpretation. The selection criteria should include the time since stroke onset, the type and severity of stroke, and the age range of the patients participating. The patients enrolled in the trial should exhibit neither mild nor severe stroke, but average baseline deficits as defined by the National Institutes of Health Stroke Scale (NIHSS); that is, scores of 7–22 (Stroke Therapy Academic Industry Roundtable, 2001). This way, the clinical benefit will be more likely to be demonstrated. In addition, the selection process should be assisted with brain imaging. CT or perfusion and diffusion MRI would provide vital information about the histological state of the patient. Furthermore, the treated and the placebo group should be identical in all prognostic aspects apart from treatment. Randomization and blinding are critical to ensure both unbiased selection of patients and unawareness of treatment assignment for the clinician and the patient.

All the patients assigned in a large-scale phase III (pivotal efficacy) trial should receive a drug dosage that is based upon appropriate dose-response studies carried out during exploratory phase I and II trials. Phase I and II trials should, therefore, provide the optimum dose range, the pharmacokinetic profile, toxicity, and safety of the compound.

The final stage of each trial includes collection and analysis of the data. The baseline data are registered as well as treatment results and follow-up data. Statistical analysis should be carried out in a non-biased fashion. The errors associated with intention-to-treat analysis should be considered in the interpretation of the data. Finally, the results should be reported according to the consolidated standards of reporting randomized trial (CONSORT) guidelines (Altman et al., 2001)

59.19. Future directions and molecular labeling

As thoroughly presented in this review, despite 10 years of thrombolysis in active clinical practice and over 100 neuroprotective trials, a neuroprotective agent that can be combined with thrombolysis is yet to be discovered (Table 59.5). It is established that by lowering glucose, temperature, or by improving blood flow, the amount of injury is reduced and by changing these parameters during ischemia, time is gained. Therefore, to date, claimed neuroprotection has not been a result of pharmacological manipulation but rather the manifestation of physiological protection. While the physiological protection is useful, it does not translate to the clinical parameter where differences in blood flow and surface area to body weight make it less likely that the same physiological events will happen, compared with a small animal such as a rat or gerbil.

Two factors are currently making translation of neuroprotection difficult. The first is the requirement of a thorough understanding of the ischemic syndrome in terms of the mechanism of injury. The second is a lack of adequate physiological yardsticks that are effective and can be measured and titrated against the neuroprotectant. Therefore, what is lacking for neuroprotection is either a surrogate or a biomarker similar to troponin for myocardial ischemia (Braunwald et al., 2000). This biomarker would illustrate and confirm the putative action of the neuroprotective agent. Therefore, imaging in the animal models would allow us to serially visualize the evolution of pathology.

Table 59.5

Summary of the different pathways induced during ischemia and approaches for intervention

Ischemic pathway	Intervention
Artery occlusion	Thrombolysis
Calcium excitotoxicity	AMPA receptor antagonists
	NMDA receptor antagonists
	TRP channel blockers
	NCX channel blocker
	Calcium chelators
Free radicals	Free-radical scavengers
	EPO
	Statins
NO cytotoxicity	Synthetic peptides
Apoptosis	Caspase inhibitors
Inflammation	IL1-RA
	NF-κB inhibitors
	EPO
	Statins
Neurogenesis	EPO

Imaging has already been very helpful for thrombolysis. In particular, the ongoing development of thrombolysis has been assisted by various imaging modalities. These include parenchymal imaging and the ability to look at magnetic resonance angiography (MRA). MRA has allowed the visualization of vascular occlusions and thus the response to thrombolysis showing the reperfusion. In addition, the advent of such agents as paramagnetic iron oxide has permitted labeling of inflammatory cells and visualization of the inflammatory response with MRI (Barber et al., 2004b). Following an ischemic insult, leukocytes are recruited to the endothelium. Leukocytes bind to the vascular endothelium by means of adhesion molecules (e.g., p-selectin) expressed on the endothelium. In particular, Sialyl–Lewis is an antigen found on the surface of leukocytes which binds to p-selectin. An attempt to visualize this process used a Sialyl–Lewis mimetic tagged to gadolinium (Sialyl–Lewis/gadolinium) (Barber et al., 2004b). MRI studies showed that Sialyl–Lewis/gadolinium successfully bound to the endothelium. Therefore inflamed endothelium can be used as a marker for ultimate injury or increased risk.

The anti-inflammatories, such as the previously described IL-1RA, might take advantage of this by showing a reduction in inflammation. Thus, the anti-inflammatory action of IL-1RA would be conclusively illustrated in both the experimental and clinical setting. Moreover, the use of a biomarker would allow the titration of the duration, depth, windows, and length of treatment against an imaging surrogate. This might ultimately lead to optimization of the intervention, before double-blind randomization in a clinical trial, on the basis of monitoring an image surrogate. The use of a biomarker would also allow positive trials to translate the efficacy studies to effectiveness in community practice. As a result, those neuroprotectants might be used for preconditioning in cases of high-risk stroke, such as immediately after a transient ischemic attack (TIA). In addition, because of the complexities of stroke with thrombolysis and the different types of stroke, such as lacunar, large-artery, or cardio-embolic, it will be necessary to use imaging to provide information on a case-by-case basis to ensure that any successful neuroprotectant is taken up by routine practice.

In conclusion, our current understanding of cerebral ischemia shows that the signaling pathways involved in ischemia can independently lead to cell death. As a result, a neuroprotective agent that inhibits a distinct pathway will either delay or reduce the deleterious effects of ischemia. Long-term protection would be therefore conferred by collective action in the signaling pathways responsible for ischemic cell

death. Therefore, a combinatory therapy approach must be considered that can prevent ischemic cell death by acting simultaneously at distinct pathways. In conjunction with the appropriate image surrogate, this would constitute the ideal neuroprotective strategy with the most promising outcome.

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Chapter 60

Endovascular therapy for acute ischemic stroke

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60.1. Introduction

Stroke represents an enormous health problem. It is the most common neurological reason for hospital admission. Despite a gradual decline in overall stroke death rates in many industrialized countries, stroke remains the third-leading cause of death in the USA (Thom et al., 2006). Large-vessel occlusions carry a particularly high mortality, estimated at between 53% and 92% (Jansen et al., 1995; Brandt et al., 1996). Stroke is also the leading cause of disability in adults. Of those individuals surviving a stroke each year, approximately 31% require assistance with activities of daily living, 20% require assistance with ambulation, and 16% require institutional care.

The discouraging statistics related to this problem have led clinicians to assume a more active attitude over the last decade. Intravenous (IV) administration of recombinant tissue plasminogen activase (rtPA) within 3 hours after symptom onset has become the "standard of care" for acute stroke treatment (NINDS rtPA Stroke Study Group, 1995). Nevertheless, as few as 1–6% of patients with acute stroke meet the criteria for IV thrombolysis (Chiu et al., 1998; Katzan et al., 2000); and endovascular techniques applying intra-arterial pharmacological and mechanical thrombolysis have emerged as a promising therapeutic alternative for select patients with acute stroke (Furlan et al., 1999; Gobin et al., 2004; Sorimachi et al., 2004; Smith et al., 2005). Recommendations for comprehensive stroke centers include the presence of an endovascular team (Alberts et al., 2000).

This chapter presents an overview of catheter-based strategies for the treatment of acute ischemic stroke. New techniques and recent advances are highlighted—notably, FDA approval in 2004 of a mechanical thrombectomy device (Merci Retriever, Concentric Medical, Mountainview, CA), for restoration of blood flow in the neurovasculature (Gobin et al., 2004). Although many of the treatment modalities mentioned in this chapter are considered investigational, they represent present and future endovascular treatment strategies for acute ischemic stroke. A combination of IV and endovascular therapies at centers staffed with experienced personnel will likely become the paradigm for acute stroke treatment.

60.2. Historical basis and rationale for endovascular therapy

Historically, stroke was a disease entity approached in terms of prevention and palliation. Endovascular therapy for acute stroke management dates back to 1958, when the successful recanalization of an acute internal carotid artery occlusion with intra-arterial fibrinolysis using plasmin was described (Sussman and Fitch, 1958). The concept of treatment for stroke was revived in 1995 with FDA approval of IV thrombolysis with rtPA administered within 3 hours of symptom onset (NINDS rtPA Stroke Study Group, 1995) and advanced in 1999 with completion of the PROACT study of intra-arterial thrombolysis with rproUK (Furlan et al., 1999).

Reperfusion of the ischemic brain is the most effective therapy for acute ischemic stroke. Restoration of

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flow to the penumbral area saves tissue from infarction. IV thrombolysis has been found successful mostly for the treatment of patients with mild or moderate stroke symptoms caused by the occlusion of second-degree vessels (i.e., distal vessels such as A2, M2–3) with small thrombi (NINDS tPA Stroke Study Group, 1997). The most likely explanation for poor outcome in patients with more severe deficits is that most large arteries are not recanalized by IV tPA (Brott et al., 1992). To achieve better results, recanalization procedures for large-vessel occlusions are necessary.

Intra-arterial therapy represents a logical approach, offering advantages of precise localization and targeted treatment. Because treatment is done locally and adjunctive mechanical devices can be used, a lower dose of thrombolytic agents is needed and recanalization rates greater than those achieved with IV therapy usually can be achieved. The interventionist can titrate and modulate the therapy (e.g., vary the dose of medication administered or the aggressiveness of mechanical device therapy/recanalization), concurrent with angiographic visualization of the response of the clot to treatment. Therapy can be tailored according to the angiographic results. Randomized trials have evaluated the safety and efficacy of intra-arterial thrombolysis administered 3–6 hours from symptom onset (del Zoppo et al., 1998; Furlan et al., 1999). The MERCI trial and several case series have shown the effectiveness of intra-arterial thrombolysis alone or in combination with mechanical thrombolysis as an alternative modality for treatment of acute ischemic stroke in a select group of patients (Qureshi et al., 2001; Eckert et al., 2002; Gobin et al., 2004; Sorimachi et al., 2004; Smith et al., 2005).

60.3. Pharmacological intra-arterial therapy

A list of the agents used for intra-arterial thrombolysis for ischemic stroke in clinical studies is provided in Table 60.1. Plasmin and microplasmin are emerging fibrinolytic agents (Schumacher et al., 2005). They act directly on fibrin, without dependency on local availability of plasminogen. The potential role of these agents for local intra-arterial therapy is appealing because of the rapid inactivation of plasmin by circulation antiplasmin. No increase in the rate of intracranial bleeding has been reported in animals receiving this agent compared with those in a control group (Lapchak et al., 2002; Marder and Stewart, 2002).

Recanalization was achieved in 45–75% of patients undergoing intra-arterial urokinase therapy for acute stroke in early reports (Mori et al., 1988; Ezura and Kagawa, 1992; Zeumer et al., 1993). The PROACT I and II trials were the first randomized, double-blinded,

Table 60.1

Agents used for pharmacological thrombolysis

	Half-life (minutes)	Description
First generation		
UK	14–20	Serine protease
Streptokinase	18–23	Protein from Group C beta (β)-hematolytic streptococci
Second generation		
Pro UK	20	Pro-enzyme precursor of UK
Alteplase (rtPA)	3–5	Serine protease
Third generation		
Tenecteplase	17	rtPA mutant
Reteplase	15–18	Deletion mutant of rtPA

multicenter studies of intra-arterial thrombolysis (del Zoppo et al., 1998; Furlan et al., 1999). In these trials, patients with acute ischemic stroke resulting from large-vessel middle cerebral artery occlusion and with symptom onset within 6 hours underwent intra-arterial thrombolysis with rproUK (Table 60.2). Mechanical thrombolysis was not allowed in these trials. Recanalization rates were based on the TIMI (thrombolysis in myocardial infarction) grading system (Table 60.3) (TIMI Study Group, 1985). In PROACT I, 6 mg of rproUK or placebo was intra-arterially administered to patients with middle cerebral artery occlusion (TIMI grade 0 or 1 occlusion of the M1 or M2 middle cerebral artery segment) within 6 hours after symptoms onset. End points were recanalization efficacy and rate of intracerebral hemorrhage causing neurological deterioration within 24 hours of treatment. Forty patients received either rproUK ($n = 26$) or placebo ($n = 14$) and were treated a median of 5.5 hours after symptom onset. Recanalization rates (TIMI 2 or 3) were 58% in the rproUK group (82% in those who received a high-dose regimen of IV heparin consisting of a 100 U/kg bolus plus continuous infusion of 1,000 U/hour for 4 hours and 40% in those who received the low-dose regimen consisting of a 2,000-U bolus plus continuous infusion of 500 U/h for 4 hours) and 14% in the placebo group in the PROACT I trial. Because of the low number of patients in PROACT I, clinical efficacy of this treatment modality could not be established. The safety and recanalization rates observed in PROACT I, led to the second PROACT trial.

PROACT II was designed to assess the efficacy of intra-arterial rproUK (9 mg given over 2 hours, rather than the 6 mg in PROACT I) as measured by a

Table 60.2

Design of PROACT trials

	PROACT I	PROACT II
No. of patients	40	180
Baseline median NIHSS	rproUK, 17; placebo, 19	rproUK, 17; placebo, 17
Heparin	All patients received IV heparin; first 16 patients received 100 U/kg bolus, then 1,000 U/hour infusion during 4 hours; remaining patients received 4,000 U bolus followed by a 500 U/hour infusion for 4 hours	All patients received 2,000 U heparin bolus IV, then 500 U/hour infusion for 4 hours
Agent used	6 mg of rproUK; 9 mg over 2 hours	9 mg of rproUK over 2 hours and heparin
Placebo group	Saline at 30 ml/hour over 2 hours	IV heparin alone

Table 60.3

Definitions of perfusion in the Thrombolysis in Myocardial Infarction (TIMI) trial (TIMI Study Group, 1985)

Grade 0 (no perfusion): no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (partial perfusion): contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—for example, the opposite coronary artery or the coronary bed proximal to the obstruction.

Grade 3 (complete perfusion): antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to obstruction, and clearance of contrast material from the involved bed in the same vessel or the opposite artery.

modifed Rankin Scale (mRS) score of 2 or less at 90 days. For the primary outcome measure of efficacy in the second PROACT trial, 40% of patients receiving rproUK plus IV heparin and 25% of those receiving IV heparin only (placebo) achieved an mRS score of 2 or better at 90 days ($p = 0.04$). Partial (TIMI 2) or full (TIMI 3) recanalization was achieved 2 hours after infusion in 66% of the rproUK group and 18% of the heparin-only group ($p < 0.001$). However, TIMI 3 recanalization was achieved in 19% of the rproUK group versus 2% of the heparin-only group. Overall, a 15% absolute increase in favorable outcome was shown with rproUK. For every seven patients treated with rproUK, one would benefit. The recanalization rate in PROACT II is purely a reflection of pharmacological lysis considering that passage of a microwire to disrupt clot was not allowed. The overall results and peri-procedural complications for PROACT I and II are presented in Table 60.4. Intracerebral hemorrhage was the most frequent peri-procedural complication. Despite this increased frequency of intracerebral hemorrhage, intra-arterial rproUK administered within 6 hours of symptom onset caused by middle cerebral artery occlusion was associated with significantly improved clinical outcome in PROACT II.

PROACT II was a landmark trial in that for the first time in a randomized study, intra-arterial thrombolysis demonstrated clinical efficacy and extended the time window for therapy to 6 hours in a homogeneous group of patients with acute ischemic stroke. This trial did not lead to FDA approval, but paved the way for additional studies involving intra-arterial thrombolysis (with newer agents) in acute ischemic stroke. In addition, the American Stroke Association guidelines for the early management of patients with ischemic stroke recognize intra-arterial thrombolysis as a treatment option for select patients with large-vessel occlusion (Adams et al., 2005).

60.4. Combination IV and intra-arterial thrombolysis

The combination of IV thrombolysis with intra-arterial thrombolysis represents an alternative strategy that combines the theoretical advantage of the speed of IV therapy with the targeted focus of intra-arterial therapy. Combination therapy has been investigated

Table 60.4

Overall results and peri-procedural complications in the PROACT trials

	PROACT I		PROACT II	
	rproUK	placebo	rproUK	Placebo
TIMI 2/3 (%)	58	14	66	18
Symptomatic intracerebral hemorrhage (%)	15	7	10	2
90-day outcome				
mRS score 0–1 (%)	31	21	40	25
mRS score 0–2 (%)				
90-day mortality (%)	27	43	25	27
Worsening neurological symptoms without intracerebral hemorrhage	Unknown	Unknown	0.8% (1/121)	0%
Worsening chronic renal insufficiency	4% (1/26)	0%	Unknown	Unknown
Aspiration pneumonia	4% (1/26)	0%	Unknown	Unknown
Anaphylaxis	0%	0%	0.8% (1/121)	0%
Groin hematoma	12% (3/26)	21% (3/14)	7% (9/121)	7% (4/59)
Intracerebral hemorrhage within 24 hours	42% (11/26)	7% (1/14)	35% (38/108)	13% (7/54)
Intracerebral hemorrhage within 10 days	Unknown	Unknown	68% (73/108)	57% (31/54)
Intracerebral hemorrhage within 90 days	50% (13/26)	36% (5/14)	Unknown	Unknown

in several series (Lewandowski et al., 1999; Ernst et al., 2000; Keris et al., 2001; Hill et al., 2002; Suarez et al., 2002) (Table 60.5). In 24 patients treated with IV tPA (0.6 mg/kg) followed by intra-arterial UK (up to 750,000 U) or tPA (maximum of 0.3 mg/kg), complete recanalization occurred in 9 patients (38%) (Suarez et al., 2002). At 3 months post-procedure, 19 patients (79%) had a Barthel index score of 95 or better. No patient was found to have symptomatic intracerebral hemorrhage. In another series, 20 patients with a median NIHSS score of 21 were treated with IV tPA (0.6 mg/kg), followed by intra-arterial tPA administration (maximum dose of 0.3 mg/kg) (Ernst et al., 2000). After treatment, 10 patients had a modified Rankin Scale score of 0 or 1. Symptomatic intracerebral hemorrhage was reported in one patient. The Emergency Management of Stroke Bridging Trial (Lewandowski et al., 1999) found no difference in 7- to 10-day or 3-month outcomes in the IV/intra-arterial versus the placebo/intra-arterial group; however, there were more deaths in the IV/intra-arterial group. The IMS trial (IMS Study Investigators, 2004) showed only a modest trend to better clinical outcomes. The 3-month mortality in IMS subjects (16%) was numerically lower but not statistically different than the mortality of placebo (24%) and rtPA-treated subjects (21%) in the NINDS rtPA Stroke Trial. The rate of symptomatic intracerebral hemorrhage (6.3%) in IMS subjects was similar to that in rtPA-treated subjects (6.6%) but higher than the rate in placebo-treated subjects (1.0%, $p = 0.018$) in the NINDS rtPA Stroke Trial. IMS subjects had significantly better outcomes at 3 months than NINDS placebo-treated subjects for all outcome measures (odds ratios ≥ 2). IMS II (IMS II Trial Investigators, 2007) found significantly better outcomes at 3 months than those in the NINDS trial, without a statistically significant increase in risk.

A different approach in which IV glycoprotein (GP) IIb/IIIa agents were administered in combination with intra-arterial thrombolysis deserves mention. In a pilot study consisting of 10 patients treated with intra-arterial UK plus IV abciximab, recanalization (TIMI 2 or 3 flow) was achieved in 90% of patients, which was a major improvement over the previously obtained 43.8% rate with intra-arterial UK alone (Lee et al., 2002).

60.5. Mechanical intra-arterial therapy

Mechanical thrombolysis and embolectomy have evolved as adjunctive and potentially primary therapies for acute ischemic stroke. The main goal of these approaches is to restore cerebral blood flow by means of removing the obstructive thrombus, disintegrating the thrombus to facilitate activation of thrombolytic agents, or a combination thereof (Nesbit et al., 2004). Snares, angioplasty balloons, embolectomy devices, and stents represent the main mechanical adjuncts currently used.

Table 60.5

Results of combined IV and intra-arterial thrombolysis*

Authors, study center	Design	Symptomatic intracerebral hemorrhage within 7 days	Outcome definition	Outcome	Mortality
Lewandowski et al. EMS Bridging Trial Investigators	Double-blind randomized placebo-controlled multicenter study comparing safety and feasibility of two treatment strategies	12% (2/17) IV/intra-arterial; 6% (1/18) placebo/intra-arterial	3 months GOS, Barthel index, mRS	No significant differences in outcome between treatment groups	At 90 days: 45% (5/11) in IV/intra-arterial; 10% (1/10) in placebo/intra-arterial
Ernst et al. University of Cincinnati	Retrospective study to assess safety and feasibility of IV tPA/intra-arterial tPA within 3 hours of symptom onset	6% (1/16)	mRS, follow-up range 2–100 months	44% (7/16) mRS of 0 or 1, 19% (3/16) mRS of 2, 25% (4/16) mRS of 4 or 5	13% (2/16)
Keris et al. Riga, Latvia	Open-label prospective study to assess safety and efficacy of IV tPA/intra-arterial tPA within 6 hours of symptom onset	None	mRS at 1 month and 12 months; good = mRS 0–3; poor = mRS 4–6	67% (8/12) mRS 0–3 at 1 month, 83% (10/12) mRS 0–3 at 12 months	17% at 12 months
Hill et al. University of Calgary, Alberta	Prospective, open-label study to assess safety and feasibility of IV tPA/intra-arterial tPA within 3 hours of symptom onset	None	NIHSS score < 3 at 90 days	67% (4/6) NIHSS < 3 at 90 days	17% (1/6)
Suarez et al. University Hospitals of Cleveland, Case Western Reserve	Pilot study to assess feasibility of IV tPA/intra-arterial UK or tPA within 3 hours of symptom onset	10% (2/21) in IV tPA group only	Barthel index at 90 days: scores of 95 or 100 = good outcome	77% good outcome at 3 months, Barthel index scores > 95: 92% (12/13) in IV tPA/intra-arterial UK group, 64% (7/11) in IV tPA/IV tPA group, 67% (14/21) in IV tPA group	16% (7/45)

*Abbreviations: EMS = emergency management of stroke; GOS = Glasgow Outcome Scale.

Snares were first developed to capture coils and other foreign bodies; their application was naturally extended to thrombo-emboli retrieval. Devices such as the Microsnare, a fine wire snare (Microvena, White Bear Lake, MN); the In-Time retriever (Boston Scientific, Fremont, CA), an expandable wire mesh; the Neuronet (Guidant), a self-expanding nitinol basket; and the EnSnare (InterV, Medical Device Technologies, Gainesville, FL), a 3-wire loop, can be passed through a microcatheter into the thrombus to retrieve or break up the clot and increase the surface area exposed to thrombolytics (Kerber et al., 2002; Nesbit et al., 2004).

The results of the MERCI trial were recently published and advanced the concept of mechanical thrombectomy (Gobin et al., 2004; Smith et al., 2005). MERCI was a prospective, non-randomized, multicenter trial investigating the use of the Merci retriever (models X5 and X6) within 8 hours after stroke onset symptoms in 151 patients ineligible for IV tPA. Part I of this trial enrolled 55 patients and focused more on safety; part II included 96 additional patients and placed more emphasis on feasibility and results. Recanalization was achieved in 68 of 141 (48%) patients in whom the device could be deployed. A good neurological outcome (mRS score $\leq$2) was observed more frequently at 90 days in patients in whom recanalization was successful than in patients in whom it was unsuccessful (46% versus 10%; $p < 0.0001$). Symptomatic intracerebral hemorrhage occurred in 5% of patients treated with the Merci retriever alone versus 24% of patients treated with the device plus additional rescue therapy (thrombolytics or angioplasty/snare) (Smith et al., 2005). This trial led to FDA approval of the use of the Merci retriever for a technical outcome (i.e., the removal of thrombus) to restore blood flow. Even though recanalization (assessed primarily via angiography) has been found to increase the odds ratio of good outcome by 5.4-fold, it is a surrogate marker that does not replace a clinical end-point (Rha and Saver, 2003). A randomized, controlled clinical trial including the Merci and other retrieval devices, the MR RESCUE trial, has been initiated to determine whether clot retriever therapy is a beneficial treatment for acute stroke (NINDS NCT00094588 [accessed March 20, 2008]; Tomsick, 2005).

A newer-generation Merci device (L5) has been launched. This device was evaluated in the Multi-MERCI trial, a prospective single-arm study consisting of patients ineligible for IV tPA or those in whom recanalization failed after IV tPA thrombolysis (Smith, 2006). In this study, subsequent passes could be made with the L5 device or the first-generation devices (X5 and X6). Adjuvant therapy with intra-arterial tPA was allowed after attempts had been made with the retriever. One-hundred eleven patients were enrolled, with a median age of 68 years (range, 24–93 years) and baseline NIHSS score of 19 (range, 4–42). Thirty patients (27%) received IV tPA before the intervention. Successful recanalization post-retriever was obtained in 60 of 111 (54%) "treatable" vessels, and successful recanalization was achieved following adjunctive therapy (intra-arterial tPA, mechanical) in 77 of 111 (69%) treatable vessels. Clinically significant procedural complications occurred in 11 of 111 (9.9%) cases. The rate of symptomatic intracerebral hemorrhage was 9.0% (10 of 111) overall (symptomatic intracerebral hemorrhage occurred in 2 of 30 patients with IV tPA pretreatment versus in 8 of 81 patients without). Good neurological outcome (mRS score of 2 or less) was achieved in 32% of the population treated.

Another modality, suction thrombectomy, has been reported to be successful in three patients with ischemic stroke related to cervical internal carotid artery occlusion (Lutsep et al., 2002). This technique is useful for aspiration of large-vessel thrombotic occlusion within the internal carotid artery. The catheter tip is positioned into the proximal third of the thrombus and a 60-ml syringe is used to aspirate the thrombus.

Another endovascular thrombectomy device is the NeuroJet (Possis Medical, Minneapolis, MN). High-pressure saline jets are directed into the primary evacuation lumen of this thrombectomy catheter to create a hydrodynamic vortex that fragments adjacent thrombus and draws it into the recovery lumen. Investigation of this device in clinical trials was stopped because vessel perforations with subarachnoid hemorrhage occurred in two, and possibly three, cases (Molina and Saver, 2005).

Ultrasound infusion microcatheters and a laser-driven thrombectomy device represent other devices under investigation. In animal models of stroke, laser technology using Argon and Nd:Yag (neodymium: yttrium aluminum garnet) radiation has demonstrated destruction of atheromatous plaque (Watson et al., 2002). This technique leads to vaporization of fresh thrombus and plaque without producing significant emboli. However, arterial wall perforation is a major concern. A pulse-dye laser is unique in that it is tuned to hemoglobin absorption peak. This technique may minimize energy absorption in the vessel wall and allow photoacoustic mechanical disruption of the thrombus. Laser-tipped catheters that emulsify thrombus, the endovascular photoacoustic recanalization (EPAR) device (Endovasix, Belmont, CA) and LaTIS (LaTIS inc, Coon Rapids, MN), have entered clinical

trial (Molina and Saver, 2005). Recanalization in 35–57% of patients has been initially reported with EPAR treatment (Berlis et al., 2004). The device was evaluated in a safety and feasibility trial at two centers in the USA. Arteries 2–5 mm in diameter could be treated, including the internal carotid artery, M1 or M2 branch of the middle cerebral artery, A1 branch of the anterior cerebral artery, basilar artery, posterior cerebral artery, and vertebral artery. Treatment was given as late as 8 hours after symptom onset in the anterior circulation and within 24 hours in the posterior circulation. The device could not be delivered to the clot in two of the first five patients enrolled in this trial, and enrollment was stopped at 12 patients. Although the catheter design was changed, an efficacy trial was not pursued.

The technique of endovascular ultrasound to augment fibrinolysis represents another therapeutic avenue. In this technique, the catheter is placed within the thrombus and activated to produce ultrasonic resonance that agitates the thrombus and thereby facilitates the action of the thrombolytic agent. Preliminary experience with a unique ultrasound infusion microcatheter (EKOS, Bothel, WA) within 6 hours of anterior circulation ischemia and 13 hours of posterior circulation ischemia suggests that the technique is safe and yields favorable recanalization rates (Mahon et al., 2003). TIMI 2 or 3 flow was achieved in 8 of 14 patients (57%) within 1 hour of therapy. Symptomatic intracerebral hemorrhage occurred in 2 of 14 (37%) patients.

Balloon angioplasty has been associated with successful recanalization (Ueda et al., 1997; Ringer et al., 2001). Angioplasty of a vessel in which the occlusive lesion is associated with an underlying atheroma can also result in improved flow and prevent reocclusion (Qureshi et al., 2004). Stenting is an appealing alternative that has been useful in achieving recanalization. Self-expanding and balloon-mounted stent-assisted recanalization of embolic occlusion has been tested in-vivo in a canine model (Levy et al., 2006b). Recanalization of 90% of vessels occluded with either soft or hard clot was achieved. Buttressing of the clot by the stent is likely the main mechanism involved. Stents seem to be of value in the clinical setting as well. Intracranial stent implantation with coronary and balloon-expandable stents after failed pharmacological and/or mechanical thrombolysis was found to re-establish flow (TICI [thrombolysis in cerebral hemorrhage] score of 2 or 3) in medium or large intracranial vessels in 15 of 19 (79%) patients in whom no other therapeutic options were available (Levy et al., 2006a). Self-expandable stent implantation also appears to have potential utility as shown in a clinical case (Sauvageau and Levy, 2006). Further evaluation is underway.

Aggressive therapy with a combination of IV abciximab and intra-arterial rtPA in conjunction with angioplasty and stenting was found to be a useful modality to improve clinical outcome in the context of acute vertebrobasilar occlusion (Eckert et al., 2005). A cohort of 47 patients presenting with acute vertebrobasilar occlusion treated with an IV bolus of abciximab (0.25 mg/kg) followed by a 12-hour infusion (0.125 μg/kg per minute), low-dose intra-arterial rtPA (median dose, 20 mg), and angioplasty with stenting for cases of residual stenosis was compared with a historical cohort of 41 patients treated with intra-arterial rtPA monotherapy (median dose, 40 mg). Rates of TIMI 2 or 3 flow were similar in both groups (72% combination therapy versus 68% monotherapy), but TIMI 3 was achieved more frequently in patients treated with combination therapy (45% versus 22%). Moreover, this group experienced improved favorable neurological outcome (mRS 0–3: 34% versus 17%) with decreased mortality (38% versus 68%).

Recently, the Penumbra (Penumbra. Alameda, CA), a microcatheter-based device used to macerate and aspirate soft clot and then remove thrombus in fibrous occlusions, was approved by the FDA. The phase I trial in 20 patients not eligible for t-PA demonstrated nearly complete restoration of flow in all patients and 45% good outcomes at 30 days (Bose et al., 2008). Considering the vast array of tools emerging, the variability of embolic and occlusive material as well as of the vascular architecture, a multimodality approach is likely to yield the maximum recanalization result. However, for successful recanalization to be associated with successful clinical outcome, patient selection for endovascular therapy is of primary importance.

60.6. Patient selection

Because of the inherent risks of endovascular therapy for acute stroke, patients who present with severe neurological deficits (NIHSS score of either $\geq$10 or >8 involving speech) may be considered for intra-arterial thrombolysis. The leading factor in patient selection is time from symptom onset. Mechanical thrombectomy with the Merci device has extended the time frame for treatment from 6 hours (in PROACT) to 8 hours. Clinical improvement and successful recanalization of basilar artery occlusion with intra-arterial thrombolysis as long as 24 hours after stroke symptom onset have been reported; and, because of the dismal prognosis of this pathological condition, consideration may be given to performing intra-arterial therapy for up to 24 hours (Brandt et al., 1996; Levy et al., 1999; Kirton et al., 2003). As reliable means of selecting potential candidates for therapy are developed on the basis of physiological rather than chronological

criteria by using advanced imaging systems, we may be able to determine which patients presenting beyond the 8-hour window may benefit from thrombolysis. A select group of patients who may be considered for intra-arterial thrombolysis include those who have undergone major surgery within 2 weeks from the onset of stroke symptoms; this is an exclusion criterion for IV thrombolysis (NINDS rt-PA Stroke Study Group, 1995; Katzan et al., 1999; Chalela et al., 2001; Moazami et al., 2001).

The strict exclusion criteria for PROACT II (Table 60.6) and the exclusion criteria for the MERCI trial (Table 60.7) can serve as relative exclusion criteria for the management of patients who are not enrolled in a study. Adherence to the imaging criteria specified by these trials for now until more clearly defined magnetic resonance imaging or other imaging-based selection criteria become available should be encouraged. Patients with intracerebral hemorrhage, hypoattenuation throughout more than one-third of the middle cerebral artery territory, or intracranial masses are typically excluded from any approach.

Table 60.6

Exclusion criteria for PROACT II (Furlan et al., 1999)

NIHSS score >30
Coma
Rapidly improving neurological signs
Stroke within the previous 6 weeks
Seizures at onset of presenting stroke
Clinical presentation suggestive of subarachnoid hemorrhage
Previous intracranial hemorrhage, neoplasm, or subarachnoid hemorrhage
Septic embolism
Suspicion of lacunar stroke
Surgery, biopsy of a parenchymal organ, trauma with internal injuries or lumbar puncture within 30 days
Head trauma within 90 days
Active or recent hemorrhage within 30 days
Known hemorrhagic diathesis, baseline international normalized ratio >1.7, activated partial thromboplastin time >1.5 times normal, or baseline platelet count $<100 \times 10^9$/l
Known sensitivity to contrast agents
Uncontrolled hypertension defined by a blood pressure ≥180 mmHg systolic or ≥100 mmHg diastolic on three separate occasions at least 10 minutes apart or requiring IV therapy
CT evidence of hemorrhage, intracranial tumors except for small meningiomas, significant mass effect from the infarction, and acute hypodense parenchymal lesion or effacement of cerebral sulci in more than one-third of the middle cerebral artery territory
Angiographic evidence of arterial dissection, arterial stenosis precluding safe passage of a microcatheter into the middle cerebral artery, non-atherosclerotic arteriopathy, no visible occlusion, or occlusion of an artery other than the M1 or M2 middle cerebral artery segment

Table 60.7

Exclusion criteria for MERCI (Gobin et al., 2004; Smith et al., 2005)

Lack of informed consent (and permission to waive consent due to emergency circumstances had not been obtained)
Current pregnancy
Serum glucose <50 mg/dl
Excessive tortuosity of cervical vasculature precluding device delivery or deployment
Known hemorrhagic diathesis
Known coagulation factor deficiency
Oral anticoagulation treatment with international normalized ratio >1.7 (part I) and >3.0 (part II)
Use of heparin within 48 hours
Partial thromboplastin time >two-times normal
Platelet count <50,000/μl part I, (<30,000/μl part II)
History of severe allergy to contrast media
Sustained systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg despite treatment
CT scan revealing significant mass effect with midline shift of greater than one-third of the middle cerebral artery region with hypodensity (sulcal effacement and/or loss of gray-white differentiation alone was allowed)
>50% stenosis of the artery proximal to the target vessel
Life expectancy <3 months

60.7. Procedural technique

The effort of each member of the endovascular team must be coordinated during an emergency stroke intervention. General endotracheal intubation should be performed before endovascular procedures in patients who have marked neurological deficit and are likely to be uncooperative. To ensure patient safety and quality imaging, sedation should be optimized with an agent such as propofol. The neuroprotective properties of this agent are valuable in the setting of ischemia and secondary brain injury. A short-acting neuromuscular blocking agent may also be a safe adjunct. Arterial access should be gained while the nursing team prepares the catheters, microcatheters, mechanical devices, and thrombolytic and antiplatelet agents. Vasopressors, vasodilators, and IV fluids must be readily available for optimization of blood pressure parameters during and after the procedure.

For acute stroke intervention using endovascular techniques, patients are placed supine on the angiography table. The femoral artery approach is the access

approach of choice. However, interventionists should also be familiar with radial and brachial approaches because coexistent severe peripheral vascular disease, femoral artery occlusion, morbid obesity, or previous femoral artery bypass graft placement may preclude successful negotiation of diagnostic and/or guiding catheters beyond the aortoiliac junction (Campeau, 1989; Spaulding et al., 1996). Both groins are prepared in usual sterile fashion to provide immediate access to a second puncture site should one be needed or if the first cannot be successfully accessed. For femoral access, an imaginary line is visualized between the anterior superior region of the iliac spine and the pubic tubercle; the pulse is felt; a local anesthetic is used to infiltrate the area; and a needle is inserted at a 45° angle toward the umbilicus. After excellent arterial blood return through the puncture needle is visualized, a J-shaped wire is inserted through the needle. The needle is removed, and an appropriately sized catheter sheath is placed in the femoral artery. A focused diagnostic angiogram is then performed with a diagnostic catheter. After an arterial occlusion has been identified, a guide catheter is placed in the cervical vessel as close to the skull base as safely possible. Heparin is administered because of the risk of thrombo-embolic complications associated with prolonged microcatheterization of intracranial vessels and the inherent thrombogenic properties of the devices used during endovascular therapy (Qureshi et al., 2000).

Using road-map guidance, a microcatheter is then guided over a microwire into the region of occlusion. The microcatheter over the microwire is then gently advanced through the occluded lumen over a distance likely to be distal to the embolus or thrombus. The microwire is then withdrawn, and a microcatheter angiogram is obtained. Microcatheter angiography with simultaneous guide catheter angiography is useful to clarify the extent, position, and length of the occlusion. At this point, a decision regarding the treatment plan should be made, and pharmacological or mechanical thrombolysis or a combination of these is performed.

For pharmacological thrombolysis, the microcatheter is drawn back into the occlusive portion of the vessel, and the lytic agent is injected through the microcatheter. The microcatheter is gradually withdrawn through the area of occlusion so as to distribute the agent within the clot. Guide catheter angiography should be done intermittently to witness any progress in revascularization. For mechanical maneuvers, the device of choice is deployed after the microcatheter has been advanced beyond the target occlusion. If a snare is used, the microcatheter and device are withdrawn back and forth within the embolus to macerate the clot and promote recanalization.

A comprehensive, stepwise approach is followed for use of the Merci retrieval system, which consists of a balloon guide catheter or dilator, a microcatheter, and a retriever. Loops of the nitinol helix of the retriever are deployed beyond the thrombus. The device is retracted to engage the thrombus, and the remaining loops are unsheathed within the clot. The helix is then twisted to more fully capture the thrombus, and the balloon positioned proximally in the internal carotid artery. The balloon is inflated to block the anterograde flow for a few seconds while the retriever and the ensnared clot are withdrawn into the guide catheter and out of the body. Continuous aspiration is maintained through the guide catheter during the retrieval phase. A case of Merci retrieval is illustrated in Fig. 60.1.

Angioplasty balloon inflation using a coronary artery balloon within the area of clot can also promote revascularization in the setting of acute cerebral occlusion. The balloon should be sized to the presumed length of the occlusion. The balloon should be undersized to the vessel diameter to prevent dissection or vessel rupture. Slow inflation is recommended (Connors and Wojak, 1999).

Recent improvements in stent technology have allowed intracranial stenting to play a role in acute stroke treatment. A balloon-mounted or self-expandable stent is brought across the lesion and deployed within the occluded segment to crush the emboli. When a stent is used, care must be taken to provide an appropriate antiplatelet regimen to prevent acute stent thrombosis. If a loading dose of aspirin (325–650 mg) and clopidogrel (300–600 mg) cannot be given, an infusion of a glycoprotein IIb/IIIa inhibitor should be administered intraprocedurally. At the conclusion of the procedure, the guiding catheter is removed. The sheath is left in place or a closure device is placed because of the use of heparin during the procedure. A cranial CT scan is obtained to check for intracranial hematoma before transfer of the patient to the intensive care unit. A case of stent-assisted revascularization is illustrated in Fig. 60.2.

60.8. Complication recognition and management

Peri-procedural hemorrhage represents the most frequent complication and warrants close evaluation of the patient. Systemic bleeding that is potentially associated with the use of heparin and thrombolytic agents includes intracerebral hemorrhage, gastrointestinal hemorrhage, urinary tract hemorrhage, retroperitoneal hemorrhage, and access site hematoma. These complications may not be clinically obvious, so close

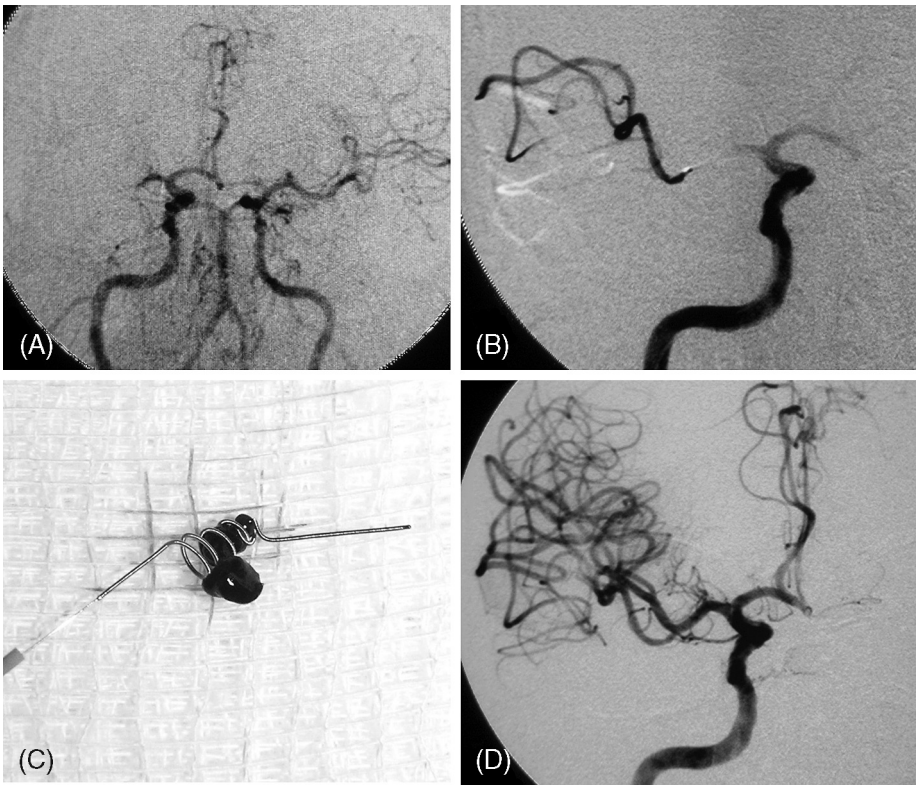

Fig. 60.1. (A) Arch injection with intracranial frontal projection demonstrating a right middle cerebral artery occlusion. (B) Right internal carotid artery guiding catheter injection and right middle cerebral artery microcatheter injection showing the extent of the occlusion. (C) Merci device (Concentric Medical, Mountainview, CA) with clot retrieved. (D) Right internal carotid artery injection demonstrating patency of the right middle cerebral artery.

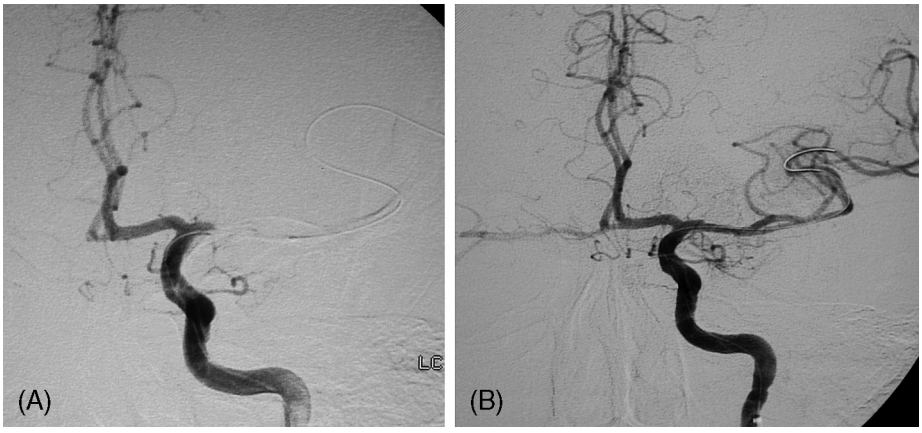

Fig. 60.2. (A) Left internal carotid artery angiogram, anteroposterior projection, showing occlusion of the proximal left middle cerebral artery. (B) Left internal carotid artery injection after stent deployment demonstrating revascularization of the middle cerebral artery.

attention must be paid to the results of daily laboratory tests, such as hematocrit and hemoglobin levels, partial thromboplastin time, prothrombin time, international normalized ratios, and platelet count. Frequent examination of the access site is essential to detect a possible pseudoaneurysm. Retroperitoneal hemorrhage with or without any abdominal symptoms, which can develop from a complication of a femoral artery puncture or inadequate closure of the puncture site, should be suspected if the patient displays signs or symptoms of hemodynamic compromise or if the patient's hemoglobin level decreases. If any doubt exists, CT imaging of

the abdomen and pelvis should be obtained on an urgent basis.

Intracerebral hemorrhage represents the most feared and potentially life-threatening procedural complication of intra-arterial thrombolysis. If intracerebral hemorrhage is suspected during the procedure because of contrast extravasation outside the vessel, the thrombolytic agent should be discontinued, and protamine should be administered to reverse the heparin effect (1 mg of protamine per 100 U of heparin given but not to exceed 50 mg). Coagulation testing should be obtained. A cranial CT scan should be obtained immediately and a neurosurgeon consulted. A blood transfusion should be considered, especially if a surgical procedure is anticipated. It may be difficult to distinguish intracerebral hemorrhage from contrast enhancement in the affected area because of disruption of the blood–brain barrier (Mericle et al., 2000). Although Hounsfield units can be used to differentiate the two similar-appearing signal densities, a follow-up CT scan obtained 24–48 hours later may show clearance of the contrast material in the absence of intracerebral hemorrhage. Intracerebral hemorrhage without significant mass effect, midline shift, uncal herniation, or neurological deterioration may be managed medically. Ventriculostomy may be indicated in cases of hydrocephalus or situations for which increased intracranial pressure needs to be controlled and monitored. The authors recommend that surgical evacuation be reserved for intracranial hematomas in easily accessible locations in select patients with progressive neurological deterioration and substantial mass effect observed on cranial CT scan.

Rigorous medical management of these patients is paramount to improved outcome. Airway protection and oxygen saturation should be optimized. The authors recommend maintaining the systolic blood pressure within the range of 120 to 160 mmHg and diastolic blood pressure less than 90 mmHg post-procedure. Fluid and electrolytic status should be closely observed to avoid dehydration and hypotension as well as fluid overload and cerebral edema. Nutrition should be initiated as soon as possible via a feeding tube for patients who are unable to eat. Patient care in stroke units may lead to a reduction in secondary complications of stroke and intracerebral hemorrhage.

In PROACT I, each of five patients found to have hypodensity exceeding 33% of the affected hemisphere on the initial CT scan (according to criteria defined by the European Cooperative Acute Stroke Study investigators) (Hacke et al., 1995, 1998; Fiorelli et al., 1999) developed intracerebral hemorrhage within 24 hours (Del Zoppo et al., 1998). In PROACT II, symptomatic intracerebral hemorrhage occurred only in 12 patients with a baseline NIHSS score of 11 or higher (Furlan et al., 1999). Death occurred after symptomatic intracerebral hemorrhage in 10 of these patients (83%). Serum glucose level exceeding 200 mg/dl at stroke onset was associated with risk of symptomatic intracerebral hemorrhage in PROACT II (Kase et al., 2001). Severity of stroke, longer time to recanalization, and high glucose levels have been reported as independent predictors of intracerebral hemorrhage in other intra-arterial thrombolysis series (Suarez et al., 1999; Ueda et al., 1999; Kidwell et al., 2002).

The use of a mechanical device as a first-line therapeutic alternative may positively affect the rate of intracerebral hemorrhage. As mentioned, symptomatic hemorrhage occurred in 5% of patients treated with the Merci retriever alone versus in 24% of patients treated with the device plus additional rescue reperfusion therapy (Smith et al., 2005). Improved patient selection and an understanding of the mechanisms involved in the development of intracerebral hemorrhage may reduce the morbidity and mortality associated with intra-arterial thrombolysis.

60.9. Future

Refinement in patient selection and device and imaging technology should benefit the treatment of acute ischemic stroke. The association of increased NIHSS score with large-vessel occlusion (Fischer et al., 2005) and the 75% decreased odds of recovery for patients with NIHSS scores >10 who receive IV tPA should warrant evaluation of early intra-arterial therapy in such patients even if they are eligible for IV thrombolysis (Tomsick et al., 1996; Albers et al., 2000). It is estimated that the typical patient loses 1.9 million neurons each minute in which stroke is untreated (Saver, 2006). Rapid and reliable distinction of irreversibly injured ischemic tissue from tissue that can be salvaged with reperfusion therapy in the first hours after stroke onset would be of great clinical value. Experiments in monkeys have defined the threshold for tissue infarction with reperfusion at 2–3 hours to be 10–12 ml/100 g/min, whereas the threshold for tissue infarction with permanent occlusion is 17–18 ml/100 g/min (Jones et al., 1981). Indeed, first-pass quantitative CT perfusion technique may be useful in determining how much tissue can be salvaged with reperfusion therapy versus how much tissue is likely to infarct (Schaefer et al., 2006). Wide availability of this tool could have a major influence on the management of patients with acute stroke.

60.10. Summary

Endovascular therapy is an effective alternative for recanalization of major vessel occlusion and has become a reality in the armamentarium of stroke

treatment. Site-specific intra-arterial delivery of thrombolytic agents has enabled recanalization of anterior and posterior circulation lesions. Mechanical techniques for clot disruption have resulted in increased vessel recanalization rates and reduced hemorrhage rates concomitant with reduced doses of thrombolytic agents. Improvement in patient selection, refinement in technology, and the incorporation of endovascular teams at stroke centers will drive the utility of these techniques forward. Collaboration among the various healthcare professionals involved in the treatment of this disease will facilitate the paradigm change and the scientific and technical research that will orient clinical decision-making in the future.

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Chapter 61

Management of subarachnoid hemorrhage, unruptured cerebral aneurysms, and arteriovenous malformations

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Intracerebral hemorrhage is associated with a high morbidity and mortality rate. The causes are multiple, including trauma, subarachnoid hemorrhage from a ruptured cerebral aneurysm, primary intracerebral hemorrhage from hypertension or vasculopathy, or hemorrhage from a ruptured arteriovenous malformation. One of the keys to management is prevention of the hemorrhage before it occurs, and thus recognition and treatment of predisposing conditions, such as hypertension, smoking, or unruptured aneurysms or arteriovenous malformations, is essential. This chapter will focus on the key aspects of management once a subarachnoid hemorrhage has occurred, as well as recommendations regarding unruptured cerebral aneurysms and arteriovenous malformations.

61.1. Subarachnoid hemorrhage

Subarachnoid hemorrhage is often a catastrophic condition, resulting in high morbidity and mortality. Traumatic brain injury accounts for the lion's share of subarachnoid hemorrhage by sheer numbers, but in non-traumatic cases it typically occurs as the result of the rupture of a cerebral aneurysm, with blood extravasation into the subarachnoid space (Fig. 61.1). The cause of formation of cerebral aneurysms is incompletely known. Potential mechanisms include a congenital weakness in the vessel wall, arterial hypertension, smoking, and abnormalities in type 3 collagen (Pope et al., 1981). Approximately 5% of subarachnoid hemorrhages are the result of bleeding from an arteriovenous malformation. Furthermore, 15–20% patients are not found to have a source for hemorrhage, despite an exhaustive evaluation. When the blood is confined to the cisterns around the midbrain, this is referred to as peri-mesencephalic subarachnoid hemorrhage, felt to be secondary to a venous source, and this carries a much better prognosis than other causes of subarachnoid hemorrhage (Rinkel et al., 1993). Affected patients are at low risk for rebleeding and cerebral vasospasm. More rare causes of subarachnoid hemorrhage include rupture of an arteriovenous malformation, which occurs in about 5% of cases. Other considerations include spontaneous subarachnoid hemorrhage from coagulopathy (Mattle et al., 1989), pseudoaneurysm formation from extension of a carotid or vertebral dissection (Massoud et al., 1992), rupture of a mycotic aneurysm with bacterial endocarditis (Steinberg et al., 1992), sympathomimetic use (Levine et al., 1991), sickle cell anemia, spinal dural arteriovenous fistulae, CNS vasculitides, and pituitary apoplexy.

Subarachnoid hemorrhage has an incidence of approximately 10–12 per 100,000 per year (Sacco et al., 1984). Predisposing factors include a positive family history, Finnish or Japanese descent, polycystic kidney disease (Chapman et al., 1992), Ehlers–Danlos syndrome, pseudoxanthoma elasticum, and coarctation of the aorta. Familial studies of aneurysms are ongoing, but no definitive genetic markers have been determined yet.

61.1.1. Clinical presentation

Patients with subarachnoid hemorrhage most commonly present with headache, which is typically explosive in nature, classically described as the "sudden onset of the worst headache" of the patient's life.

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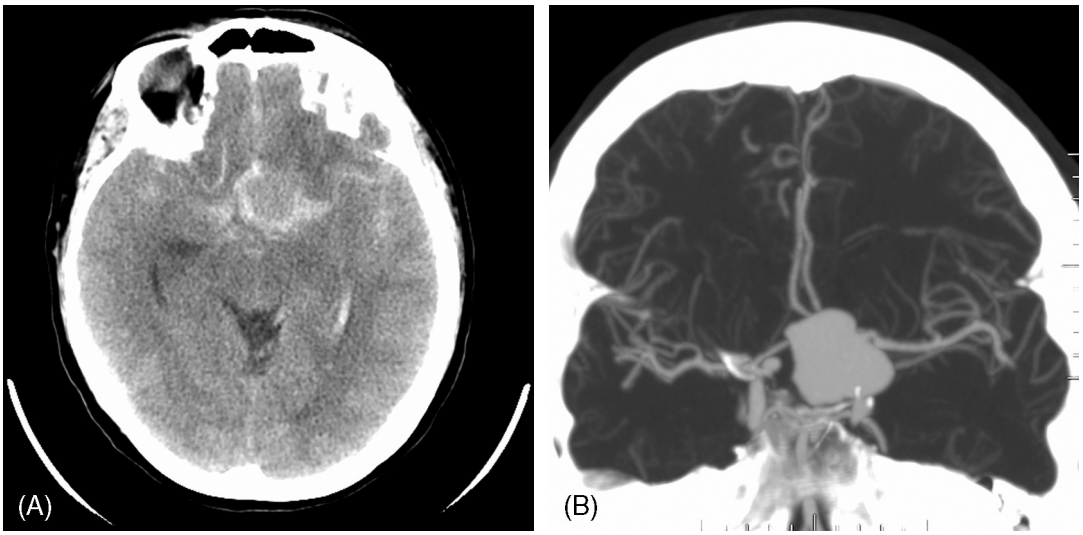

Fig. 61.1. Subarachnoid hemorrhage. (A) Non-contrast head CT shows blood in the interhemispheric fissure and sylvian fissures, as well as a large aneurysm originating in the anterior cerebral artery. (B) CT angiogram reconstruction shows the aneurysm in more detail. The size of this aneurysm would classify it as a "giant" aneurysm.

Meningeal signs are common, as the blood tracks in the subarachnoid space causing neck stiffness and pain. Patients commonly have photophobia, and may have confusion, lethargy and seizures. More severe clinical grades may be associated with more significant intracerebral processes, such as focal mass effect from a parenchymal hematoma, communicating or non-communicating hydrocephalus, or increased intracranial pressure. Cerebral vasospasm is typically seen later in the course of the presentation, but can be hyperacute as well, typically when the intracranial pressure is highly elevated. Some patients who present with headache may not seek immediate medical attention, or do so but fail to have the subarachnoid hemorrhage correctly diagnosed. This is known as a "sentinel headache," and is often followed by a more major subarachnoid hemorrhage. Initial misdiagnosis of subarachnoid hemorrhage is associated with a higher morbidity and mortality rate (Kowalski et al., 2004). Patients commonly present with subarachnoid hemorrhage during sleep, during routine daily activities, or during activities that involve the Valsalva maneuver, such as heavy weightlifting, sexual intercourse, or defecation.

Several grading scales are used in the assessment of subarachnoid hemorrhage patients, and these are helpful in providing prognostic information, not just in terms of survival, but also in regard to the predicted location for future vasospasm during their intensive care unit course. The Hunt and Hess classification scheme is a clinical grading scale, ranging from 0 to V in increasing severity (Hunt and Hess, 1968) (Table 61.1). The World Federation of Neurological Surgeons (WFNS) grading system takes into account the Glasgow Coma Scale (GCS) and the presence or absence of a major focal deficit (World Federation of Neurological Surgeons, 1988) (Table 61.2).

Table 61.1

Hunt and Hess grading scale for subarachnoid hemorrhage

Grade	Criteria	Index of peri-operative mortality (%)
0	Unruptured	0–5
I	Asymptomatic or with minimal headache or slight nuchal rigidity	0–5
II	Moderate to severe headache, nuchal rigidity, but no neurological deficit other than a cranial nerve palsy	2–10
III	Somnolence, confusion, medium focal deficits	10–15
IV	Stupor, hemiparesis medium to severe, possible early decerebrate rigidity, vegetative disturbances	60–70
V	Deep coma, decerebrate rigidity, moribund appearance	70–100

Once the patient has been stabilized, the diagnostic work up for patients suspected of having a subarachnoid hemorrhage should include the rapid performance of a non-contrast computed tomography (CT) scan of the brain. CT is highly sensitive for the presence of

Table 61.2

World Federation of Neurological Surgeons grading scale for subarachnoid hemorrhage

Grade	GCS score	Motor deficit
I	15	Absent
II	13–14	Absent
III	13–14	Present
IV	7–12	Present or absent
V	3–6	Present or absent

acute blood, and can also assess for hydrocephalus, stroke, and other lesions. A minority of subarachnoid hemorrhage patients will have a falsely negative CT scan, mostly those with small amounts of bleeding, especially in the posterior fossa where there is significant bony artifact. When there is a clinical suspicion of subarachnoid hemorrhage, all patients with negative CT imaging should undergo a lumbar puncture. Care should be taken during lumbar puncture, as rapid removal of cerebrospinal fluid could precipitate more bleeding from a ruptured aneurysm by causing pressure shifts. The opening pressure should be measured. Red blood cell counts are elevated in subarachnoid hemorrhage, but may also be the result of trauma at the time of lumbar puncture, and thus xanthochromia should be used as the indication of subarachnoid hemorrhage. The cerebrospinal fluid protein may be elevated, but glucose is typically normal.

Once the diagnosis of subarachnoid hemorrhage has been established, the search for an aneurysm should begin. This may be done with CT angiography (CTA), although smaller aneurysms may be missed with this technique, thus indicating the need for cerebral angiography. In a study of 50 patients in whom 51 aneurysms were detected by conventional angiography, only 48 of these were detected by CTA (Dammert et al., 2004). The sensitivity of aneurysm detection significantly improved with increasing size of the aneurysm, but was only 83% for small (<4 mm) aneurysms. Few studies have compared magnetic resonance angiography (MRA) with conventional angiography, but its usefulness in evaluating small aneurysms is felt to be inferior to CTA. Conventional angiography should include imaging of all four major intracerebral vessels, as well as the external carotid views.

61.1.2. Management

In the acute setting, patients with subarachnoid hemorrhage may be medically unstable, and particular attention should be given to ensuring airway protection and hemodynamic stability. Patients with a higher clinical grade may have a depressed level of consciousness, and may require intubation and mechanical ventilation. Subarachnoid hemorrhage induces a massive surge of catecholamines, which often leads to cardiac dysrhythmias, severe hyper- or hypotension, and even myocardial infarction. The recommended goal systolic blood pressure for subarachnoid hemorrhage patients in the acute setting is 100–140 mmHg. Higher blood pressures pose a risk for repeat hemorrhage, but lower blood pressures may compromise the cerebral perfusion pressure if the intracranial pressure is raised. Often further complicating the situation is a state of depressed cardiac output; echocardiography commonly shows globally depressed myocardial function, often with apical sparing (Zaroff et al., 2000).

After initial stabilization and diagnostic testing, consideration should be given to placement of a ventriculostomy if hydrocephalus is present, or if the patient has a poor clinical state. This may be used to drain cerebrospinal fluid and to monitor the intracranial pressure (ICP). Nimodipine, a calcium channel blocker, has been shown to be helpful in the prevention of vasospasm, and should be instituted as early as possible (Petruk et al., 1988). The dose is 60 mg orally every 4 hours, but it may cause significant hypotension, and thus can be given as 30 mg every 2 hours. Other agents that have been suggested to be of benefit in preventing vasospasm include statins (Tseng et al., 2007) and magnesium (Stippler et al., 2006). Seizures are common in subarachnoid hemorrhage patients, occurring in up to 25%, and are more common in patients with higher clinical grades. The use of prophylactic anticonvulsants is controversial, but a stronger case can be made for their use in patients with a poor clinical grade who may have further deterioration if seizures were to occur (Butzkueven et al., 2000). Comatose or poorly responsive patients should undergo electroencephalography (EEG) to rule out non-convulsive seizures (Towne et al., 2000). Predictors of epilepsy following subarachnoid hemorrhage include focal pathology, such as from a hematoma or cerebral infarction (Claassen et al., 2003).

All subarachnoid hemorrhage patients should be admitted to an intensive care unit, and should have frequent neurological examinations to monitor for any signs of deterioration. They should be placed on a cardiac monitor, and most, especially those with higher clinical grades, should have continuous arterial pressure monitoring and a central venous catheter or pulmonary arterial catheter placed, especially if they are hemodynamically unstable. Blood should be sent for complete blood counts and chemistries, liver function studies, coagulation parameters, and type and crossmatching for blood products.

Early treatment of the aneurysm is recommended, not only to prevent rebleeding, but also to allow for hypertensive treatment if necessary, should the patient develop cerebral vasospasm. Options for treatment include surgical clipping via a craniotomy, or endovascular therapy with coiling of the aneurysm. In a multicenter trial of 2,143 patients who were randomized to endovascular coiling versus neurosurgical clipping, in which either option was felt to be acceptable and there was clinical equipoise, the group treated with endovascular coiling appeared to be more likely to be independent at 1 year, with the benefit extending to at least 7 years (absolute risk reduction of 7.4% [95% CI 3.6–11.2, $p = 0.0001$]) (Molyneax et al., 2005). In a smaller, single-center study, a slight benefit in favor of surgical clipping was found (Hoh et al., 2004). In considering which technique is most appropriate, one must consider the anatomy of the aneurysm, the endovascular accessibility of the aneurysm by the feeding vessels, and the comorbid factors of the individual patient, which may make them a less viable surgical candidate. In patients who are unable to have either technique performed, aminocaproic acid (amicar) is a potential option to prevent rebleeding (Schisano, 1974).

61.1.3. Management of cerebral vasospasm

The next potentially dangerous situation that arises for the subarachnoid hemorrhage patient is cerebral vasospasm. The incidence of vasospasm reaches its peak at 5–12 days after the hemorrhage, but can occur earlier, or continue for up to 21 days (Mayberg et al., 1990). The Fisher Group Score (Table 61.3) is helpful in predicting cerebral vasospasm. It assigns patients to different groups, based on the amount and location of the hemorrhage, emphasizing that the amount of blood seen on the initial CT strongly correlates with the risk of developing vasospasm (Kistler et al., 1983).

Table 61.3

Fisher group scale for prediction of cerebral vasospasm

Fisher Group	Blood on CT
1	No subarachnoid blood detected (lowest risk of vasospasm)
2	Diffuse or vertical layers <1 mm thick
3	Localized clot and/or vertical clot >1 mm thick (highest risk of vasospasm)
4	Intracerebral or intraventricular clot, with diffuse or absent subarachnoid blood (low risk of vasospasm)

Furthermore, this landmark work also provided clinicians with a strong indicator of not just *whether* a patient would develop vasospasm, but specifically *which* cerebral vessels would be affected. The pathogenesis of vasospasm is not completely understood, but involves a cascade of delayed inflammation of the smooth muscle of the arteries around which the subarachnoid blood is located (Weir et al., 1999). The result is a constricted vessel lumen, which can cause ischemia and infarction due to hypoperfusion of the distal brain tissue. Intracisternal thrombolysis at the time of surgical clipping has been demonstrated to decrease the risk of developing vasospasm (Amin-Hanjani et al., 2004).

Detection of vasospasm can be challenging. The clinical examination remains a highly sensitive and reproducible means of assessing the neurological status of a patient at risk for vasospasm, but may be unreliable in patients with encephalopathy or coma. Transcranial Doppler is commonly implemented in the evaluation of vasospasm, but false elevations in flow velocities can occur with hyperemia, fever or systemic hypertension (Laumer et al., 1993). CTA and MRA are under investigation for the evaluation of vasospasm, but have yet to be validated. MRI with diffusion- and perfusion-weighted imaging has been purported to be useful for detecting vasospasm in a small study of eight patients (Rordorf et al., 1999). The "gold standard" for the diagnosis of vasospasm remains cerebral angiography.

The standard treatment of vasospasm consists of volume expansion (hypervolemia), induced hypertension, and hemodilution, or "HHH therapy," although there have not been any randomized studies to definitively prove its efficacy (Kassell et al., 1982). The volume status is addressed by either a central venous catheter or pulmonary arterial catheter. Often a challenge is maintaining an adequate volume status if the patient develops congestive heart failure in the acute setting of the subarachnoid hemorrhage, or if they concurrently have developed polyuria secondary to cerebral salt wasting (see below) (Levy et al., 1991). Replacement fluids can include isotonic fluids, albumin, and sometimes hypertonic saline. Induced hypertension is performed to increase flow through the narrowed vessels and to increase flow via collateral channels.

The clinical scenario dictates the blood pressure that is required; in some patients the vasopressor requirement may be mild, while in others more significant. Typically, the blood pressure will be raised to the point at which the symptoms of vasospasm reverse. Hemodilution is based on the principle of decreased viscosity with a lower hematocrit, and often the goal

hematocrit is around 30%, at which point there is decreased viscosity but still adequate oxygen-carrying capacity.

When HHH therapy fails, either due to continued symptoms/signs of vasospasm or due to poor medical tolerance (e.g., congestive heart failure), the patient may need to undergo cerebral angiography, where more invasive measures may be undertaken. Although randomized trials of angiographic techniques in the treatment of vasospasm are lacking, therapeutic options include direct infusions of vasodilating agents, such as alpha-adrenergic antagonists (papaverine) (Liu et al., 2004), calcium channel blockers (nicardipine) (Tejada et al., 2007), or direct balloon angioplasty (Firlik et al., 1997).

Potential medical complications following subarachnoid hemorrhage are many. There is commonly a profound release of catecholamines, especially with hypothalamic dysfunction, and this sympathetic surge may lead to myocardial infarction, cardiac dysrhythmias, and globally depressed myocardial function. Subarachnoid hemorrhage patients may thus develop cardiogenic or neurogenic pulmonary edema, and may require pulmonary arterial catheters to guide the fluid and vasopressor management. Hyponatremia may occur, either from hypothalamic dysfunction or as a result of vasospasm itself, and is more often the result of cerebral salt wasting rather than the syndrome of inappropriate antidiuretic hormone (SIADH) (Wijdicks et al., 1988). Treatment of cerebral salt wasting requires aggressive fluid replacement (rather than fluid restriction, as is used to treat SIADH) with iso- or hypertonic fluids, and salt tablets and/or fludrocortisone may also be helpful (Mori et al., 1999). Other potential medical complications include deep venous thrombosis, gastritis, pancreatitis, and infection complications, most commonly including pneumonia and urinary tract infections. If the patient has a ventriculostomy and fever, the cerebrospinal fluid should be sent for Gram stain and culture to rule out an infectious ventriculitis, which carries a high rate of morbidity and mortality if untreated.

61.1.4. Prognosis

As many as 20% of patients with subarachnoid hemorrhage die before reaching the hospital, and the overall mortality rate, including those who survive to reach the hospital, approaches 50%. Of those who survive, the prognosis directly correlates with multiple factors, including the patient's age, the clinical state at the time of presentation, comorbid diseases, and the complications during the hospitalization, including vasospasm. The Hunt–Hess grade has shown a strong correlation with outcome, with increasingly worse outcomes with higher clinical grades. The prognosis precipitously worsens with rebleeding of the aneurysm, which occurs in 4% in the first 48 hours, and 20% in the first 2 weeks (Kassell and Torner, 1983). The mortality rate with rebleeding reaches 60–70%. Of those who survive the hospitalization, 50% suffer permanent neurological disability, including the results of strokes from vasospasm, epilepsy, hydrocephalus, and cognitive impairment.

61.2. Unruptured cerebral aneurysms

The exact prevalence of unruptured cerebral aneurysms is unknown, but is estimated to be 2–3% of the population. The prevalence increases with advancing age, and appears to be more common in families, ranging from 2% to 30% (Nishimoto et al., 1985). Multiple aneurysms can occur in the same patient about 20% of the time, more commonly in women. The most common locations for aneurysms are in the anterior circulation (anterior communicating artery > posterior communicating artery > middle cerebral artery). Aneurysms of the vertebrobasilar system, however, are associated with a higher complication rate with treatment.

61.2.1. Clinical presentation

Most unruptured cerebral aneurysms are asymptomatic, and often discovered incidentally. Patients may sometimes present with headache, which may be the result of increasing size of the aneurysm, but can also be seen with aneurysm thrombosis. More acute headaches suggest impending rupture, and should prompt consideration for urgent therapy to prevent rupture. The location of the headache does not necessarily aid in localizing the aneurysm; most headaches are diffuse. Cranial nerve palsies, however, can be quite helpful in localization. Posterior communicating artery aneurysms often produce a third nerve palsy by compression. Ophthalmic artery aneurysms can compress the optic nerve or chiasm and cause vision deficits. Anterior-inferior cerebellar artery aneurysms and basilar aneurysms can sometimes cause a fourth nerve palsy. Aneurysms within the cavernous sinus can cause a cavernous sinus syndrome, with involvement of the third, fourth, fifth and the upper sensory division of the fifth nerve.

Neuroimaging for cerebral aneurysms has greatly improved over the past several years. Many aneurysms are detected on MRA in patients presenting with headaches, but this technique may miss smaller aneurysms. CTA has evolved as more sensitive means of detecting

even small aneurysms (Teksam et al., 2004). Conventional cerebral angiography, however, remains the gold standard.

61.2.2. Natural history

The largest study of the natural history of unruptured aneurysms is the International Study of Unruptured Intracranial Aneurysms (ISUIA) (International Study of Unruptured Intracranial Aneurysms Investigators, 2003). Four-thousand sixty patients were included in this study, of whom 1,692 did not have treatment and 2,368 underwent surgical or endovascular treatment. This study found that the 5-year cumulative risk of rupture correlated with the aneurysm site and size, with increasing risk in aneurysms of greater size or located in the posterior circulation. For the 1,692 patients who did not undergo treatment, the rupture risk correlated highly with an increasing size of the aneurysm. This is in contrast, however, with most studies of subarachnoid hemorrhage, which have found that most aneurysms that rupture are indeed small. In the ISUIA study, patients with an unruptured aneurysm <7 mm in diameter had a rupture rate of 0.1% per year, a risk that was not increased if there was a family history of rupture. In patients with aneurysms ≥ 7 mm, the risk of rupture was higher, but when compared with the risks associated with surgical or endovascular techniques, it was unclear if there was a benefit to treating these aneurysms. It was clear from this study that an increasing size of the aneurysm appeared to be associated with a higher risk for rupture, but there is an inherent bias to the study—the natural history of these lesions remains unclear, as they are often treated either surgically or endovascularly without knowing what the outcome would have been if left untreated.

61.2.3. Management

Numerous factors contribute to the decision to treat an unruptured intracerebral aneurysm. If the aneurysm is symptomatic, either causing headaches, seizures by compression on adjacent brain tissue or by compressing a cranial nerve, treatment may be helpful in alleviating these symptoms. Older patients tend to have more complications with surgery or endovascular treatment, and may not be exposed to the same number of years of risk of rupture; thus clinicians will often weigh in favor of treatment for younger aneurysm patients but will be more conservative with older (Vindlacheruvu et al., 2005). Patient preference and anxiety are other important considerations.

The location of the aneurysm is also important; posterior circulation aneurysms are associated with a higher rate of rupture, but also carry a higher risk of surgical complications. Many posterior circulation aneurysms are treated endovascularly, but the lesions must also be amenable to this approach morphologically. Coiling of the aneurysm requires a favorable dome–neck ratio, otherwise the coils may extrude into the feeding vessel, potentially leading to thrombosis and stroke (Regli et al., 1999). Technological advances in the next several years are likely to push the field toward more endovascular treatment, with the advent of such techniques as using balloon-assisted coiling and concomitant stenting and coiling (Malek et al., 2000).

In the ISUIA trial, 1,917 patients underwent surgical clipping and 451 endovascular repair. The groups were not evenly balanced—the endovascular group included a greater number of older patients, had a higher mean size of aneurysm, and had more cavernous carotid and basilar tip aneurysms. In the surgical group, age was a strong predictor of poor outcome ($\geq$50 years associated with a relative risk of 2.4 (1.7–3.3), $p < 0.0001$), as was aneurysm diameter >12 mm (RR 2.6 (1.8–3.8) $p < 0.0001$), location in the posterior circulation (RR 1.6 (1.1–2.4), $p = 0.025$), previous ischemic cerebrovascular disease (RR 1.9 (1.1–3.0), $p = 0.01$) and aneurysmal symptoms other than rupture (RR 1.59 (1.2–2.4), $p = 0.004$). In the endovascular group, poor outcome was associated with aneurysm diameter >12 mm (RR 2.4 (1.0–5.9), $p = 0.03$) and location in the posterior circulation (RR 2.25 (1.1–4.4), $p = 0.02$).

In patients who do not undergo treatment of the aneurysm, risk factor management remains important. Cigarette smoking has been correlated with aneurysmal growth (although not with aneurysm formation), and thus smoking cessation counseling is paramount (Knekt et al., 1991). These patients should also have aggressive management of hypertension. Anti-platelet agents and oral anticoagulation may be indicated in these patients for other systemic reasons, and although these agents are not known to increase the risk for aneurysm rupture, they may increase the amount of bleeding that occurs at the time of subarachnoid hemorrhage due to inhibition of thrombosis.

61.3. Arteriovenous malformations

Cerebral vascular malformations can be separated into four categories: arteriovenous malformations (which will be the main focus of this section), cavernous malformations, developmental venous anomalies, and capillary telangiectasias. Most vascular malformations are felt to exist from birth, although some can develop

de novo, or may be appreciated only in later life. The reasons for their formation are unclear, and most occur sporadically. However, type 1 and type 2 hereditary hemorrhagic telangiectasia are associated with mutations in genes coding for proteins expressed in the endothelium (Vikkula et al., 2001). Also, although the genetics have not yet been determined, cavernous malformations also appear to occur in some families.

Vascular malformations exist in approximately 4.5% of autopsy studies of the brain (Wascher et al., 1992). Pathologically, arteriovenous malformations (arteriovenous malformation, comprising about 15% of all malformations) consist of an abnormal direct connection between the arterial and venous circulations with no capillary phase. They can grow over time, and can be anywhere in the brain, but most commonly occur in the distribution of the middle cerebral artery. They can have numerous arterial feeding vessels, as well as complicated venous drainage systems. They can also have associated aneurysms, placing them at higher risk for hemorrhage. Cavernous malformations (about 15% of all malformations) consist of dilated vascular spaces in a compact mass, with no intervening neural tissue. They are typically well circumscribed, and can be up to several centimeters in size. They can also occur in other organs, such as the liver, kidney, and skin, and anywhere in the brain. Capillary telangiectasias consisted of dilated capillaries with intervening normal brain tissue. They most commonly occur in the posterior fossa and brainstem. Developmental venous anomalies (about 70% of all malformations) are thickened, dilated veins, felt to represent an anomalous fetal development. They can be superficial, deep, or both. They are associated with cavernous malformations in a minority of cases, but when they are this raises the risk of subsequent hemorrhagic events (Topper et al., 1999).

61.3.1. Clinical presentation

Most arteriovenous malformations are asymptomatic until they rupture, when they typically present with a sudden severe headache, focal deficits depending on the location of the hemorrhage, or coma (Fig. 61.2). More than 50% of patients with arteriovenous malformation present with a hemorrhage (Hofmeister et al., 2000). Observational studies estimate a risk of rupture ranging from 1% to 4% per year (Crawford et al., 1986). However, in patients who have already experienced a hemorrhage, the risk of rehemorrhage is 6–18% per year. Other factors associated with an increased risk of hemorrhage are a history of hypertension, presence of an associated aneurysm, deep venous drainage, deep location, small nidus size (<3 cm), high feeding artery pressure, slow arterial filling, and venous stenosis (Fleetwood and Steinberg, 2002), as well as patients with larger, deep arteriovenous malformations (Stephani et al., 2002). Hemorrhages can be intraparenchymal, intraventricular, or subarachnoid. The risk of hemorrhage is increased if aneurysms are present, as these are commonly the source of hemorrhage.

Short of rupture, arteriovenous malformations can present with progressive focal neurological deficits or seizures. Seizures occur in approximately 30% of

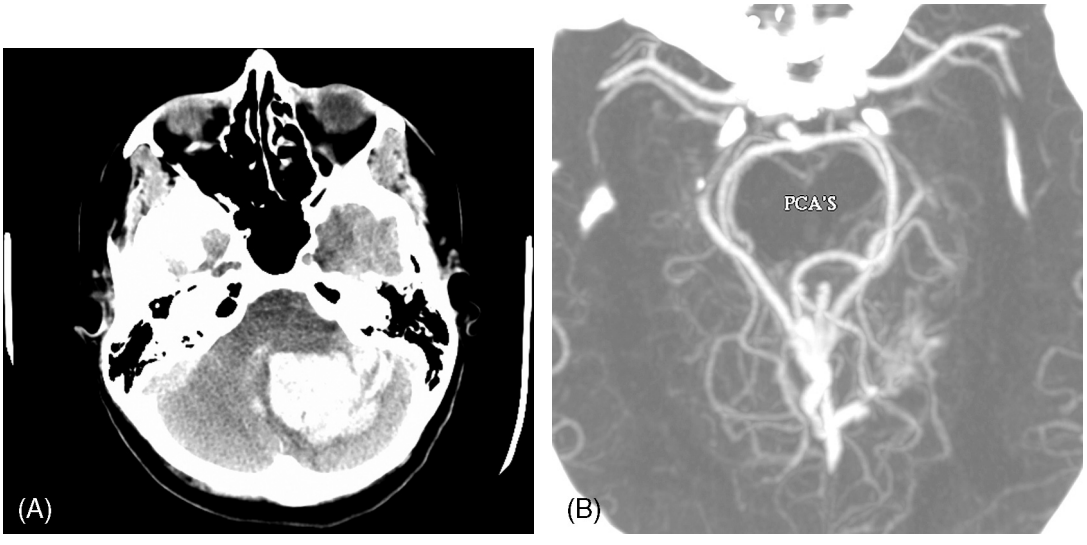

Fig. 61.2. Arteriovenous malformation. A 32-year-old woman, 17 weeks pregnant, developed a sudden severe headache. (A) Non-contrast head CT shows an intraparenchymal hemorrhage in the left cerebellar hemisphere. (B) CT angiogram reconstruction reveals an underlying arteriovenous malformation.

patients (Hofmeister et al., 2000), more commonly in younger patients. The location directly correlates with the risk of seizures, as cortically based lesions (especially frontal or temporal) carry a higher risk. Focal deficits are more common with lesions adjacent to eloquent areas, such as the motor strip, or infratentorial lesions due to mass effect. Obviously, patients with a prior hemorrhage may be left with a residual deficit.

Cavernous malformations most commonly present with seizures, but may also have focal neurological deficits as a result of the hemorrhage (Fig. 61.3). The hemorrhage rate with cavernous malformations is estimated to be 1–5% (Kondziolka et al., 1995; Maraire and Awad, 1995), but most hemorrhages are small and are usually only life-threatening if situated in a crucial area, such as the brainstem. Most cavernous malformations remain asymptomatic. Developmental venous anomalies are also typically silent, incidental findings, but can be associated with seizures or venous outflow problems (Fig. 61.4). When developmental venous anomalies are associated with hemorrhage, it is usually because there is an associated cavernous malformation, which occurs between 8% and 33% of the time. Capillary telangiectasias are of little clinical consequence, and are typically an incidental finding.

61.3.2. Management

In arteriovenous malformation patients who have had a rupture, surgery is typically delayed if possible so that the entire lesion may be better visualized, the brain

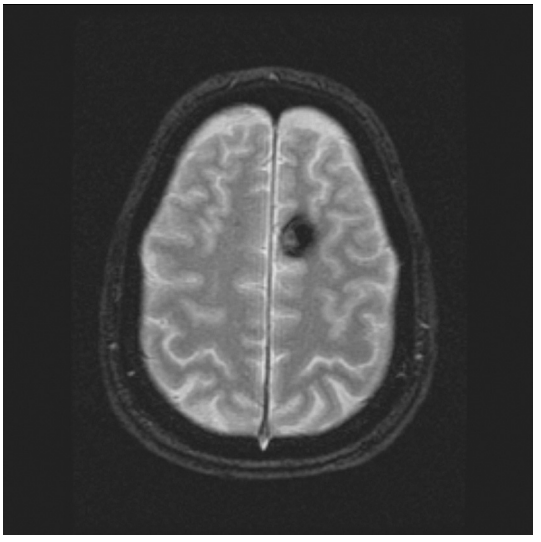

Fig. 61.3. Cavernous malformation. A 45-year-old man presented with personality changes and headaches. A susceptibility-weighted MRI shows a left frontal cavernous malformation.

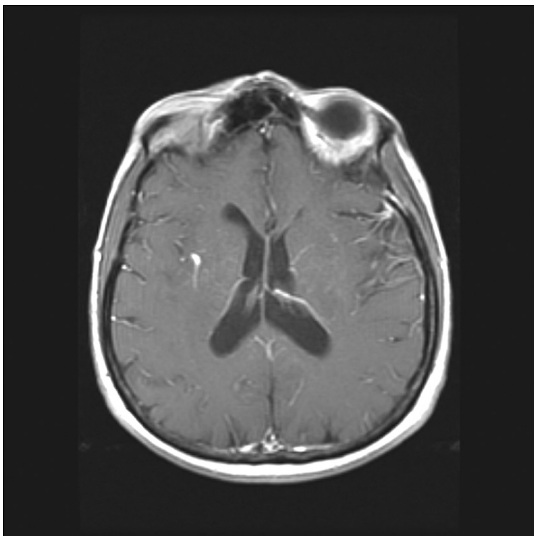

Fig. 61.4. Developmental venous anomaly. Brain MRI with gadolinium shows a right basal ganglia DVA. This was an incidental finding.

becomes less edematous, the patient becomes more clinically stable, and the lesion may undergo preoperative embolization. However, acute surgery may be required if the patient is clinically at risk due to the size of the hemorrhage, or if the lesion is infratentorial, given the risk for herniation. If there is significant intraventricular blood, a ventricular drain may be required, and if there is significant subarachnoid blood, the patient may be at risk of vasospasm.

The goal of treatment, whether it be surgical, endovascular, or radiosurgical, should be obliteration of the lesion; if some of the lesion remains, the risk of hemorrhage remains, and may even be increased due to changes in the flow dynamics of the lesion. Surgical treatment is preferable if possible, but factors to consider include the size of the lesion, the location, the type of lesion, and the age of the patient. The Spetzler and Martin grading scale (Spetzler and Martin, 1986) (Table 61.4) assigns the risk for surgical resection of a lesion, taking into account the size, location, and pattern of venous drainage (deep versus superficial). Small, superficially draining lesions in a non-eloquent area carry the lowest risk for surgical treatment, whereas larger lesions in eloquent areas with deep drainage carry the greatest risk.

Endovascular techniques have greatly enhanced the ability to provide curative resection of arteriovenous malformations, and can obliterate the lesion in up to 11% of patients, or significantly reduce the size of the nidus (Gobin et al., 1996). A number of embolic agents and devices are being explored in the treatment of arteriovenous malformations, but long-term efficacy data is lacking. Factors involved in the success of

Table 61.4

Spetzler–Martin grading scale for arteriovenous malformations

Graded feature		Points assigned
Size of arteriovenous malformation		
	Small (<3 cm)	1
	Medium (3–6 cm)	2
	Large (>6 cm)	3
Eloquence of adjacent brain		
	Non-eloquent	0
	Eloquent	1
Pattern of venous drainage		
	Superficial only	0
	Deep	1

endovascular therapy also include the anatomy of the lesion and the amenability of the approach based on the feeding vessel anatomy. Potential complications of endovascular therapy include hemorrhage due to changes in the outflow pattern, ischemic stroke, arterial dissection, and incomplete treatment, and the complication rates increase with the complexity of the lesion.

Stereotactic radiosurgery is also a potential treatment option, and is typically performed in smaller lesions felt to be at high risk from a surgical or endovascular standpoint, or due to patient preference. It involves a focused high dose of radiation to a defined specific region. This causes injury to the vascular endothelium, leading to smooth muscle proliferation, increased vascular stenoses, and hopefully obliteration. This process takes time, however, and during the 1–2 years it takes to achieve obliteration, the hemorrhage risk persists. Several methods exist, including the "Gamma knife," which uses gamma rays concentrated in a focal manner by means of a helmet (Shin et al., 2004); linear accelerators, which use accelerated electrons to penetrate into the lesion (Scarbrough et al., 2005); and proton beams, which are also accelerated into the lesion, with the advantage of being able to focus at a particular depth, thereby reducing the risk of damage to adjacent tissue (Silander et al., 2004).

There are reports of spontaneous regression or obliteration of arteriovenous malformations, but this is a rare occurrence (Buis et al., 2004). Some lesions are not safely amenable to any therapy, such as Spetzler–Martin grade 5 lesions in the basal ganglia or thalamus, most intrinsic brainstem lesions, and elderly patients with more difficult lesions.

In terms of the other vascular lesions, these usually do not require treatment. Cavernous malformations that are associated with seizures are commonly treated with anti-epileptic medications, but may require surgical resection if the seizures are refractory, or if the hemorrhages are recurrent or are causing significant deficits. Developmental venous abormalities are most typically benign, and should only be considered for surgery if there is a symptomatic associated cavernous malformation, as above. Capillary telangiectasias are benign and do not require treatment.

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Chapter 62

Methodology of acute trials in stroke

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62.1. Introduction

Clinical trials are a tool of modern medicine used to establish evidence for therapeutic interventions. Years ago therapeutic strategies were developed based on personal experience and intuition of a limited number of medical practitioners. This concept of truth finding works only in very simple models, such as the repositioning of a dislocated shoulder for example. However, in complex pathophysiological conditions such as cerebrovascular disease it is more difficult to prove safety and efficacy of medical strategies, pharmaceutical or interventional.

The design of clinical trials in cerebrovascular disease, like any other condition, is separated into four stages (phases) (http://www.Ida.gov). The pivotal phase proving clinical efficacy is phase III. However, well-designed earlier stages are needed to guide the design of the usually much larger and more expensive phase III trials. The resources needed to complete a phase III clinical trial are so vast that a limited number of scientifically well-founded questions must be answered using the available resources.

Despite an impressive international effort through governmental and private organizations over the last decades, only a few new therapeutic strategies for stroke in men have been discovered (Kidwell et al., 2001). This chapter will review strategies used in the development and execution of clinical trials and help explain why trials may have failed to reveal well-founded evidence and how future trials can be designed to better find new treatment modalities.

62.2. Preclinical phase

The goal of the preclinical trial phase is the search for a compound or therapeutic concept, using cell cultures and animal data (Zivin and Grotta, 1990). In addition to the therapeutic concept, this phase examines early safety data, side-effects, and dosing regimens. It establishes the optimal mode of delivery, per oral or intravenous and schedule (bolus versus infusion for example).

New concepts or ideas can come from innovative biological ideas, which are rare, such as the use of proton pump inhibitors in gastric disease. Nobel prizes are often awarded for such discoveries. Other sources are new animal models, as seen after the development of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) using monkeys for Parkinson's disease (Burns et al., 1985), which led to the development of new chemical compounds through testing strategies not possible without non-human models. Sometimes new biological or chemical compounds are synthesized and introduced as therapeutic medications. These are often similar to existing drugs but have better side-effect profiles. Other strategies for the development of new medical treatments include modifications of older drugs or chemicals, which is often done to extend patent protection for existing therapies; new use of old drugs, as seen in amantadine, which was first used against influenza and later on found to aid Parkinson's patients (Monto et al., 1979); and adverse reactions to old drugs.

The most prolific and widely used way to find new therapeutic compounds over the years has been through random screening. Many companies and agencies have

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access to compound libraries, in which millions of chemical and biochemical agents are kept and screened using receptor and cell culture arrays. Once a compound or treatment strategy is identified through any of these mechanisms it is further tested in cell culture and animal models. These tests are crucial in the understanding of a compound mode of action and potential safety profile. However, strategies successfully used in cell culture or animal model often cannot be transferred to human treatment. Major reasons for failure of clinical trials based on promising preclinical data are discrepancies between the preclinical model and human disease.

These discrepancies often involve the treatment window, and many neuroprotective trials have failed because the experimental efficacy was only proven in preclinical trials using the compound prior to the insult or immediately afterwards. During human studies the drug could not be delivered within the time it was proven efficacious in preclinical experiments and failed to show benefit in patients. We now know that neuroprotective agents are effective for at least 3 hours after artery occlusion (Zivin, 1998; Grotta, 1999). However, many clinical trials have used far longer treatment windows, as long as 6–48 hours. Laboratory data has shown that cell death is initiated within minutes of vessel occlusion and may not be reversible within minutes (Jones et al., 1981).

A second discrepancy is premorbid condition. Most animal research is done in young and previously healthy animals, while human stroke occurs mostly in the elderly with multiple medical comorbidities (Demchuck and Buchan, 2001). A drug with neuropsychiatric side-effects, for example, may be used safely in young, healthy subjects, but might cause severe behavioral changes in the elderly. Some neuroprotective trials involving NMDA receptor blockers failed partly because elderly stroke victims could not tolerate the medication, which had caused only minor side-effects in young animals and healthy human volunteers.

Third, drug-dosing schedules used in preclinical trials may not always be safely transferred to human studies. To avoid toxicity, some trials have used a significantly lower dose than that shown to be efficacious in animals. On the other hand, many animal studies used prolonged infusions of compounds while subsequent clinical trials used single bolus infusions.

Another issue of discrepancy between preclinical and clinical trials is the way outcome and functional status is assessed. Animal studies often use histological outcomes. However, regulatory agencies generally require clinical trials to measure outcome by neurological function such as the NIHSS (National Institutes of Health Stroke Scale) or modified Rankin Scale (mRS). A compound proven to reduce infarct size in an animal may not show benefit in clinical outcomes, since infarct volume correlates poorly with functional outcome. Functional assessment in animals is usually limited to simple tasks of limb pacing, and beam and grid walking, while many outcome measures in clinical trials assess social function and activities of daily living. The Barthel Index (BI) focuses on patients' activities of daily living, while NIHSS and mRS assess global changes in activity.

The anatomical differences between humans and animal models may be an important discrepancy causing failure to translate preclinical to clinical data. Most animal models of stroke use middle cerebral artery occlusion, but patients in clinical trials may suffer strokes in diverse brain regions. Rodent brain consists of 90% gray matter; human brain of 50% (Zhang and Sejnowksi, 2000). Damage to white matter plays a larger role in human stroke and may limit the value of interventions primarily targeting gray matter (Dewar et al., 1999).

Obtaining good preclinical data is the foundation of all clinical trials and the data must be considered in light of its applicability for use in humans. It is not helpful to find a compound that reduces stroke size in animal models, but requires prestroke use or shows highly toxic side-effects that would not be tolerated in human stroke victims.

62.3. Phase I

The goals of phase I are defining the choice of drug dose and initial investigation of a therapy's safety in humans. This phase is the first involving human subjects. Initially healthy volunteers are often used to examine safety, tolerability, and pharmacokinetics. Usually, patients are then included in phase I studies, but the outcome measures should reflect concerns of safety not efficacy.

In stroke trials, the safety concerns often relate to risk of hemorrhage, worsening of the stroke, and cognitive and metabolic side effects. In ischemic stroke, some therapeutic strategies target recanalization. Thrombolytic and other revascularizing strategies such as mechanical recanalization all carry a risk of intracranial and systemic hemorrhage. Neuroprotective agents carry a risk of cognitive, cardiac, hepatic, and nephritic toxicity.

One major hurdle in a phase I study is the determination whether the incidence of certain serious adverse events (intracranial hemorrhage, pneumonia) is above the level expected for a given patient population. In stroke patients the severity of the initial stroke correlates strongly with outcome and the occurrence of adverse events, death, intracerebral hemorrhage, and pneumonia (NINDS, 1997). The NIHSS scale is often used as a measure of initial stroke severity. The score

varies from 0 to 42, with higher scores reflecting more severe deficits. Patients with a NIHSS >20 have a 17% risk of symptomatic intracerebral hemorrhage; patients with a NIHSS ≤ 20 a risk of $\leq 5\%$. Phase I studies involving patients with severe strokes are expected to have a higher rate of symptomatic intracerebral hemorrhage than studies enrolling mildly affected stroke patients (NINDS, 1995).

The design of phase I studies should focus on stopping rules based on substantial deviations above the expected rate of death or symptomatic serious adverse events for the population under study. Comparison with previous studies with similar related design and similar populations can be helpful in planning the projected sample needed to assess the safety of a given technique. For some interventions designed to improve the safety profile, the expected rate from previous studies might be unacceptably high and the stopping rule might be based on a lower value. Rigid prespecified stopping rules can unfairly stop therapy development prematurely, so often data monitoring and safety boards who are independent from the clinical investigators make these decisions after looking at all of the data collected up to that time.

62.4. Phase II

While phase I is designed to identify safety concerns and establish a range of dosages deemed safe in human studies, phase II includes early controlled clinical studies to obtain preliminary data on the effectiveness of a drug or medical intervention. This phase of testing helps determine common short-term side-effects and risks. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people. The primary goal is to develop a protocol that will be successful at phase III.

Most mistakes in past trials were made in this phase. A therapeutic concept is often rushed from phase I to phase III. Promising therapeutic ideas may fail to show benefit in phase III studies if the sample size was not well calculated or dosing regimens not carefully evaluated in preliminary phase II trials. The cost, both in human resources and finances, is usually vastly larger for phase III trials than phase II. Therefore most therapeutic concepts will only be tested in a limited number of phase III trials. Preparation for this phase through earlier stages assures that one gets it "right." Phase I and II studies help screening out therapies that may not be taken to phase III and provide data needed to develop sample size estimates for a phase III pivotal trial.

Additionally, phase II trials are used to seek out the optimal study end-points, which are reproducible, valid, clinically meaningful, and resistant to bias (Broderick et al., 2000). Most end-points are validated clinical outcome measures, such as the mRS or NIHSS. However, some phase II studies have used non-clinical endpoints, such as surrogate outcomes that were anticipated to correlate with important clinical results.

The use of appropriate surrogate markers allows us to find suggestions of therapeutic efficacy in a smaller sample size or with shorter follow-up time. Radiological variables are used as surrogate markers in cerebrovascular disease. The three most common radiological markers are: (1) arterial patency on cerebral angiogram; (2) lesion size on CT or MRI; and (3) diffusion-weighted MRI (DWI) and perfusion-weighted (PWI) mismatch. The last relies on a recently developed concept, assuming that PWI affected tissue surrounding the DWI core represents areas of decreased cerebral blood flow with the potential for tissue preservation (Warach et al., 1996; Barber et al., 1998; Albers, 1999; Darby et al, 1999). Assuming the validity of this idea, one could use the preservation of PWI-affected tissue from converting into DWI as a marker of arterial blood flow restoration and/or neuroprotective efficacy (Schlaug et al., 1999; Warach, 2001). The Desmoteplase in Acute Stroke (DIAS) trial using a novel thrombolytic within 9 hours after ischemic stroke used the DWI/PWI mismatch as surrogate marker to test the hypothesis that this mismatch represented potentially viable brain tissue (Hacke et al., 2005). More recently introduced serological markers for stroke such as neuron-specific enolase, S-100, thrombomodulin, and so on, are in the early phases of testing (Lynch et al., 2004).

Surrogate markers should truthfully reflect or highly correlate with outcome that matters to the patient (Fleming and DeMets, 1996). Arterial patency on cerebral angiogram matters to the patient only if functional outcome is improved. Lesion size on a 30-day CT does not correlate well with neurological status, because small strokes in the brainstem can cause much more profound deficits than larger cortical ones (NINDS, 2000). Additionally the patients' sociological and premorbid status determines what impact a stroke has on life. A concert pianist's life will be dramatically changed by a small stroke affecting the dexterity in his hand, while a similar stroke may only mildly affect a retired landscaper. The complexity of cerebrovascular disease makes it difficult to correlate one aspect of the pathophysiological concept with clinical function.

Occasionally, hybrid phase II and III trials are conducted. Such a phase IIb trial may incorporate a dose-finding portion, but include a sufficient number of subjects to detect efficacy. This concept is very popular in the pharmaceutical industry, because it has the potential to advance a compound to market approval

rapidly. However, phase IIb trials fail many times because the dose finding is not done carefully enough, and without preliminary efficacy data the power analysis underestimates the number of subjects needed to show benefit.

62.5. Phase III

Phase III of a clinical trial is the pivotal step in finding proof of efficacy of the tested medical or interventional procedure. The sample size is calculated based on the expected effect of the intervention (Bland, 2000). The magnitude of this effect is usually based on historical experience and earlier trial phases. To calculate the sample size one uses statistical power analysis which indicates how many subjects need to be studied to detect a treatment effect or safety concern. Many phase III trials fail because they are underpowered. For example, a neuroprotective trial with 200 subjects in a placebo-controlled double-blinded study may only be able to detect a relative treatment effect of larger than 30%. However, many therapeutic interventions affect stroke outcome to lesser degree. Although this neuroprotective trial may have reduced bad outcomes by 25%, using such an underpowered study might have produced an inconclusive result.

As discussed earlier, proper use of outcome measures contributes greatly to the success of phase III trials. Success in a well-designed clinical trial should not only mean finding a positive answer, but answering the question definitively. Earlier neuroprotective trials were underpowered or showed other design flaws and although the results of these studies were negative, the statistical power was insufficient to role out a type I error and the medical community may have missed promising therapeutic interventions for stroke (Davis and Donnan, 2004). More recent trials with better statistical design, although still producing negative results, were sufficiently powered to probably reject a hypothesis (Lees et al., 2000 ; Lyden et al., 2002). Even a negative trial can give important clinical information and finding that a therapy does not improve patient outcome is important information.

In a separate, but equally important matter, the study population should closely represent the general patient population and clinically relevant outcome measures should be studied. Some trials have included a highly selective patient population. Results of these studies could only partially be applied to routine patient care. For example, if a stroke study excludes patients with comorbid conditions, but most stroke patients who present to a general practitioner additionally have arterial hypertension and other conditions, the results of such study may not be applicable to the majority of the patients. Trials for the prevention of stroke related to atrial fibrillation have excluded patients with cardiac comorbidity or age above 75 (SPAF, 1991). Since atrial fibrillation is most common in the elderly and many patients suffer from cardiac comorbidities, the study results were not applicable for the majority of patients, and subsequent studies had to be completed to include more common patient populations (SPAF, 1996).

Safety and data monitoring throughout the trial is important to avoid harming patients. Some trials found serious safety concerns and were aborted to avoid harming more patients. Fewer found such dramatic treatment effects that continuing a controlled trial was deemed unethical.

Outcome measures or end-points for efficacy in phase III trials should be based on the selection of end-points from phase II studies as well as previously performed similar phase III studies, if available. In contrast to a phase II study, wherein one wants to rule out potentially ineffective treatments with the smallest number of patients possible, the purpose of phase III studies is to demonstrate a clinically significant efficacy (generally functional long-term outcome), easily recognized by physicians as well as patients. Phase III studies often contain many ancillary secondary end-points, including imaging end-points. If these secondary end-points are all positive and in the same direction as the primary end-point, then they can greatly strengthen the results of a study. However, these secondary end-points alone are generally not sufficient to demonstrate efficacy as determined by regulatory agencies.

Most trials in stroke use clinical outcome scales as primary outcome measures. These include neurologic impairment scales, disability measures, and handicap scales. Examples of neurologic impairment scales include the NIHSS (Brott et al., 1989), Canadian Neurologic Scale (Côté et al., 1989), and Scandinavian Stroke Scale (Lindenstrom et al., 1991). These scales might be sensitive to change and have the greatest capacity to differentiate between treatment groups, making them particularly useful for phase II studies. Disability and handicap scales include such scales as the BI (Mahoney and Barthel, 1965), mRS (van Swieten et al., 1988), and the Stroke Impact Scale (Duncan et al., 1999). Handicap and disability scales are generally not the primary outcome measures in phase I and II trials but should always be included in these earlier studies to provide information used in designing the phase III trial and to provide data for comparing the new treatment to previous studies. Scales assessing the quality of life after stroke, such as the EuroQol (Brooks, 1996), have found little use in phase III stroke studies. These scales are so variable that they are not useful as end-points.

Most treatments influence multiple aspects of stroke impairment, such as motor function and cognition. Outcome measures should reflect the multiple dimensions of post-stroke impairment. However, no single scale is weighted equally across all neurological findings and when planning and analyzing clinical trials, one has to consider that some outcome measures are affected mostly by motor function, while others are affected more by memory and mood. If the treatment is expected to influence only one aspect of post-stroke impairment, the primary outcome measure for the phase III trial might be chosen accordingly. Although one outcome might be chosen as primary, it is also important to collect data on outcomes describing the multiple dimensions of post-stroke impairment so that the full range of treatment benefit and harm can be understood and compared with previous studies. Currently, the most successful long-term, functional end-point has been the modified Rankin scale (Young et al., 2003). The NINDS trial, which randomized acute stroke patients within 3 hours to receive placebo versus intravenous tPA, was first and many followed analyzing the results in a dichotomized fashion, defining good outcome as a score of 0 or 1 and poor as higher (NINDS, 1995).

Comparing the trial end-points between similar studies in thrombolysis after acute ischemic stroke illustrates how the use of outcome measures affects the statistical success or failure of a clinical trial (Hacke et al., 1998; Furlan et al., 1999; Weir et al., 2004). Analyzing data from past clinical trials, one can calculate the sensitivity of different outcome measures, based on the sample size needed to show statistical benefit. Using the NINDS study data, an mRS of 0 or 1 in this trial would have revealed a difference between groups with only 91 patients in each treatment arm, an mRS of 0 to 2 required 212 per treatment arm to show a similar difference (Broderick et al., 2000).

The PROACT-II and ECASS-II studies were additional trials of thrombolytics and only showed benefit when good outcome was defined as mRS 0–2, but not 0–1. PROACT-II had prespecified end-point of mRS 0–2 and the published results were positive (Furlan et al., 1999), while ECASS-II used an mRS 0–1 as a prespecified end-point and the reported results were negative (Hacke et al., 1998). Only a post hoc analysis using mRS 0–2 in this study revealed a positive result. However, such post hoc analysis cannot disprove the null hypothesis and is therefore of limited value.

A more recent trial of surgery for intracranial hemorrhage has used a new approach and took the pre-existing neurological deficit into consideration. The outcome measure was defined as change in mRS from baseline. If a patient entered with a mRS of 3 and remained at 3, the differential mRS was 0 which was considered good outcome (Mendelow et al., 2005). This outcome measure takes into account that many stroke patients have abnormal premorbid function and may be a more effective measure of treatment intervention.

In addition to clinical outcome markers, surrogate markers can be used in phase III trials. Some of the benefits and complications of the use of surrogate markers in clinical trials were presented earlier. In phase III trials they mainly serve as secondary outcome measures, while primary outcome remains measured by clinical scales (NINDS, 2000). Measurement of the volume of cerebral infarction with CT at 24 hours or at 3 months did not correlate well with the clinical outcome scales of the NINDS tPA Stroke Trial or the PROACT studies, and would not have shown a positive result if used as primary outcome measure. The trend of CT and clinical outcomes were in the same direction, but all clinical scales were more sensitive for treatment effect. The reasons for the relative lack of sensitivity of imaging, as discussed earlier, indicates the poor correlation between functional status and lesion volume.

Vessel patency may also not correlate with good clinical outcome. In the PROACT-I study, recanalization of the main middle cerebral artery, M1, and M2 segments 2 hours after initiating drug treatment was the primary end-point of the study and a surrogate marker for activity of the drug (Del Zoppo et al., 1998). It showed that IA recombinant pro-urokinase plus heparin was more effective in reopening the artery than heparin alone. However, the follow-up study, PROACT-II, revealed a potential downside of this surrogate end-point. Recanalization rates at delayed time periods did not correlate with clinical outcome if infarction had already occurred. Angiographic recanalization may be a helpful surrogate in studies of intra-arterial therapies. However, it might not be equivalent to demonstration of brain salvage and improved functional outcome, especially at later time-points. On the other hand, findings using surrogate markers can be used to create new experimental hypotheses. In some clinical trials the primary outcome was negative or inconclusive, but secondary outcome measures such as lesion volume or vessel patency was able to spur new ideas and guidance in the planning for future trials.

62.6. Post-marketing

The first three phases are completed before the drug or intervention is approved by the regulatory agencies. A later phase, often referred to as post-marketing surveillance is completed after approval. While even large phase III trials usually include a few thousand patients, in

post-marketing surveillance, data on millions of users can be collected and analyzed over a longer period (longitudinal).

Many medications, which were shown to be safe in phase I–III trials revealed rare but serious safety concerns in post-marketing surveillance. Examples for these are ticlopidine, natalizumab, valdecoxib, and rofecoxib. The side-effects were not apparent during phase III trials including thousands of patients. In some cases the findings of new safety concern led to withdrawal of licensure or restriction of approval. Currently, most market surveillance studies are voluntary, but regulatory agencies are making it mandatory. The larger-scale patient populations and use of the substance by the general public of healthcare providers is thought to show information about an approved drug's risks, benefits and best uses associated with "real-life" conditions.

62.7. Statistical approaches

Statistical analysis and the understanding of its calculation are vital when examining the results of clinical trials. Each well-designed trial should have one statistical hypothesis—the null hypothesis—which could be the following: the use of the new therapy does not improve outcome as measured as an mRS of 0 or 1 over the use of placebo. If the data are well balanced, and randomization and blinding are adhered to, a simple statistical test can be used to calculate the likelihood that the results of the trial wrongfully reject this hypothesis. In most studies it is assumed that a type I error of less than 5% indicates statistical significance.

In recent years, new statistical approaches have been proposed to increase the power of phase II and III studies. First, a global, clinical end-point, which is a statistical measure that uses two or more ratings, has been found sometimes to be a more powerful measure of drug efficacy than the individual end-points themselves. Part of the advantage of the global measure is that "there is no one perfect stroke outcome measure that measures all areas of clinical relevance." (Duncan et al. 2000). For example, a global outcome measure that was used in the NINDS tPA Stroke Trial looked at the effect of tPA across four related but separate clinical rating scales: the NIHSS score, the Rankin score, the BI, and the Glasgow Outcome Scale (GOS). In the NINDS tPA Stroke Trial, the global outcome measure was slightly more powerful than the individual end-points in this trial (Tilley et al., 1996). In retrospect, the global outcome method has been applied to other studies in stroke, which were negative as judged by their primary end-points and the new calculation showed positive results (Hacke et al., 1995). However, most global measures are based on clinical scores, which are not truly independent. mRS, NIHSS, BI, and GOS all depend on motor function for example and a high (poor) score on the NIHSS caused by decreased motor function produces a high score on the mRS as well. These measures are not statistically independent and when they are used in combination to create a global test score. This global score is at risk of amplifying any potential error in the values, which are represented in more than one of the scales. On the other hand, potential benefit from the intervention or medication can be amplified too (Tilley et al., 1996). It might be possible to combine findings on appropriate selected other outcome measures, such as images or blood tests, to produce improved global tests.

Another and more recently used statistical method in clinical stroke trials is the Bayesian approach of continuous learning (Berry, 2004). In conventional (frequentist) trial design, the information accruing during a trial remains untouched in a sealed database as the trial progresses (Berry, 2003). This approach assures blinding of treatment effect of all parties involved in a clinical trial until the database seal is broken. The Bayesian approach makes immediate use of newly acquired data during the trial. Each new data point is entered into the database and changes the probability of future occurrences. This can affect trial design such as allocation of patients to various dosage levels. For example in a phase II dose-finding trial, using this method, a dose tier can be abandoned once futility or safety end-points are reached so it is not necessary to wait until a prespecified number of patients is accrued. This can result in a markedly decreased number of subjects required for a drug development program because the trial may terminate early. However, since there is possible bias introduced by use of comparisons with historical controls, this design is most useful for phase II trials.

62.8. Study logistics

The logistics in conducting clinical trials are as important as planning and design. Even the best-planned research protocol is only as good as its logistical structure. In clinical trials careful selection of the most appropriate research facilities and clinicians is important (STAIR-II, 2001). The clinical trial may be planned and sponsored by academic centers or the pharmaceutical industry. Often academic research centers will seek funding through governmental agencies or through private sponsors within the pharmaceutical industry.

Although the industry could organize a clinical trial without outside assistance, the use of academic centers enables access to qualified clinicians and medical institutions, and lends credibility to an industry-sponsored

trial. While academic centers benefit from research freedom, high credibility, and independence from marketing restraints, they suffer from lower personal incentives to expedite research and the high level of bureaucracy plus organizational overheads, which are collected by the universities and may exceed 50% of the overall research grant.

The highest credibility is accorded to research projects funded through governmental grants. To obtain these grants the research plan and its creators are held to a high level of scrutiny. In the USA this is done through the National Institutes of Heath (NIH). NIH grants are often given to scientifically important projects, which are not sponsored by private industry because of low yield in potential financial gain. This way of research funding was vastly propelled in the late 1970s when the Baye–Dole Act regulated ownership transfer of intellectual property funded through federal research grants to universities and investigators (Abramson et al., 1997). However, NIH-funded research suffers from inflexibility, bureaucracy, and a lengthy decision process, involving multiple committees within the NIH and associated institutions. This often delays the phase from initial planning to first subject enrollment by years.

Many pharmaceutical companies have outsourced the organization of clinical trials to Clinical Research Organizations (CROs). CROs are independent from the sponsor, have medical expertise, know who the best and most productive investigators are, and know how to avoid poorly performing research sites. CROs are highly flexible and often specialized in one area of medical research. Some CROs are focused on stroke research and know how to establish quickly a network of well-trained and performing research sites, which enable a shorter lapse in time between planning and enrollment phase of a clinical trial. However, using a CRO is more expensive and may carry less credibility than trial organization through academic centers.

Besides deciding on who is organizing the trial and which research centers are used for subject recruitment, decisions have to be made if the study is best done at academic centers or community facilities and if the project can be completed locally or nationally, or requires international enrollment.

Before the research plan is finalized, applicable regulatory agencies should be contacted to help coordinate and unify study design. If the study is international, multiple national and international regulatory authorities should be involved and special consideration should be given regarding variations in practice patterns among countries. A trial clinical trial can suffer from discrepancies in referral and enrollment pattern between regions, which may create bias. Second, a study with mostly tertiary academic centers may have an enrollment bias much different from a study based in community clinics or hospitals.

Phase I and II clinical trials often require clinician teams with high levels of research experience able to address all expected and unexpected adverse events, while larger and pivotal phase III trials usually use academic and community centers. In order to capture a true-to-life patient population and receive regulatory approval for a broad use, referral and treatment bias should be kept to a minimum. This is usually obtained by a diverse enrollment site selection and patient population.

Once a trial design has been established, communication between sponsor and investigators at participating sites can be direct or through CROs. Most CROs employ medical specialists in the field of study and facilitate communication between the sponsor and investigators. A steering committee can help in the planning of a trial, but also improve the interaction between the sponsor and individual sites for issues related to study design and execution, safety, and interim data analysis. This committee most often consists of senior clinicians with research clinical trial experience, who all participate in the trial. The committee is involved in the trial oversight and gives credibility to the project, which in turn enables the recruitment of competent researchers into trial participation.

The sponsor, steering committee, and CRO try to assure good trial performance and data collection. The final trial result can only be as good as the data collected. Therefore data are collected from various sources and constantly monitored through CRO and sponsor to ensure accuracy and data security. Regulatory agencies may inspect the sponsor and research sites to assure patient safety and proper data collection, especially after pivotal phase III trials, which may lead to approval of a novel therapy.

In addition to the steering committee, which is involved in design and guidance throughout the clinical trial, an independent safety committee ensures that patients are not being put at excessive risk. The safety committee reviews adverse events occurring throughout the trial and monitors the study for any safety concerns, expected or unexpected. In cases of frequent adverse events and safety concern, the committee may temporarily halt enrollment, stop the trial, or suggest proceeding under an amended protocol.

62.9. Summary

Clinical trials are the backbone of evidence-based medicine. To understand the structure and pitfalls of trial design and conduction has to be part of modern

medical education. Clinical trials are conducted in phases and each phase has specific goals. The pivotal step to treatment approval is phase III. Post-marketing research and surveillance leads to the detection of low-frequency adverse events and can yield important additional safety information.

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Chapter 63

The future of stroke prevention by risk factor modification

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63.1. Introduction

Stroke is the most important preventable neurological disease of adult life (Gorelick, 1994, 1995, 1997, 2001a,b; Gorelick et al., 1999). Stroke is ideally suited for prevention as it is characterized by a high prevalence of disease, a substantial number of modifiable risk factors, therapies that have proven to reduce stroke risk, a high rate of disability, and a high economic burden. Observational epidemiological studies have led to the identification of risk factors for stroke, and clinical trials have established a robust armamentarium of preventions for first or recurrent stroke (Gorelick, 2005). During the past several decades our knowledge about specific interventions for stroke prevention such as blood pressure lowering, antithrombotic therapy, and surgical revascularization procedures for high-grade extracranial or intracranial cerebral arterial occlusive disease has grown significantly. Of the modifiable risk factors for stroke, hypertension is the most important. It is estimated that about 25% and up to almost 50% of strokes are attributable to hypertension (Gorelick, 2001a,b). However, although we have substantial evidence that blood pressure lowering results in reduction of first or recurrent stroke, we have not been successful in controlling blood pressure in the community or in individual patients (Gorelick, 2002). Blood pressure control in the USA population is estimated to be only 34% (Chobanian et al., 2003) and is less in many parts of the world. New public health strategies are needed to enhance blood pressure control at both the individual and population level.

Stroke prevention is undergoing a transformation. Bolstered by identification of new cardiovascular disease risk factors (e.g., hs-CRP, lipoprotein-associated phospholipase A2), new observations about the interrelationships of traditional cardiovascular risk factors (e.g., metabolic syndrome) and their management, and the development of new therapies to prevent or treat vascular risk factors (e.g., renin inhibitors, endocannabinoid system manipulation), and new and refined stroke prevention guidelines (Goldstein et al., 2006; Sacco et al., 2006; Buse et al., 2007; Mosca et al., 2007), we are well positioned for new advancements in stroke prevention. In addition, major legislative efforts in the USA and other parts of the world are leading the way for heightened awareness about stroke and improving the quality of stroke treatment, prevention, and overall care (Wattigney et al., 2003). Organization of stroke care, a centerpiece for the delivery of quality stroke treatment and prevention, has become a major focus in many parts of the world. Better organization of stroke care is likely to lead to better outcomes, for this often fatal or disabling disease. In this chapter we will explore future directions in stroke prevention. First, we will review some of the existing principles from which future advances in stroke prevention are likely to be based.

63.2. Traditional approaches to stroke prevention: the high-risk and mass approaches

63.2.1. Rationale for prevention

Why prevent stroke or other chronic disease one may ask? For these types of disease, the prevention process may be a laborious one with a long latency period until a definite effect may be observed. Without an immediate benefit it may be difficult for the individual, the community, and legislators who appropriate funds for disease prevention, to be willing to support such

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programs (Gorelick, 2001a,b). In general, health promotion and prevention programs have not been well funded. In the 1990s it was estimated that less than 5% of health care expenditure was spent on these types of programs, and local public health investment in essential public health services averaged only a dime per day in the USA (Atwood et al., 1997; Gordon et al., 1997). Physicians continue to be trained to care for the acutely ill, yet disease prevention may receive only relatively minor emphasis in the teaching curriculum. Interest in prevention, however, has occurred as an offshoot of increasing prosperity within society. Future health, healthy living, and healthy environment become important to persons who wish to enjoy their leisure time activities and avoid disability and premature mortality, especially in the latter years of life (Rose, 1994).

63.2.2. Approaches

There are two traditional and complementary approaches to chronic disease prevention: the high-risk and the mass approaches (Rose, 1994). In the example of stroke prevention, the high-risk approach seeks to identify people at heightened risk for stroke (e.g., people with multiple cardiovascular risk factors or substantial elevations in blood pressure or some other modifiable risk factor) and aggressively manage the risk factor or factors. Because the risk factor or factors are usually severe, medication is generally required to control the factors. This is the approach that may be taken by the clinician in an office setting as he or she screens patients to find those at high risk for disease based on the severity of the risk factor profile. When applied to a population, this approach may turn out to be an extensive and expensive case-finding exercise. Ironically, it may fail to identify those in the population who experience the majority of strokes. For example, in the case of hypertension, the majority of strokes do not occur among those with the highest level of blood pressure, but rather among those with more modest blood pressure abnormality (i.e., those that might not be detected by this type of screening process).

The mass or population approach, on the other hand, is geared to reduce the risk factor burden in an entire population rather than at the individual level, through health education, legislation, and economic measures that reduce or lessen exposure to the risk factors (Rose, 1994). This approach leads to more modest reductions of the targeted risk factor levels as lifestyle modification and allied measures are employed. However, this approach may lead to substantial benefits for prevention in the community at large. The irony of this approach is that while the community stands to benefit overall, the individual may not. Consider the high-risk individual who may require medication to control his or her risks. The mass or population approach may not be effective in this case as a lifestyle change may not be an adequate means of reducing risk in a person at high risk and who is in need of medication to control it. To overcome deficiencies of the high risk and mass approaches, the two are combined or used in a complementary manner. The mass approach is likely to have the greatest effect at the population level, whereas the high-risk approach is likely to have a smaller but complementary benefit on stroke prevention in the population but a substantial impact on stroke prevention at the individual level (Hankey, 2001).

Persons who are at immediate high risk for stroke are those who have had a recent stroke. Guidelines for recurrent ischemic stroke prevention have been updated recently and are reviewed elsewhere (Gorelick, 2002a, 2003; Albers et al., 2004; Sacco et al., 2006). The primary focus of this chapter will be future prevention of a first stroke (Gorelick et al., 1999; Goldstein et al., 2001, 2006).

63.3. Screening for stroke prevention: now and in the future

63.3.1. Principles of screening

Screening is a means to separate those with higher risk of disease from those with lower risk (Gorelick, 2001a,b). Those who screen "positive" are then referred to medical care for definitive diagnosis and treatment. Guidelines for screening have been established (Sackett et al., 1985). For screening to be an effective exercise, the following questions must be considered. Is the screening program judged to be effective based on high-level epidemiological evidence? If an effectiveness trial has not been carried out on a specific screening program, are there safe and efficacious therapies for the target disease or condition, and does the disease merit screening based on its public health impact? Is there a reliable, valid, and safe screening test? Is the screening program focused on those who may benefit from it? Is the healthcare system geared to accommodate the demands of the screening program? And, will those screened follow through with the advice and treatments that have been recommended?

Prevention efforts are believed by many to be most effective when screening and early intervention are carried out (Gorelick, 2001a,b). From the perspective of screening, risk factor modification is ideal when the factor is highly prevalent in the population; there is a substantial relationship between treatment of the risk factor and prevention of the target disease

or condition; and screening procedures are safe, valid and cost-effective. Early screening is advantageous as it helps to maintain an "upstream" position (i.e., before frank disease is manifest) rather than a "downstream" one where the ravages of disease may be observed. Our prevention paradigms are shifting more upstream from prevention of disease by identification and treatment of risk factors to primordial prevention (i.e., prevention of the risk factor).

63.3.2. Role of diagnostic technology

Diagnostic technology is often central to conducting a good screening program. The most important characteristics of diagnostic technology to those being screened are efficacy and safety. That is, does the test do what it is designed to do in a reliable and valid manner, and is it safe (Sox et al., 1989)? These characteristics are described under the following diagnostic technology rubric: technical capacity (the diagnostic test meets the standards of showing what it is expected to); diagnostic accuracy (true positive rate or sensitivity and true negative rate or specificity are combined to form accuracy or the true positive plus true negative divided by the total number of tests administered); and diagnostic and therapeutic impact (i.e., impact on diagnosis and management). When evaluating a diagnostic test, one must consider the gold standard to which the screening test is being compared. Have the screening test definitions been prospectively defined? Has the test assessment been done in a blind manner within a wide spectrum of disease and practice settings? And has validity been specified, and if so, how do other types of tests compare (Nuwer, 1992)? A diagnostic screening test that is not reliable and valid, and does not lead to a positive impact may have disastrous public health consequences.

63.3.3. Illustrative example: should we be screening for asymptomatic carotid artery stenosis?

Let us explore the application of a screening program in stroke prevention for the detection of asymptomatic carotid artery stenosis. Screening programs to detect asymptomatic carotid artery stenosis have again become popular as part of overall cardiovascular screening programs. Mobile units may be deployed to deliver the screening program to a target community or population. As part of these programs, carotid duplex ultrasound/Doppler ultrasound, ankle–brachial index measurement, and other diagnostic screening tests or procedures may be employed to define occlusive atherosclerotic disease within systemic vascular beds. Is this approach justified?

Carotid non-invasive blood flow technologies have been shown to be valuable diagnostic tests for detecting carotid artery stenosis with reasonable reliability and validity when diligently applied (Blakely et al., 1995). This specific technology may fail, however, to determine whether the extracranial carotid artery is 100% occluded or there is a very high-grade occlusion but the vessel is still patent, and when there is mid-level stenosis to determine whether the clinical trial thresholds for surgical intervention are met or not (Barnett and Meldrum, 2001). Furthermore, clinical trials have shown that there is only a modest benefit (an estimated absolute benefit for stroke reduction of about 1.2% per year) of carotid endarterectomy over medical management when there is at least 60% extracranial carotid artery stenosis (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995; MRC Asymptomatic Carotid Surgery Trial [ACST] Collaborative Group, 2004). In aggregate, cost-effectiveness models suggest that this approach may be useful as long as the prevalence of high-grade asymptomatic carotid stenosis is relatively high ($\geq$20%), the surgical risks are relatively low, and quality of life will be significantly impaired should a stroke occur (Lee et al., 1997; Obuchowski et al., 1997).

Unfortunately, the latter model assumptions for asymptomatic carotid artery stenosis may not hold for the population that is being screened. For example, application of the aforementioned diagnostic screening technology to detect carotid artery stenosis in a shopping mall or other mass venue where presumably there are healthy individuals, is not anticipated to yield a high percentage of those with asymptomatic higher grade carotid artery atherosclerotic lesions. Furthermore, there is a risk of false-negative test findings leading to a potentially risky procedure, conventional cerebral angiography. In addition, should there be higher grades of asymptomatic carotid artery stenosis and surgical intervention is recommended, does the surgeon who will perform carotid endarterectomy, for example, have adequate experience and excellent surgical results to meet expected standards when there is asymptomatic carotid artery stenosis (i.e., 3% cut-off point for surgical morbidity and mortality) (Gorelick, 1999)? One must keep in mind that relatively small increases in surgical morbidity and mortality associated with carotid endarterectomy in asymptomatic patients may lead to loss of any benefit from the procedure or even lead to harm associated with the procedure. These considerations influenced the Canadian Stroke Consortium to recommend against screening patients for asymptomatic carotid artery stenosis (Perry et al., 1997). Unless one can find a high-risk population for screening and low surgical risks associated with the intervention, the recommendation against screening for asymptomatic carotid stenosis is a propitious one (Gorelick, 1999).

63.3.4. Future screening: a voluntary national Internet-based program for chronic disease risk screening and prevention?

What does the future hold for screening in stroke prevention? Because many of the same risk factors for coronary heart disease are risk factors for stroke, future stroke prevention screening in a population or that which has been conducted traditionally at a doctor's office might be carried out off-site (e.g., in the comfort of one's home) via an Internet-based system as part of an overall voluntary cardiovascular risk assessment or cardiovascular-cancer risk assessment. Answers to questions that pertain to stroke-specific risk could then be automatically transferred to a stroke-specific screening instrument such as the one developed in the Framingham study (D'Agostino et al., 1994) or some other appropriate instrument, to calculate stroke risk. The calculated stroke risk could then be communicated back to the individual by email with an educational message and instructions on how to proceed in the screening system. The system would generate a "report card" (Gorelick, 1997) with stroke risk and prevention recommendations which the subject could share with his or her doctor as he or she seeks consultation with their respective physician. The goal would be to identify those at high risk so that appropriate stroke prevention measures could be carried out and to educate all users of the system about stroke prevention to maintain a stroke-free existence within the population of users. This voluntary system might become part of a national project for chronic disease prevention. Risk assessment and prevention feedback for coronary heart disease and major forms of cancer could be shared with the user in a similar manner. Support from legislators would be necessary to assure that the system could be developed and tested for feasibility and maintained. Stroke prevention messages to support the population or mass approach would be included in the "report card" educational format.

Should exploratory study show that the Internet-based screening program is effective and feasible, it might be adopted at a national level or adapted on a country-by-country basis as an international program. Overall, there has been a paucity of evaluation of global health interventions and evidence-based global health programs (Buekens et al., 2004). Too frequently, up-to-date evidence about the burden of chronic diseases is not available to policy makers and beliefs persist that chronic diseases afflict only the affluent and elderly by freely acquired risks and that control is ineffective or too expensive (Yach et al., 2004). These beliefs have led in part to a lack of financial support for prevention, treatment, and research of these diseases, especially in developing countries. A more concerted, strategic, and multisectoral policy approach is needed to help reverse these trends.

In addition, there remains an evidence-based gap between the introduction of clinical guidelines and the application of the recent evidence to patient care (Grol and Grimshaw, 2003). It has been suggested that to change behavior in the healthcare system, comprehensive approaches at different levels are needed. These levels include the physician, team practice, hospital system, and the wider environment. Better interventions to enhance adherence to prevention components, such as medication prescriptions, are needed (Haynes et al., 2002; McDonald et al., 2002). Financial incentives have been used in an attempt to increase prevention behaviors as motivators in the larger economic context of the health plan level, as provider incentives, and as consumer incentives to remove barriers, improve health education, and to reward healthy behavior (Kane et al., 2004). Further study of these potential synergies is indicated.

An obvious limitation of the aforementioned program is the need for and maintenance of sophisticated Internet-based technology and the provision of Internet access for the user. The majority of stroke deaths occur in developing countries which include some areas that do not have Internet-based resources or access, or general resources to carry out screening programs which satisfy the requirement to meet treatment and counseling needs of those screened.

Future stroke prevention will likely take advantage of genomic (Dominiczak and McBride, 2003; Gretarsdottir et al., 2003; Dwyer et al., 2004; Helgadottir et al., 2004; Lloyd-Jones et al., 2004; O'Donnell, 2005) and proteomic advances (Wilson, 2004) to select those at high risk and for novel therapies. This approach or "personalized medicine" (Christensen and Murray, 2007; Lupski, 2007) may be expensive at the population or mass level, and is therefore likely to be reserved for application at the individual level. Similarly, the identification of some subclinical markers that may predict stroke risk (e.g., intimal-medial thickness of the carotid artery, silent strokes detected by brain MRI) is likely to be employed at the individual level. Because of cost considerations, it may be necessary to limit such measures to the individual rather than the population. Fortunately, one of the most important predictors of stroke, blood pressure, is relatively easy and inexpensive to measure.

63.4. Future identification of those at risk: shifting the paradigm to a continuum of risk

Our conceptualization of cardiovascular disease risk is changing (Gorelick, 2002; Elkind, 2005). We now take into consideration not only traditional risk factors, but also novel risk factors (discussed in a section below).

In addition, determination of overall risk stratification helps to influence our prevention decisions (Radziszewska et al., 2005). Hypertension, the most important modifiable risk factor for stroke, is an excellent example of how our thinking has changed with regard to treatment of a factor in relation to the assessment of overall risk stratification. We now review how hypertension and other key-stroke risk factors are being impacted by this paradigm shift.

Not long ago, there was a debate about whether or not hypertension should be treated. The argument, that hypertension was a physiological adaptation and that it might be dangerous to lower blood pressure, was largely put to rest by a plethora of clinical trial results that showed blood pressure lowering to be beneficial for the prevention of a number of important cardiovascular disease outcomes (Chobanian et al., 2003; Moser, 2004). These studies showed that stroke reduction was one of the most important and consistent end-points reduced with treatment of blood pressure. Our knowledge of hypertension has advanced to the point that we now have age-specific data to suggest that systolic hypertension is important in the elderly and that diastolic or diastolic plus systolic hypertension is important in those who are younger.

63.4.1. Concept of a continuum of risk across blood pressure levels

Based on initial observational studies of the relationship of blood pressure level to stroke risk and initial clinical trials of blood pressure lowering, it was suggested that the relationship between blood pressure and stroke or other cardiovascular disease outcomes was a dichotomous one. That is, there was a threshold whereby elevated blood pressure (i.e., hypertension) led to the occurrence of stroke or other cardiovascular disease. With more extensive long-term study, however, the relationship has been clarified. Specifically, there appears to be a continuum of risk across blood pressure levels (Gorelick, 2002). Furthermore, although the relative risk of stroke is highest at the highest blood pressure levels, the highest absolute number of strokes occurs in the aggregate group of those with normal, high normal, and only mild hypertension (Joseph et al., 1998). Therefore, we now view blood pressure across a continuum of blood pressure risk levels rather than as a threshold effect (Gorelick, 2002). This concept is supported by two major studies showing that for both stroke risk and vascular (and overall) mortality risk, respectively, usual blood pressure is associated with a continuous risk without evidence of a threshold effect down to at least levels of 115/75 mmHg (Prospective Studies Collaboration, 2002; Lawes et al., 2004). Our newer conceptualization of blood pressure suggests that "high" blood pressure places one at risk, whereas "hypertension" denotes treatment of the condition with resultant benefit (Levy, 2005).

63.4.2. New definition proposed for "hypertension"

At the May 2005 20th Annual Scientific Meeting and Exposition of the American Society of Hypertension, a new definition was proposed for hypertension to reflect the more novel conceptualization of a continuum of risk based on blood pressure level; to acknowledge that hypertension is not a lone risk but rather one that may be accompanied by other risks (e.g., components of metabolic syndrome such as diabetes mellitus, lipid abnormalities, obesity); and to acknowledge that these other risks as well as associated bio-risk markers need to be taken into account when assessing overall cardiovascular risk in persons with hypertension (Giles, 2005).

How will the new definition and conceptualization of hypertension influence future stroke prevention and modification of other risk factors such as lipids or other factors that may display a continuum of risk in relation to stroke? The paradigm shift in our thinking about these factors will likely translate to lower guideline target blood pressure or other continuum of risk factor goals in stroke prevention. Also, more emphasis will be placed on the consideration of multiple risks, as might occur in metabolic syndrome, and their treatment rather than treatment of a single, isolated factor such as blood pressure. Given the relatively low control rates of major cardiovascular and stroke risk factors in the community at large, it is clear that we need to redouble our efforts and seek novel ways to implement control of blood pressure and other major risk factors (Gorelick, 2002).

63.5. Traditional risk factors for cardiovascular disease and stroke and the impact of these factors on stroke reduction

63.5.1. The importance of traditional (conventional) risk factors

Traditional risk factors are important antecedents in conferring risk for cardiovascular disease, and many of these factors are shared among the various cardiovascular diseases. Several recent studies have highlighted the important role of these conventional factors. For example, in the Chicago Heart Association Detection Project in Industry (CHA), Multiple Risk Factor Intervention Trial (MRFIT), and the Framingham Heart Study (FHS), three prospective cohort studies, the frequency of exposure to traditional coronary heart disease risk factors was assessed (Greenland et al., 2003). Specific factors studied

were total cholesterol (≥240 mg/dl or ≥6.22 mmol/l), systolic blood pressure (≥140 mmHg), diastolic blood pressure (≥90 mmHg), and history of cigarette smoking or diabetes mellitus. For fatal or non-fatal coronary heart disease, the presence of at least one traditional risk factor occurred in at least 87%. These findings have been replicated in another study (Khot et al., 2003).

Previously, it had been held that smoking, hypertension, diabetes mellitus, and hypercholesterolemia accounted for only about 50% of coronary heart disease risk. The above data certainly challenge this contention and suggest the importance of screening for traditional risk factors and redoubling our efforts to control them (Canto and Iskandrian, 2003). Similarly, in the INTERHEART case-control study of potentially modifiable risk factors associated with myocardial infarction in 52 countries representing every inhabited continent, nine risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity) accounted for about 90% of the population attributable risk in men and 94% in women (Yusuf et al., 2004). The authors concluded that approaches to prevent most premature cases of myocardial infarction could be carried out by similar principles worldwide.

63.5.2. Outcome with absence of traditional risk factors

Complementary to the findings from CHA, MRFIT, FHS, and INTERHEART studies regarding the presence of traditional risk factors, are the interesting results of CHA and MRFIT for persons without traditional risk factors in relation to their long-term outcome. When serum cholesterol (<200 mg/dl or <5.17 mmol/l), blood pressure (≤120/80 mmHg), and histories of no current cigarette smoking or diabetes, myocardial infarction, or ECG abnormalities in three of five cohorts were studied, individuals with a favorable risk factor profile (i.e., absence of the aforementioned risk factors) had lower long-term mortality and much greater longevity (Stamler et al., 1999). However, less than 10% of the cohorts were comprised of persons at such low risk. Table 63.1 summarizes the findings from these important studies about traditional risk factors or their absence in cardiovascular disease risk (Stamler et al., 1999; Greenland et al., 2003; Yusuf et al., 2004).

63.5.3. What are the conventional risk factors for stroke?

Table 63.2 summarizes non-modifiable and well-documented modifiable risk factors for stroke. Many of these factors are shared antecedents of coronary heart disease (e.g., hypertension, cigarette smoking, diabetes mellitus, and hyperlipidemia). Future efforts in stroke prevention will focus on the development of strategies that will lead to better control of these factors as clinical trials and other epidemiological studies suggest that control of many of these factors leads to significant reduction of stroke (Radziszewska et al., 2005). Novel risk factors (see section below) may play a role in future stroke risk assessment but need to be placed in the appropriate prevention context based on their attributable risk (Gorelick, 1994).

63.6. Novel cardiovascular risk factors and how they may impact on future stroke prevention

Atherosclerotic vascular disease includes coronary heart disease, cerebrovascular disease, and peripheral arterial disease (Hackam and Anand, 2003). Worldwide, atherosclerotic vascular disease is responsible for the majority of cases of cardiovascular disease, the leading cause of death and disability in many countries. Some patients have only mild elevations of the traditional vascular risk factors such as hypertension or hypercholesterolemia. While many patients with atherosclerotic vascular disease do have traditional risk factors, some present without these factors and thus stimulate the search for new or novel factors that might explain why they experienced an atherosclerotic vascular disease event.

63.6.1. Rationale for detection of novel risk factors

The search for novel risk factors is predicated on the following rationale (Kullo and Ballantyne, 2005). The ability to predict cardiovascular risk in an individual may be limited based on traditional risk factors. Residual variability in atherosclerotic vascular disease risk, for example, may be predicted by novel biochemical and genetic factors. Finally, the risk of cardiovascular disease may vary among different ethnic groups and novel factors may explain, at least in part, the variation.

When assessing the impact of novel risk factors, the clinician should be aware of the following issues (Manolio, 2003). Reported measures of risk should be adjusted for known confounders and indicate that the marker adds independent information of clinical importance. The measure should also account for a high proportion of the risk associated with the disease. The relative risk, for example, is a measure of the strength of association between the risk factor and the disease in a cohort study. Novel factors that have

Table 63.1

Summary of findings relating to the importance of traditional cardiovascular risk factors on conferring risk of coronary events

A. Antecedent major CHD risk factor exposures (total cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking and diabetes mellitus) in CHA, MRFIT, and FHS (Greenland et al., 2003)

1. For fatal CHD, exposure to at least one clinically elevated traditional risk factor occurred in 87–100%.
2. For those 40–59 years of age at baseline with fatal CHD, exposure to at least one major risk factor ranged from 87% to 94%.
3. For non-fatal myocardial infarction, prior risk factor exposure was observed in 92% of men and 87% of women in the age group 40–59 years.

B. Population attributable risk (PAR) of key risk factors for acute myocardial infarction in the INTERHEART case-control study (Yusuf et al., 2004)

Factor	**PAR**
Smoking	35.7%
Raised ApoB/ApoA	49.2%
Hypertension	17.9%
Diabetes mellitus	9.9%
Abdominal obesity	20.1%
Psychosocial factors	32.5%
Daily consumption fruits/vegetables	13.7%
Regular alcohol use	6.7%
Regular physical activity	12.2%

C. Risk of coronary heart disease and cardiovascular disease among low risk persons (serum cholesterol <200 mg/dl or <5.17 mmol/l, blood pressure $\leq 120/80$ mmHg, and no current cigarette smoking, history of diabetes mellitus, myocardial infarction, or electrocardiographic abnormalities in three of five cohorts) in CHA and MRFIT (Stamler et al., 1999)

Outcome	**Age-adjusted relative risk**	**Group**
CHD mortality	0.08	CHA men ages 18–39
	0.23	CHA men ages 40–59
Cardiovascular disease mortality	0.15	MRFIT men ages 35–39
	0.28	CHA men ages 40–59
All-cause mortality	0.42	CHA men ages 40–59
	0.60	CHA women 40–50
Outcome	**Years**	**Group**
Greater life expectancy	5.8	CHA women ages 40–59
	9.5	CHA men ages 18–39

high relative risk and are prevalent in the population, generally explain a high proportion of disease risk which is expressed as the population attributable risk. The measure should be reproducible and if it is a diagnostic test, it should be sensitive, specific, and have a high predictive value. Biological markers usually show a continuum of risk pattern such that risk increases as the level of the risk marker increases. Finally, the test measure should be available in clinical practice, and preferably be of low cost and easy to perform.

63.6.2. Risk factor classification

As we have been discussing previously, risk factors may be classified as traditional or conventional because these have a direct role in atherogenesis (Grundy et al., 1999; Kullo and Ballantyne, 2005). Examples of traditional risk factors include elevated blood pressure, diabetes mellitus, and elevated cholesterol. Predisposing factors are thought to mediate risk through other associated causal factors or independently and include such factors as male sex, obesity, insulin resistance, and physical inactivity. Conditional factors are associated with increased risk but their causative, independent, and quantitative contributions are not well documented. Homocysteine, Lp(a), C-reactive protein (CRP), and small LDL particle size are examples. Emerging factors include those that need further confirmatory study. Candidate gene polymorphisms are an example. Table 63.3 summarizes novel or conditional/emerging risk factors for cardiovascular disease (Boersma et al., 2003; Hackam and Anand, 2003; Kullo and Ballantyne, 2005). We will now focus on select conditional, novel, or emerging risk factors for stroke.

Table 63.2

Nonmodifiable and well-documented modifiable risk factors for stroke (Goldstein et al., 2001)

Nonmodifiable risk factors
Age
Race (blacks and Hispanics)
Sex (men)
Family history of stroke/TIA
Well-documented modifiable risk factors
Factor PAR
Hypertension 40% for 50-year-olds and 30% for 70-year-olds
Smoking 12–18%
Diabetes mellitus 14–58%
Asymptomatic carotid stenosis 2–7%
Sickle cell disease
Hyperlipidemia 25%
Atrial fibrillation 1.5% for 50–59-year-olds and 9.9% for 70–79 year olds

Table 63.3

Novel risk factors for atherosclerotic vascular disease (Boersma et al., 2003; Hackam and Anand, 2003; Kullo and Ballantyne, 2005)

Inflammatory markers
Lipoprotein-associated phospholipase A2 (Lp-PLA2 or PLAC)
C-reactive protein (CRP)
Interleukins
Serum amyloid A
Vascular and cellular adhesion molecules
Soluble CD40 ligand
Leukocyte count
Pregnancy associated plasma protein A
Chronic infection (e.g., *C. pneumoniae*, *H. pylori*)
Procoagulant/hemostasis/thrombosis markers
Homocysteine
Tissue plasminogen activator
Plasminogen activator inhibitor
Lipoprotein A
Fibrinogen
von Willebrand factor antigen
Factors V, VII, and VIII
D-dimer
Fibrinopeptide A
Prothrombin fragment 1 + 2
Platelet related factors
Platelet activity, aggregation, size, and volume
Lipid-related factors
Small, dense LDL
Lipoprotein(a)
Apolipoproteins A1 and B
HDL subtypes
Oxidized LDL
Other factors
Microaluminuria
Insulin resistance
Angiotensin converting enzyme genotype
APoE genotype
Psychosocial factors
Sleep-disordered breathing

63.6.3. Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Lp-PLA2 is a subtype of the phospholipase A2 super family. These are enzymes that hydrolyze phospholipids (Sudhir, 2000). Lp-PLA2 is upregulated in atherosclerosis and binds predominantly to LDL cholesterol. The main role of Lp-PLA2 in atherogenesis is the hydrolysis of oxidized LDL which produces proinflammatory atherogenic byproducts, lysophosphatidylcholine (lyso-PC) and oxidized fatty acids. Lyso-PC has several functions including a role as a mediator chemo-attractant of monocytes, impairs endothelial function, disrupts cell membranes and causes cell death, and induces apoptosis in smooth muscle cells and macrophages. Lp-PLA2 is believed to be a marker of vascular inflammation and may be a predictor of atherosclerotic plaque rupture. A large-scale epidemiological study has shown Lp-PLA2 to be a novel risk factor for coronary heart disease (Packard et al., 2000; Caslake and Packard, 2003; Ballantyne et al., 2004; Koenig et al., 2004). This effect appears to be independent of CRP, and Lp-PLA2 and CRP may be additive in terms of their ability to predict coronary heart disease. Previously, the US FDA approved an enzyme immunoassay for the quantitative determination of Lp-PLA2 in human plasma to be used with clinical data and patient risk assessment as an aid in predicting risk for coronary heart disease with atherosclerosis. More recently, the US FDA approved the Lp-PLA2 test for risk assessment in predicting ischemic stroke. The evidence for the added value of the Lp-PLA2 test for prediction of ischemic stroke comes from important, large-scale, cohort studies (Ballantyne et al., 2004a; Oei et al., 2005).

High levels of both Lp-PLA2 and CRP predict the highest risk for ischemic stroke (Ballantyne et al., 2004a). Therefore, Lp-PLA2 and CRP may be complementary beyond traditional risk factors (including non-HDL cholesterol levels below and above the median) for identification of middle-aged individuals at increased risk of ischemic stroke (Ballantyne et al., 2004a; Oei et al., 2005). Lp-PLA2 is a specific marker of vascular

inflammation that is relatively unaffected by such factors as body mass index (BMI), smoking, or age. It should be used as a risk marker but not as a treatment target until further study is carried out to determine outcomes associated with lowering of Lp-PLA2. Statins, fenofibrates, aspirin, and certain antihypertensive agents such as beta-blockers may lower Lp-PLA2 concentration. Lp-PLA2 looms as an important predictor of stroke risk, and possibly in the future as a predictor of reduction of stroke risk when the Lp-PLA2 concentration is lowered.

63.6.4. Inflammation

Ross (1999) popularized the idea that atherosclerosis is an inflammatory disease. With endothelial dysfunction there is an associated increase in adhesiveness of the endothelium with respect to leukocytes or platelets, increase in permeability, procoagulant instead of anticoagulant properties, and migration and proliferation of smooth-muscle cells. With continued inflammation there is an increase in the number of macrophages and lymphocytes which may activate and release hydrolytic enzymes, cytokines, chemokines, and growth factors which may lead to further damage to the vessel wall. These events set the stage of the development of atherosclerosis and plaque rupture.

The inflammatory hypothesis of atherosclerosis has led to a search for infectious and other inflammatory mechanisms that may trigger or lead to atherosclerosis and major cardiovascular events. Evidence to support the inflammatory hypothesis of atherosclerosis has been reviewed previously by Gorelick (2002a), Spence and Norris (2003), and Hansson (2005). The systemic inflammatory marker CRP and the vascular inflammatory marker Lp-PLA2 (see above section), leukocyte count, and other markers, organisms such as *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori*, periodontal infections, and history of recent infection have been implicated in this process (Engstrom et al., 2002; Van der Meer et al., 2002; Lindsberg and Grau, 2003; Magyar et al., 2003; Desvarieux et al., 2004; Grau et al., 2004; Pussinen et al., 2004; Smeeth et al., 2004). In fact, the use of influenza vaccination may be associated with a reduced risk of stroke (Grau et al., 2005). Further interventional studies, however, are needed to clarify this relationship. The use of antibiotic therapy such as azithromycin or gatifloxacin for the prevention of secondary cardiovascular events, on the other hand, has not been shown to favorably alter the rate of events despite long-term treatment (Anderson, 2005; Cannon et al., 2005; Grayston et al., 2005).

Future stroke preventive therapy may target specific factors involved in the inflammatory process such as metalloproteinases, adhesion molecules, the CD40/CD40 ligand system, and interleukins, or plaque stabilizing factors such as transforming growth factor-B1 as we continue to search for targets to prevent atherosclerotic plaque rupture or development (Axisa et al., 2002; Nuotio et al., 2003; Cipollone et al., 2004). Future randomized clinical trials are needed to determine the effect of commonly used drugs such as angiotensin receptor blockers, angiotensin converting enzyme inhibitors (ACE-Is) and statins to reduce inflammatory markers and the resultant risk of stroke. Dental hygiene, which may be linked to prevention of tooth loss and gum inflammation, may prove to be a future predictor of reduced cardiovascular disease risk. We await interventional studies to determine if this proves to be the case.

63.6.5. Metabolic syndrome

Metabolic syndrome defines a cluster of cardiovascular risk factors which are believed to be linked. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP Adult Treatment Panel [ATP] III) defines metabolic syndrome as the presence of three or more of the following risk determinants: (1) abdominal obesity (waist circumference for men >102 cm [or >40 inches] and for women >88 cm [or >35 inches]) (2) triglycerides ≥ 150 mg/dl; (3) HDL cholesterol for men <40 mg/dl and for women >50mg/dl; (4) blood pressure $\geq 130/\geq 85$ mmHg; and (5) fasting glucose ≥ 110 mg/dl (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The World Health Organization criteria are similar but have incorporated hyperinsulinemia (fasting insulin levels in the upper quartile of the non-diabetic population) as one of the components of the syndrome (Lakka et al., 2002).

Recognition of metabolic syndrome in cardiovascular disease risk assessment is important as risk factors for cardiovascular diseases may not occur in isolation but rather in clusters. Up until recently there has been a paucity of information about metabolic syndrome as it relates to stroke risk. In this regard, previous studies emphasized the role of insulin resistance as a prevalent risk factor for stroke and as one that could be modified for stroke prevention (Pyorala et al., 1998; Kernan et al., 2002), or other individual components of metabolic syndrome. Several studies have now addressed the issue of risk of stroke associated with the many factors that make up metabolic syndrome. Overall, the weight of the early evidence suggests that metabolic syndrome identifies persons at risk of ischemic stroke or transient ischemic attack (Boden-Albala et al., 2008; Koren-Morag et al., 2005; Milionis

et al., 2005). The contribution of metabolic syndrome will need to be taken into account when future screening and assessment for risk of stroke are carried out.

63.6.6. Sleep-disordered breathing

Many of us spend about 5–8 hours of our day asleep. Because sleep is generally a quiescent period, it has been more difficult to capture information about possible risks that might occur during this time period. Those of us who have fitful or noisy sleep may be at risk for stroke. A signal that this may be occurring, is sleep-disordered breathing (Mohsenin, 2001; Malhotra and White, 2002; McArdle et al., 2003; Shamsuzzaman et al., 2003; Tishler et al., 2003; Young et al., 2004; Caples et al., 2005). Sleep-disordered breathing encompasses reductions in airflow associated with upper-airway collapse or narrowing that occurs with the change from wakefulness to sleep (Caples et al., 2005). The apnea–hypopnea index may be used to describe and quantify this state. Apneas are defined as upper-airway collapse with nearly complete cessation of airflow associated with oxygen desaturation or an arousal from sleep. Hypopneas are defined as partial upper-airway collapse and make up the majority of sleep-disordered breathing events. Individuals with sleep-disordered breathing are prone to snore, and may have excessive daytime sleepiness (obstructive sleep apnea syndrome). It is estimated that the 5-year incidence of moderately severe sleep-disordered breathing is 7.5% and mild to moderate sleep-disordered breathing incidence is 16% or less. The incidence of sleep-disordered breathing is influenced by sex and age (predominance in men which diminishes with increasing age), BMI (increases with increasing BMI), and serum cholesterol level (a high level heightens risk) (Tishler et al., 2003).

How might sleep-disordered breathing influence cardiovascular or stroke risk? With sleep fragmentation there may be increased sympathetic activation, increased platelet aggregability, vascular endothelial dysfunction, increased oxidative stress, inflammatory response, metabolic dysregulation, altered cerebral autoregulation, and paradoxical embolism (Shamsuzzaman et al., 2003). Increase in food consumption may occur with sleep deprivation leading to increased consumption of calories and its attendant metabolic risks (e.g., hyperinsulinemia/insulin resistance, diabetes, overweight/obesity). Also, sleep-disordered breathing may be associated with hypertension, stroke, cardiac ischemia, congestive heart failure, and cardiac arrhythmias. In fact, with oxygen desaturation there may be atrial fibrillation or atrioventricular block.

Treatment of obstructive sleep apnea has proven to be beneficial. In a small clinical trial of medically-treated patients with heart failure, continuous positive airway pressure has been shown to reduce obstructive sleep apnea, daytime systolic blood pressure, heart rate, and left ventricular end-systolic dimension, and improve left ventricular ejection fraction (Kaneko et al., 2003). In an observational study, men with severe obstructive sleep apnea–hypopnea were at significant risk of fatal and non-fatal cardiovascular events, whereas continuous positive airway pressure treatment reduced the risk (Marin et al., 2005). Future studies are needed to clarify the epidemiological relationship, mechanism, and effect of sleep-disordered breathing and its treatment on stroke risk. This common problem with a relatively simple solution (continuous positive airway pressure) could prove to be an important factor in future stroke risk determination and prevention.

63.7. Organization of stroke care and the future of stroke preventive services

63.7.1. Rationale

Organization of stroke care promises to substantially reduce stroke morbidity and mortality (Gorelick, 2002b). We have learned in elementary chemistry class from the laws of free energy that disordered states (i.e., positive entropy) are the lowest energy states. By pumping energy into the system, the state can reach a higher energy level and achieve order. In the field of stroke prevention, an ordered or organized structure is preferable, and appropriate resources, good management, and vision are needed to ensure the delivery of high quality prevention and treatment services. Human and financial "energy" are needed to support this activity. Although stroke is highly preventable and treatable, barriers to stroke prevention and care exist based on availability of personnel, diagnostic technology, and programs (Ruland et al., 2002; Camilo and Goldstein, 2003).

63.7.2. Role of stroke centers

Modern stroke care is being organized around the concept of a stroke center (Alberts et al., 2000, 2005). The stroke center may be a "primary center" or a higher-level center, such as a "comprehensive center." Whereas the primary stroke center emphasizes acute stroke teams, stroke units, written care protocols, and an integrated emergency response system, the comprehensive stroke center adds healthcare personnel with specific expertise in a number of disciplines including vascular neurology and neurosurgery, advanced neuroimaging techniques, surgical and endovascular techniques such as clipping and coiling of intracranial aneurysms, carotid endarterectomy, and intra-arterial thrombolytic therapy, and other infrastructure and programmatic elements such as an intensive care unit and a stroke registry. Stroke centers

help to provide high visibility for recurrent and first stroke prevention at the community and individual levels. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), now called the Joint Commission, as well as some state departments of public health are now offering disease-specific primary stroke center certification (see website: www.jcaho.org). Ten stroke disease-specific care performance measures are the focus of quality improvement efforts in the Joint Commission system (Table 63.4), and the American Stroke Association "Get With the Guidelines Stroke Continuum Tool" is being employed at most of the stroke centers as an aid in the USA. The Joint Commission stroke performance measures have undergone revision and can be found on their website. Stroke center certifications coupled with the Paul Coverdell Acute Stroke Registry projects at the state level are providing the foundation for the development of future national and state stroke system initiatives.

63.7.3. Role of a "stroke system"

The American Stroke Association's Task Force on the Development of Stroke Systems has developed recommendations for the establishment of stroke systems of care (Schwamm et al., 2005). Table 63.5 summarizes the seven key components of the system. Primordial and primary prevention activities are included as one of the seven key areas. As we prevent risk factors from developing and treat risk factors to prevent disease in the community more successfully, we note improvements over time with regard to appropriate prescription of preventatives in older people (Jencks et al., 2003). Future stroke prevention programs will likely focus on support mechanisms to assist communities and providers in initiating preventatives applicable to the population; and support tools to assist the population as a whole, individual patients, and providers to achieve long-term adherence to primordial prevention and primary prevention regimens. The key to success will be the development of a systems' approach to stroke care.

Models such as the Five-Dimensional Health Improvement Model whereby evidence-based health improvement guidelines and epidemiological data are integrated to achieve intervention partnerships with the individual, healthcare provider, health system, employer and community, merit further exploration and study to determine their applicability, feasibility, effectiveness and cost to a large health system or the community at large (Tipton and Fleming, 2002). Gorelick (2001b) has reviewed previously published community-based cardiovascular prevention programs that have focused on risk factor reduction, maintenance of risk factor reduction, and surveillance of cardiac and stroke morbidity and mortality. Only modest program effects have been noted in community intervention or demonstration studies overall, and this has been attributed to contamination of the control communities with the intervention community message, insufficient sample size or insensitive outcome measures. Development of new stroke and chronic disease models are needed to help stem the gap between our evidence base and what is actually happening in the community with regard to control and prevention of cardiovascular risk factors (Favre et al., 2004; Wood et al., 2004).

Table 63.4

Joint Commission on Accreditation of Healthcare Organizations stroke-disease-specific care performance measures

1. Administration of deep vein thrombosis prophylaxis
2. Discharge on antithrombotics
3. Patients with atrial fibrillation receive anticoagulation therapy
4. Administration of tissue plasminogen activator (tPA) is considered
5. Administration of antithrombotic therapy within 48 hours of hospitalization
6. Lipid profile during hospitalization
7. Screen for dysphagia
8. Administer stroke education
9. Administer smoking cessation education/program
10. Consider a plan for rehabilitation

(Adapted from http://www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters/standardized_stroke_measure)

Table 63.5

The seven key components of a stroke system of care (Schwamm et al., 2005)

1. Primordial and primary prevention
2. Community education
3. Notification and response of emergency medical services
4. Acute stroke treatment, including the hyperacute and emergency department phases
5. Subacute stroke treatment and secondary prevention
6. Rehabilitation
7. Continuous quality improvement (CQI) activities

63.7.4. The challenge

Although the organization of stroke care makes good intuitive sense and is in concert with available data on its potential virtues, systematically collected outcomes examining public health benefits of primary stroke centers are needed (Goldstein, 2005). This type of health outcome research will most certainly be a feature of future stroke prevention efforts.

63.8. Future prevention strategies: is the polypill the answer?

The polypill strategy is a single pill containing six components (e.g., atorvastatin 10 mg or simvastatin 40 mg; three blood pressure lowering drugs [a thiazide diuretic, beta-blocker, and ACE-I] each at half standard dose; folic acid 0.8 mg; and aspirin 75 mg) designed to prevent heart attacks and strokes. Wald and Law et al. (Law et al., 2003, 2003a; Wald and Law, 2003) have suggested that this treatment be taken by everyone aged 55 years and older and everyone with existing cardiovascular disease, as it is a safe and effective prevention. They estimate that the polypill will reduce 88% of ischemic heart disease events and 80% of stroke events. Furthermore, measurement of blood pressure, cholesterol, and homocysteine may not be necessary. The polypill strategy represents a population or mass approach to cardiovascular disease prevention. The strategy has been challenged based on possible under-treatment of persons at the upper extreme of the risk profile and over-treatment of those at the lower extreme of the risk profile (Radziszewska et al., 2005). Furthermore, the approach remains intriguing but requires validation in a clinical trial.

Underlying the polypill strategy is an assumption that risk factors make poor screening tools based on conventional definitions of high risk factor levels. Specifically, 10% of the population with the most extreme values represent only about 20% of disease events. Yet risk factor levels represent a continuum, and treatment benefits are similar over a continuous range of risk factor values (Vasan et al., 2005). Using data from the Framingham study and the Third National Health and Nutrition Examination Survey (NHANES III), Vasan et al. (2005) showed that the polypill strategy might be inappropriate for several reasons: (1) about one-sixth of coronary heart disease events in men and one-tenth in women occurred before age 55 years; and (2) for women the 10-year absolute coronary heart disease event rate did not cross the 10% threshold (i.e., high risk), even when there were two coronary heart disease risk factors that were elevated. The authors concluded that the polypill strategy might merit consideration for men older than 55 years with an absolute coronary heart disease rate exceeding the 10% threshold given a single elevated risk factor. In an accompanying editorial, Mulrow and Kussmaul (2005) raise healthy skepticism about the polypill strategy according to the following considerations: (1) based on guidelines, most USA physicians feel obligated to treat higher levels of risk factors more intensively than borderline levels; (2) polypills for those at age 55 and older will not prevent cardiovascular disease events among those less than 55 years; (3) there is risk of side-effects among those treated and it may not make sense to put at-risk from side-effects those who are at low risk for disease events; and (4) the benefits and harms of a low-dose combination pill are unproven, and further testing is needed to verify the benefit/harm profile.

63.9. Conclusion

Future stroke prevention promises to open up new avenues for stroke risk reduction. Whether we are lowering treatment goals for risk targets along the continuum of risk, using genomics and proteomics to identify risk and to develop drug treatment strategies that are more likely to be beneficial in a given person, using intravascular ultrasound to detect carotid artery plaque burden (Nissen et al., 2004), or testing polypills for benefit/harm profile in appropriate populations, primary prevention strategies using the complementary population and high-risk approaches, which have largely gone untested in primary stroke prevention, need to be tested. The future of stroke prevention is likely to follow a pathway similar to the one developed by a recently held NINDS Workshop on Stroke Risk Assessment and Future Stroke Primary Prevention Trials (Radziszewska et al., 2005). Major directions for future stroke prevention as advocated in the workshop are summarized in Table 63.6.

Table 63.6

Future directions for stroke research: summary points from the NINDS Workshop on Stroke Risk Assessment and Future Stroke Primary Prevention Trials (Radziszewska et al., 2005)

1. Additional research is needed to accurately predict those at high risk for a first stroke, especially among high-risk minority populations.
2. Additional research is needed to validate MRI-based brain imaging and other vascular imaging to detect surrogate outcomes for testing interventions.
3. Relatively brief, sensitive, and applicable, standardized cognitive batteries need to be developed as vascular cognitive impairment is an important consequence of cerebrovascular injury.
4. Additional research is needed to determine the acceptability of interventions in at-risk populations before the interventions are rolled out to the at-risk population.
5. Reasons for failure to control modifiable and prevalent cardiovascular risk factors with well-established preventions need to be elucidated.
6. Clinical trials are warranted to study attractive potential treatments for primary prevention of stroke.

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Chapter 64

Antithrombotic agents for stroke prevention

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64.1. Introduction

Antithrombotic therapy is one of the fundamental medical approaches for prevention of brain ischemia. Antiplatelet and anticoagulant agents are the focus of intensive development efforts to identify novel compounds, as well as many large and complex clinical trials to test their safety and efficacy. Although these agents do not treat the underlying cause of stroke, which is typically vascular (i.e., atherosclerotic) or cardiac in origin, they can decrease the incidence of further sequela from both vascular and cardiac lesions. The efficacy of currently available antithrombotic agents is generally less than that obtained from aggressive reduction of primary risk factors for stroke such as smoking cessation, hypertension, and hyperlipidemia. It has been estimated that even modest reductions in blood pressure, obesity, cholesterol, and tobacco use would more than halve cardiovascular disease incidence, if these reductions were population-wide and simultaneous (World Health Organization, 2002). Once set into motion, however, these processes often lead to durable injury to underlying tissue, and remain an important risk for thrombosis, even if the underlying condition is removed or well controlled. In this setting, antithrombotic agents have their greatest utility.

Without question, antithrombotic agents prevent ischemic stroke. Their use in selected patients with specific indications provides cost-effective and safe stroke prevention. The primary cerebrovascular indication for antiplatelet agents is secondary stroke prevention; they prevent recurrent vascular events in patients who have suffered a prior ischemic stroke or transient ischemic attack (TIA). Oral anticoagulants are highly effective for both primary and secondary prevention of cardioembolic stroke from high-risk cardiac sources such as mechanical heart valves or atrial fibrillation. The prevention of ischemic stroke is best viewed as a multipronged effort which includes risk factor reduction, antithrombotic therapy, and surgical or neurointerventional procedures for selected patients. This chapter will focus on currently available antithrombotic agents that have demonstrated efficacy for stroke prevention. The use of antithrombotic agents and thrombolytics for treatment of acute cerebral ischemia is discussed elsewhere.

Antithrombotic agents fall broadly into two general categories, those that exert their effect via platelet inhibition (i.e., antiplatelet agents), and those that influence various factors in the clotting cascade (i.e., anticoagulants). There is an important interaction between these agents at the level of thrombin, which is a platelet agonist. Anticoagulants such as heparin, low-molecular-weight heparins, antithrombins, and anti-factor Xa drugs reduce the activation of platelets by the modulation of thrombin generation (Messmore et al., 2005). Additional anti-inflammatory or neuroprotective effects of these agents have been demonstrated in experimental models, but the primary mechanism of action for stroke prophylaxis is prevention of thromboembolic phenomenon. In the following chapter, the agents will be discussed sequentially with a focus on their mechanisms of action, indications, efficacy, and safety profiles.

Our understanding of the clinical utility of antithrombotic agents stems from scores of large multicenter trials conducted over the last 20 years. Once a patient has suffered an ischemic stroke or TIA, it is highly likely that their next vascular event will be cerebrovascular, even if they have a prior history of cardiac disease

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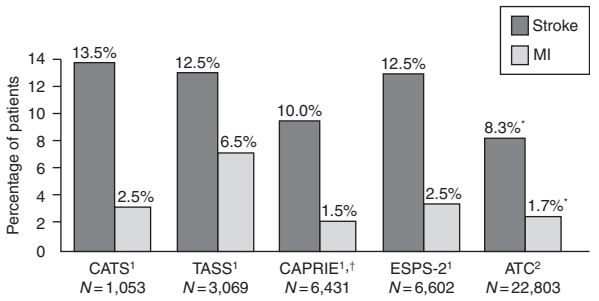

Fig. 64.1. Stroke and myocardial infarction in patients with TIA or stroke from antiplatelet trials, as calculated for all treatment groups combined, over the entire follow-up period of each study. CATS data include only first events and exclude events that occurred more than 28 days after discontinuation of the study drug. TASS data also reflect only first events for stroke but include all myocardial infarctions that occurred during the study. CAPRIE data reflect the first event to occur in the outcome cluster stroke, myocardial infarction, or vascular death in the stroke patient subgroup only (n = 6,431). ESPS-2 data include only first events. CATS = Canadian American Ticlopidine Study; TASS = Ticlopidine Aspirin Stroke Study; CAPRIE = Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events; ESPS-2 = European Stroke Prevention Study-2; ATC = Antithrombotic Trialists' Collaboration.
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†Stroke patient subgroup only (N = 6,431)
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(Fig. 64.1). Further, the risk of recurrent stroke is greatest in the period shortly after a minor stroke or TIA (Johnston et al., 2000; Weimar et al., 2002; Rothwell et al., 2005). Therefore, it is important to direct therapy towards the goal of safely and effectively reducing the risk of recurrent stroke. The relative risk reductions achieved for the prevention of stroke are particularly relevant for studies of antithrombotic agents in cerebrovascular populations (Albers, 2000).

The causes of ischemic stroke are widely diverse, ranging from cardioembolism to small-vessel disease to large-artery atherosclerosis. Rarer causes of stroke include paradoxical embolism, arterial dissection, vasculitis, venous thrombosis, and various hypercoagulable states. Preventative studies that do not sufficiently identify and subcategorize stroke subtypes can lead to fallacious conclusions. As diverse pathophysiological mechanisms underlie the various subtypes of stroke, caution must be taken in generalizing results across all causes of cerebral thromboembolism. In general, however, anticoagulation is indicated for patients with presumed or proven moderate- to high-risk cardioembolic sources (Albers et al., 2004; Sacco et al., 2006). There are other specific situations, such as antiphospholipid antibody syndrome, extracranial cervical artery dissections, cerebral venous sinus thrombosis, and various hypercoagulable states where anticoagulation may be indicated, but data based on randomized clinical trials for these relatively rare conditions are lacking. In general, antiplatelet agents are the favored agents for the prevention of most ischemic strokes not secondary to the above causes. There has been a clear evolution in thinking over the last decade regarding the role of anticoagulants for stroke prophylaxis. Recently published clinical trials have demonstrated that for the prevention of non-cardioembolic strokes warfarin is no more effective than aspirin. Based on the inconvenience involved with monitoring these agents and a higher rate of hemorrhagic complications, most clinicians and clinical guidelines now recommend antiplatelet agents for patients with non-cardioembolic stroke subtypes, while reserving anticoagulation for conditions that are associated with a substantial risk of cardiac embolism.

64.2. Pathophysiology of thrombosis

Thrombosis is the final common pathway that leads directly to tissue ischemia in most stroke subtypes. Atherosclerosis, however, is the most common underlying mechanism of heart disease and stroke. This progressive inflammatory disorder of the arterial wall can lead to acute stroke when a plaque ruptures and thrombosis ensues (Ross, 1999; Lusis, 2000). Contact between circulating blood and thrombogenic lipid material in the core of the lesion leads to clot formation. In the case of an occlusive thrombus, tissue distal to the blockage suffers damage from ischemia. This process is highly variable and is influenced by the duration of the arterial occlusion, its location, the presence of collateral blood flow, and a variety of other factors. Ischemic symptoms may be temporary, clinically producing a TIA, if the thrombus dissipates rapidly or collateral circulation can quickly compensate. Platelets themselves may be involved in the development of atherosclerosis (Ruggeri, 2002), but genetic and environmental factors such as hypertension, diabetes, dyslipidemia, and tobacco use are the main identifiable culprits (Lusis, 2000).

Unlike venous thrombosis, arterial thrombosis typically does not occur in the absence of underlying vascular damage. Arterial thrombi form under conditions of elevated sheer stress at sites of endovascular injury. Endothelial cells play a key role in the normal balance between blood fluidity and thrombus formation, the latter occurring in response to injury. Inhibitors and activators of platelet function and clotting factors are synthesized by endothelial cells (Ware and Heistad, 1993; Gross and Aird, 2000). Inhibitors of platelet

function include prostacyclin (PGI_2), nitric oxide (NO), CD39, thrombomodulin (TM), heparan sulfate (HS), and tissue plasminogen activator (tPA). These molecules have a diverse array of functions including increasing intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), degrading adenosine diphosphate (ADP), changing the substrate specificity of thrombin, and generating plasmin (which degrades thrombin). These actions contrast with those of a host of thrombogenic substances synthesized by endothelial cells, including von Willebrand factor (vWF), P-selectin, tissue factor (TF), and plasminogen activator inhibitor 1 (PAI-1). In the setting of vascular injury, the loss of the endothelial cell barrier between extracellular matrix components and flowing blood leads to hemostatic thrombosis.

Platelets are created when disintegrating megakaryocytes in the bone marrow release anucleate fragments of their cytoplasm into the bloodstream. Normally the concentration of platelets in the blood is between 150,000/μl and 400,000/μl. Circulating in an inactive state, the platelets travel in the outer lane of the column of red and white blood cells, ideally situated to survey the integrity of the vascular endothelium. In the absence of activation, the platelet lifespan is approximately 10 days. Platelet shape change, adhesion, spreading, activation (release reaction), and subsequent aggregation occur when disrupted or denuded endothelium is encountered. At rest, platelets are disk-shaped with an approximate diameter of 3 μm. When platelets contact exposed endothelium (specifically vWF and collagen) they round up and elaborate filopodia and lamellipodia; these cell wall extensions give them a stellate appearance. Platelet activation results in multiple membrane and intracellular reactions, ultimately leading to the release of ADP and various proteins stored in α-granules. Platelet activation also induces phospholipase A_2 (PLA_2)-mediated hydrolysis of arachidonic acid (AA) from membrane phospholipids. Free AA is quickly metabolized to the prostaglandin endoperoxidases PGG_2 and PGH_2 by cyclooxygenase (COX), and then to thromboxane (TXA_2) by thromboxane synthase. Binding of ADP and PGH_2/TXA_2 to their respective receptors on the platelet further amplifies activation (Fig. 64.2). Additionally, TXA_2 leads to blood vessel constriction and local stagnation of blood flow. This activation is under stringent negative control through the action of PGI_2 and NO. An occlusive thrombus is formed at the site of endothelial injury when activated and degranulated platelets attach to each other (aggregation). Platelets are linked to each other with the aid of integrins, such as the platelet glycoprotein (Gp)Ib/IX–V complex that binds vWF and the GpIIb/IIIa ($\alpha_{IIb}\beta_3$) receptor

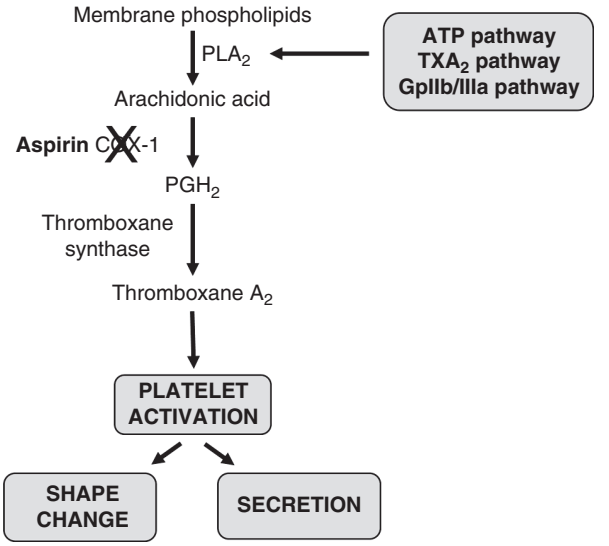

Fig. 64.2. Thromboxane A_2 leads to platelet activation (see text). TXA_2 = thromboxane; ATP = adenosine triphosphate; PLA_2 = phospholipase A_2; PGH_2 = prostaglandin H_2; COX-1 = cyclooxygenase-1.

that binds fibrinogen in a calcium-dependent manner. The tripeptide amino acid sequence arginine–glycine–aspartic acid ("RGD") mediates the binding of fibrinogen or vWF to their platelet GpIIb/IIIa receptors (Plow et al., 1985).

64.3. Antiplatelet agents

In contrast to "red thrombi" seen in venous thrombosis, arterial thrombi tend to be platelet rich with a paucity of red blood cells and fibrin (so-called "white thrombi"). For this reason it has been hypothesized that antiplatelet agents are more appropriate for stroke prophylaxis, as opposed to anticoagulants (Evans et al., 1971). This oversimplifies the complex pathophysiology of clot formation. There is a closely linked reciprocal relationship, for example, between platelets and thrombin generation, with thrombin being a potent platelet activator, and activated platelets forming a surface for enhanced fibrin formation (Schafer, 1996). Further, both arterial and venous clots are in a dynamic state of remodeling, with an ever-changing composition (Schafer and Kroll, 1993). Despite these complexities on the cellular level, clinical research over the last 20 years has favored the use of antiplatelet agents over anticoagulants for the prevention of ischemic arterial stroke that is not due to atrial fibrillation or other cardiac conditions associated with a high risk of embolism (European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Albers et al., 2004; Sacco et al., 2006).

Several general classes of antiplatelet agents are currently available for the prevention of vascular thrombosis. Various molecular pathways linked to discrete proteins provide multiple targets for the inhibition of platelet activity. Combination therapy aimed at blocking separate processes simultaneously may have synergistic effects, although cumulative side-effects must be considered. Additionally, other antithrombotic actions independent of antiplatelet activity have been identified. The major antiplatelet agents include a TXA_2 inhibitor (acetylsalicylic acid or aspirin), ADP-receptor antagonists (clopidogrel and ticlopidine hydrochloride), a phosphodiesterase (PDE) inhibitor (dipyridamole), and GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, and tirofiban) (Table 64.1).

Antiplatelet agents are effective for the prevention of stroke, TIA, myocardial infarction, angina, and intermittent claudication. A meta-analysis of 287 clinical trials by the Antithrombotic Trialists' Collaboration that included more than 23,000 patients with prior stroke or TIA demonstrated a significant 2.5% absolute risk reduction (ARR) for the recurrence of non-fatal stroke or TIA in patients using antiplatelet agents for three years (Antithrombotic Trialists' Collaboration, 2002). The included trials used a variety of antiplatelet agents, as well as combination antiplatelet therapies. This benefit amounts to a relative risk reduction (RRR) of 23%, and a number needed to treat (NNT) of 40 in three years to prevent one non-fatal stroke or TIA. Vascular death and non-fatal vascular events were shown to be reduced by approximately 15% and 30%, respectively. Patients above and below 65 years of age and with various vascular risk factors benefit equally. Although antiplatelet efficacy is relatively modest (only about one-quarter of all major vascular events are prevented), the safety of these agents in comparison to their low risk of adverse effects provides for a favorable risk/benefit ratio for the majority of patients who have suffered an ischemic stroke or TIA. Further, the high prevalence of stroke means that even modest reductions in stroke recurrence can have a major impact on worldwide neurologic disability.

64.3.1. Aspirin

64.3.1.1. Historical use

Aspirin is the oldest, least expensive, and most commonly utilized antiplatelet agent in the world. It has been in clinical use for antithrombosis for over 50 years (Mueller and Scheidt, 1994). The history of aspirin, however, goes back thousands of years to the use of plants containing salicylates. The earliest uses exploited the ability of salicylates to combat pain and inflammation. The first recorded use of salicylates seems to have been by Hippocrates (*c*. 400 BC), who recommended a brew of willow tree (*Cortex salicis*) leaves for the relief of pain in childbirth. The pharmaceutical manufacturing house of Frederick Bayer began to search for a derivative of comparable or better efficacy to salicylic acid. Felix Hoffman found a way of acetylating the hydroxyl group on the benzene ring to form acetylsalicylic acid (ASA). Beyer's chief pharmacologist Heinrich Dreser coined the name "aspirin" (Dreser, 1899), a name which may have been derived from *Spiraea*, the genus of plant to which the salicylaldehyde-containing meadowsweet belongs (Gross and Greenberg, 1948). In the 1950s French investigators noted a prolongation of bleeding time with aspirin use (Beaumont et al., 1956; Blatrix, 1963). In the USA, Quick confirmed these results and showed that sodium salicylate had no effect on bleeding time (Quick, 1966). This suggested the potential use of aspirin as an antithrombotic agent. Dr. Lawrence L. Craven helped pioneer the prophylactic antithrombotic uses of aspirin, although the lack of rigor

Table 64.1

Comparison of commonly used antiplatelet agents

Aspirin	Clopidogrel	Dipyridamole
Active	Pro-drug	Active
Irreversibly modifies COX-1 enzyme	Irreversibly binds to and modifies $P2Y_{12}$ receptor	Reversibly affects several different pathways in different cells
Inhibits platelet TxA_2 pathway	Inhibits ADP pathway of platelet aggregation and granule release	Inhibits breakdown of cGMP by PDE_5 facilitating NO-induced cGMP Increases cAMP levels
At >100 mg/d inhibits endothelial cell PGI_2 pathway.	No known direct effects on endothelial cells	Increases PGI_2 release from endothelial cells

ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; COX-1 = cyclooxygenase-1; PGI_2 = prostacyclin; PDE_5 = phosphodiesterase type 5; TxA_2 = thromboxane.

of his uncontrolled clinical observations delayed widespread publication and acceptance of his conclusions. He urged "friends and patients to adopt the practice of taking aspirin, one or two 5 grain tablets daily." He stated that in the "[a]pproximately 8000 men and women [who] adopted the regime . . . not a single case of detectable coronary or cerebral thrombosis occurred among patients who faithfully adhered to this regime during a period of eight years" (Craven, 1956). Sir John Vane's Nobel prize-winning work in the 1970s elucidated aspirin's mechanism of action as the inhibition of prostaglandin synthase (see below). In 1980, the use of aspirin after TIA in men to reduce the risk of stroke was recognized by the Food and Drug Association (FDA), but it was not until 1988 that aspirin was given approval for this indication. In 1998 the indication was broadened to prevent stroke in women after TIA, and to prevent a second or recurrent stroke in both women and men who had previously suffered a stroke.

64.3.1.2. Mechanism of action

Aspirin's best-characterized mechanism of action is its ability to permanently inactivate the cyclooxygenase activity of prostaglandin (PG) H-synthase-1 (COX-1) and PGH-synthase-2 (COX-2; Burch and Majerus, 1979; Majerus, 1983). These isozymes are homodimers of an approximately 72-kDa monomeric unit. Each dimer has an epidermal growth factor-like domain, a membrane binding domain, and an enzymatic domain (Smith et al., 1996). There are some important differences in COX-1 and COX-2 which may contribute to variable inhibitor selectivity (Patrono et al., 2004). COX-1 and COX-2 catalyze the first committed step in the conversion of AA to PGH_2. PGH_2 is the immediate precursor of PGD_2, PGE_2, $PGF_{2\alpha}$, and TXA_2 (Fig. 64.2). As discussed above, TXA_2 is a strong platelet activator. Aspirin, as well as other nonsteroidal anti-inflammatory medications (NSAIDs), acetylates COX and ultimately prevents the generation of TXA_2 (Roth and Majerus, 1975). This occurs at strategically located serine residues, Ser529 in COX-1 and Ser516 in COX-2, thereby preventing access of the substrate to the catalytic site of the enzyme (Loll et al., 1995). COX is also responsible for the conversion of AA to PGI_2 (prostacyclin) in vascular endothelial cells (Majerus, 1983). Mice lacking the PGI_2 receptor are predisposed to experimentally induced thrombosis (Murata et al., 1997). Despite the concern of paradoxically promoting platelet aggregation by blocking prostacyclin synthesis with higher doses of aspirin, it has not been established that this is sufficient to initiate or predispose humans to thrombosis. TXA_2 activates the GPIIb/IIIa binding site on the platelet allowing fibrinogen to bind. Other NSAIDs, such as the commonly used anti-inflammatory ibuprofen, reversibly antagonize COX-1, leading to a less robust antiplatelet effect. These agents may compete with low-dose aspirin if given simultaneously, theoretically leading to decreased clinical effectiveness of aspirin (Patrono et al., 2004). Because high concentrations of ADP, collagen, and thrombin can activate platelets through alternative pathways, aspirin does not completely abolish platelet function (Awtry and Loscalzo, 2002). This may partly explain the phenomenon of aspirin resistance (see below).

64.3.1.3. Efficacy

Aspirin is the most thoroughly investigated antiplatelet agent for recurrent stroke prophylaxis. There is ample uncontroversial data proving the effect of this agent for the prevention of stroke and other vascular events (Antithrombotic Trialists' Collaboration, 2002). The benefit of aspirin for the prevention of myocardial infarction and vascular death, however, appears to be higher than its benefit for stroke prevention (Albers et al., 2004). A mini-meta-analysis of 10 trials that evaluated the benefit of aspirin in patients who initially presented with stroke or TIA showed a modest reduction in the odds of stroke, myocardial infarction, or vascular death of 16% (RRR = 13%; Algra and van Gijn, 1996). Patients who initially present with stroke or TIA often die of cardiovascular causes, as well as recurrent stroke (Broderick et al., 1992; Sacco, 1995; Bronnum-Hansen et al., 2001; Hartmann et al., 2001). Because of this, composite end-points of stroke, myocardial infarction, or vascular death are often chosen in clinical trials of antithrombotic agents (Albers, 2000).

A number of large international trials have demonstrated the benefit of aspirin for the secondary prevention of stroke. A 75 mg daily dose of aspirin in 1,360 patients with a history of minor stroke was compared to placebo in the Swedish Aspirin Low-Dose Trial (SALT) (Swedish Aspirin Low-Dose Trial Collaborative Group, 1991). There was an 18% RRR in stroke plus all deaths in the aspirin group. The effect of immediate aspirin use (within the first 48 hours) in stroke has been investigated in over 40,000 patients in the Chinese Acute Stroke Trial (CAST) (CAST Collaborative Group, 1997) and the International Stroke Trial (IST) (International Stroke Trial Collaborative Group, 1997). The duration of treatment was 2 weeks in the IST, and 4 weeks in the CAST. In these very large studies, medium-dose aspirin (160–300 mg daily) produced a modest risk in early death or non-fatal stroke. There was a highly significant reduction of 7 per 1,000 in recurrent ischemic stroke, with 1.6% in the aspirin group as compared to 2.3% in the control group having early stroke recurrence (Chen et al., 2000). This result was not offset by early hemorrhage.

64.3.1.4. Dose

Aspirin has a short half-life (15–20 minutes) when circulating in the blood. As platelets are anucleate cells and unable to synthesize new enzymes, aspirin is ideally suited for inducing a permanent defect in TXA_2-dependent platelet activity. However, aggregation of platelets may be sustained through the thromboxane pathway even if only 10–15% of the platelets remain functional (Catella-Lawson et al., 2001). Because only 10% of the platelet pool is replenished on a daily basis, complete inhibition of TXA_2 production is achieved with once daily dosing. COX-2-dependent processes such as inflammation require larger doses of aspirin because of the decreased sensitivity of the COX-2 isozyme. More frequent dosing of aspirin is needed to combat inflammation because of the constant replenishment of COX-2 by nucleated cells.

The dose of aspirin for recurrent stroke prevention has been a subject of much discussion, and is one of the commonest questions asked of stroke specialists by patients and physicians from other specialties. Various trials have used daily doses ranging from 30 mg to 3,000 mg. The SALT trial showed a significant benefit for stroke prevention with a 75 mg daily dosage of aspirin (Swedish Aspirin Low-Dose Trial Collaborative Group, 1991). The Dutch TIA trial compared aspirin doses of 30 mg/day to 283 mg/day in 3,131 patients with minor stroke or TIA. The lower dose was as effective in preventing the composite outcome of stroke, myocardial infarction, or vascular death, and had fewer bleeding complications (Dutch TIA Trial Study Group, 1991). A similar result was seen in the United Kingdom Transient Ischemic Attack (UK-TIA) aspirin trial which compared aspirin doses of 600 mg twice a day to 300 mg once a day (Farrell et al., 1991). A mini-meta-analysis of aspirin trials supports the use of low-dose aspirin, perhaps as little as 30 mg/day, for recurrent stroke prevention (Algra and van Gijn, 1996). The European Stroke Prevention Study-2 (ESPS-2) used daily aspirin doses of 50 mg, compared to placebo and dipyridamole alone and in combination (see section below on dipyridamole). In patients who had initially presented with stroke or TIA, a RRR of 18% for stroke and 13% for stroke or death was obtained with low-dose aspirin (Diener et al., 1996). The aspirin and carotid endarterectomy (ACE) trial looked at low-dose (81 or 325 mg daily) versus high-dose (650 or 1,300 mg daily) aspirin in over 2,800 patients undergoing carotid endarterectomy. At 3 months, there was no significant difference between the two groups for stroke, death, and ipsilateral stroke and death (Taylor et al., 1999).

A meta-regression analysis of 11 randomized-placebo controlled trials with over 9,600 patients showed a virtually flat dose-response curve for aspirin doses of 50 mg/day to 1,500 mg/day (Johnson et al., 1999). This lack of a dose-response of aspirin for stroke prevention has been confirmed in a number of meta-analyses (Barnett et al., 1995; Cappelleri et al., 1995; Algra and van Gijn, 1996; Antithrombotic Trialists' Collaboration, 2002). Taken together, the data suggest that daily doses of aspirin as low as 50 mg appear to provide the same degree of stroke prophylaxis as aspirin doses many times higher (Fig. 64.3). Given that the side-effect profile (particularly for bleeding) is dose related, it is prudent to recommend the lowest convenient daily dose of aspirin (greater than or equal to 50 mg). In the USA, this comes in the form of a "baby" aspirin (81 mg), while in Europe 100 mg is standard. In 1998, the FDA formally recommended a daily aspirin dose of 81–325 mg for ischemic stroke prevention in those patients requiring antiplatelet therapy.

64.3.1.5. Safety

Higher and more frequent doses of aspirin are associated with a greater risk of side effects, most notably gastrointestinal (GI) upset (Sudlow and Baigent, 2000; Patrono et al., 2004). Both the antiplatelet effect of aspirin and the inhibition of gastric mucosal cytoprotection are likely responsible. The United Kingdom Study Group found that patients randomized to 1,200 mg of aspirin per day were more likely to have GI tract symptoms and hemorrhage than patients taking a daily dose of 300 mg (Farrell et al., 1991). Meta-analyses have also supported the contention that higher-dose aspirin is related to more GI symptoms (Roderick et al., 1993; Cappelleri et al., 1995). Major GI hemorrhage with aspirin use is rare, in the order of 1 to 2 per 1,000

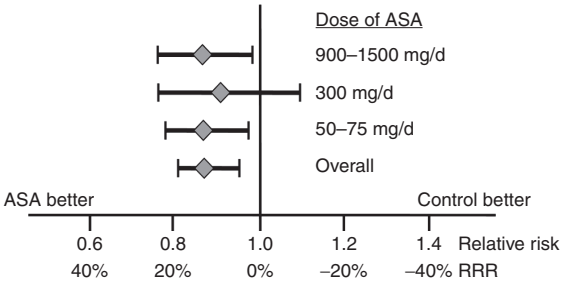

Fig. 64.3. Meta-analysis of the efficacy of aspirin in preventing stroke, myocardial infarction, or vascular death, combining the results of trials according to the aspirin dose used. Values to the left of the vertical bar favor aspirin over control. Shown are relative risks and 95% CI for three dose categories and for all doses combined. Vascular events comprised stroke, MI, or vascular death. Adapted from Albers GW, Tijssen JGP. *Neurology*. 1999;53(suppl 4) S25–S31.

patient-years (Patrono et al., 2004). Intracerebral and subarachnoid hemorrhages associated with aspirin use are among the most serious of potential complications. Overall, the risk of hemorrhagic stroke from aspirin has been estimated at 0.2 events per 1,000 patient-years in primary prevention patients at risk for coronary heart disease (Gorelick and Weisman, 2005). A large meta-analysis of nearly 200,000 patients supports the low risk of bleeding in patients taking low-dose aspirin (<100 mg/day), but suggests a somewhat higher rate of both minor and major hemorrhage at doses greater than 100 mg/day (Serebruany et al., 2005). Patients with established cerebrovascular disease have a slightly greater bleeding risk than cardiac patients. This modest risk of bleeding must be weighed against the potential benefit for the reduction of cardiac and cerebrovascular events. Additional risk factors for hemorrhagic stroke, such as uncontrolled hypertension or advanced age, should factor into decisions regarding the use of aspirin as a prophylactic agent in individual patients.

64.3.1.6. Resistance

Despite being on aspirin therapy, a considerable number of patients continue to have atherothrombotic events. Approximately one in eight high-risk patients will have a recurrent event within 2 years despite aspirin therapy (Eikelboom and Hankey, 2003). Although the reasons for "aspirin failure" are many, there are in vitro data to suggest that aspirin may not provide adequate antiplatelet efficacy in some patients. Various measures of platelet function, including optical platelet aggregometry, the PFA-100 system, urinary 11-dehydrothromboxane B_2 levels, and flow cytometry are available, but each has limitations (Eikelboom and Hankey, 2003; Sztriha et al., 2005). In a pilot experiment, platelet reactivity index was calculated in 180 stroke patients after a single 500 mg dose of aspirin. During the 2-year follow-up period, major vascular end-points (stroke, myocardial infarction, or vascular death) were more likely to be reached in the aspirin non-responders (Grotemeyer et al., 1993). A larger study using urinary 11-dehydrothroboxane B_2 levels in 973 patients from the Heart Outcomes Prevention Evaluation (HOPE) trial failed to show an association of platelet function with recurrent stroke (Eikelboom et al., 2002). The possible mechanisms for aspirin resistance are several. Genetic polymorphisms for COX-1 and platelet glycoprotein genes, augmented COX-2 expression in the setting of chronic inflammation, oxidative stress, and the presence of vascular risk factors (cigarette smoking, hyperlipidemia, obesity, and diabetes) may all be involved (Sztriha et al., 2005). As there are no known prostaglandin-independent mechanisms for the antithrombotic action of aspirin, platelet activation caused by other factors remains unchanged; these factors, including platelet activation by shear stress and ADP, can result in a resistance against inhibition of platelet function by aspirin (Schror, 1997). In patients with prior stroke, an increase in aspirin has been shown to improve the anti-aggregant efficacy (as measured by platelet aggregometry) in most of the patients with partial inhibition (Helgason et al., 1994). This ex-vivo result, however, has to be interpreted in the context of multiple clinical trials (discussed above) that have not demonstrated a dose–response curve for the prevention of ischemic stroke with aspirin.

64.3.2. Thienopyridines

64.3.2.1. Mechanism of action

Found in the dense granules within platelets, ADP exerts its action on several distinct membrane receptors resulting in the activation of platelets. ADP binding to $P2Y_1$ receptors results in the release of calcium from intracellular stores, as well as platelet shape change, while $P2Y_{12}$ receptor activation inhibits cAMP formation and the granule release response. The aggregation response requires activity at both receptors (Rao, 2003). Ticlopidine hydrochloride and clopidogrel, the two clinically available thienopyridines, are metabolized via the p450 system in the liver to molecules that selectively inhibit ADP-induced platelet activation, degranulation, and aggregation (Savi et al., 1994, 2000). Specifically, the $P2Y_{12}$ receptor is irreversibly altered by a metabolite of clopidogrel (Hollopeter et al., 2001) (see Table 64.1). Clopidogrel is dosed once per day and has a slow onset of action. A loading dose, however, can lead to an antiplatelet effect in as little as 2 hours (Curtin et al., 2002). This is of uncertain significance, as the benefit of a loading dose has not been investigated in a controlled clinical trial with stroke patients. After 4–7 days of daily treatment steady state levels of platelet inhibition are reached. Normal platelet function returns a week after cessation of therapy. A short-acting intravenous formulation of a $P2Y_{12}$ receptor antagonist (cangrelor) is in development (Van Giezen and Humphries, 2005).

64.3.2.2. Efficacy

Clopidogrel is a potent inhibitor of platelet aggregation. A large randomized placebo-controlled international trial, Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE), examined the safety and efficacy of a 75 mg daily dose of clopidogrel versus 325 mg of aspirin in over 19,000 patients with prior stroke, myocardial infarction, or peripheral vascular disease (CAPRIE Steering Committee, 1996).

Clopidogrel was more effective than aspirin in preventing the combined end-point of stroke, myocardial infarction, or vascular death. The intention-to-treat analysis showed that patients treated with clopidogrel experienced a 5.32% annual vascular event rate, versus 5.83% in the aspirin group; this translates into a very modest absolute risk reduction of 0.5% per year and a RRR of 8.7%. Among the 6,431 patients who entered the study with a recent ischemic stroke, there was a non-statistically significant 7.3% RRR of clopidogrel over aspirin for the compound end-point, and a non-statistically significant 8.0% RRR for the stroke end-point. The benefit for patients with peripheral artery disease was significantly higher, with an RRR of 24%. In post-hoc analyses of the CAPRIE data, the benefit of clopidogrel was shown to be amplified in various high-risk subgroups, including patients with a history of previous ischemic stroke or myocardial infarction (Ringleb et al., 2004), those with diabetes (Bhatt et al., 2002), those with previous cardiac surgery (Bhatt et al., 2001), and those receiving lipid-lowering therapy (Bhatt et al., 2000).

Multiple agonists and signaling pathways are involved in the activation of the GPIIb/IIIa receptors and platelet activation (Schafer, 1996). This has led to the hypothesis that potentiation of antiplatelet effects could be obtained by inhibiting the $P2Y_{12}$ ADP receptor on a background of TXA_2 inhibition. Findings of randomized controlled trials in patients with coronary manifestations of atherothrombosis, such as the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) (Yusuf et al., 2001) and Clopidogrel for the Reduction of Events During Observation (CREDO) (Steinhubl et al., 2002) trials have shown the sustained benefit of clopidogrel on top of standard treatment including aspirin. These trials provided the rationale for the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study, the aim of which was to find out whether aspirin added to clopidogrel would further reduce the risk of recurrent ischemic vascular events in high-risk patients after TIA or stroke. In this trial, almost 7,600 patients with a recent stroke or TIA, many of whom had diabetes and hypertension, were randomized to receive clopidogrel or clopidogrel plus aspirin (75 mg/day). During the 18-month follow-up period there was no statistically significant benefit of dual antiplatelet therapy for preventing stroke or myocardial infarction, but there was a significant increase in the bleeding risk. Life-threatening hemorrhage occurred in twice as many patients in the clopidogrel/aspirin group versus the clopidogrel group (2.6% versus 1.3%), with intracranial hemorrhage occurring in 40 subjects versus 25 subjects, respectively (Diener et al., 2004).

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial failed to show an advantage of clopidogrel plus aspirin for stroke prevention (Bhatt et al., 2006). In this large trial, 15,603 patients were randomized to either clopidogrel or placebo, with patients in both groups taking aspirin (81–162 mg daily). It should be noted that the CHARISMA trial pitted clopidogrel plus aspirin against aspirin, while MATCH compared clopidogrel plus aspirin to clopidogrel. Further, this trial included high-risk asymptomatic subjects in addition to those patients with a history of ischemic events. After over 2 years of follow-up, there was a small non-significant decrease in stroke, myocardial infarction, or vascular death in the clopidogrel plus aspirin group (6.8% versus 7.3%). There was a trend toward more severe bleeding episodes in the dual-antiplatelet group (1.7% versus 1.3%; NS). Interestingly, for patients who entered the study with vascular risk factors but without a preceding ischemic event, the clopidogrel plus aspirin group experienced a significant increase in cardiovascular death (3.9% versus 2.2%). The reasons for this surprising result in the "primary prevention" subgroup are not entirely clear. In subgroup analysis, patients with a history of symptomatic atherothrombosis taking clopidogrel plus aspirin had a 12% risk reduction over the aspirin only group ($p = 0.046$). The aforementioned data weigh against the routine use of the combination of aspirin and clopidogrel for stroke prophylaxis in most patients (Hankey and Eikelboom, 2005; Weir et al., 2005). In MATCH, the increased bleeding risk did not become apparent until approximately 3 months after the initiation of dual antiplatelet therapy, suggesting there may be a narrow early window for the use of clopidogrel plus aspirin for select patients under certain circumstances (e.g., in the setting carotid stenosis; see below).

Ticlopidine hydrochloride is a thienopyridine that inhibits ADP-induced fibrinogen binding to platelets, a key step in the process of platelet aggregation. Ticlopidine has been shown to be more effective than aspirin for recurrent stroke prevention in two large multinational clinical trials, the Ticlopidine Aspirin Stroke Study (TASS) and the Canadian American Ticlopidine Study (CATS). In TASS, a daily dose of 500 mg ticlopidine (given twice daily) was compared to 1,300 mg/day of aspirin (given twice daily) in over 3,000 patients with stroke or TIA. There was a statistically significant 21% RRR in stroke at 3 years in the patients who received ticlopidine; there was a non-significant RRR of 9% for the combined end-point of stroke, myocardial infarction, or vascular death in the ticlopidine arm (Hass et al., 1989). CATS was a

randomized, double-blind, placebo-controlled trial to assess the effect of ticlopidine (250 mg twice daily) in reducing the rate of subsequent stroke, myocardial infarction, or vascular death in patients who have had a recent ischemic stroke. Over 1,000 patients were treated and followed for up to 3 years. In the efficacy analysis, the event rate per year for stroke, myocardial infarction, or vascular death was 15.3% in the placebo group and 10.8% in the ticlopidine group, representing a RRR with ticlopidine of 30.2% in the on-treatment analysis. The relative risk of ischemic stroke was reduced by ticlopidine in the on-treatment analysis by 33.5% (Gent et al., 1989). Ticlopidine has been compared to aspirin for the prevention of stroke in the African American Antiplatelet Stroke Prevention Study (AAASPS). No significant benefit was seen for this population of 1,800 African-American stroke or TIA patients for ticlopidine over aspirin (Gorelick et al., 2003).

A meta-analysis by the Cochrane Stroke Group of four trials with 22,656 patients (9,840 presenting with stroke or TIA) involving either clopidogrel or ticlopidine hydrochloride suggests that the thienopyridines may have a slight advantage over aspirin, with a 9% RRR of serious vascular events; this corresponds to avoiding 11 vascular events per 1,000 patients treated for about 2 years (Hankey et al., 2000). The 95% confidence interval, however, is very wide and suggests the odds reduction of a vascular event could be as low as 2% or as high as 16%. The side-effect profile (see below) and relative cost of these agents should be factored into decisions regarding their use in individual patients. Multiple clinical trials are currently underway to better characterize which patients may benefit most from thienopyridines, either as single agent therapy or in combination with other antithrombotic agents (Easton, 2003).

64.3.2.3. Safety

Overall, the safety profile of a 75 mg daily dose of clopidogrel is similar to that of 325 mg of aspirin. In a large meta-analysis comparing the thienopyridines to aspirin, there was no significant difference in the frequency of intracranial or extracranial hemorrhage (Hankey et al., 2000). The thienopyridines produced more skin rash and diarrhea than aspirin, both being more common with ticlopidine hydrochloride than clopidogrel. In the CAPRIE study, there were no major differences between aspirin and clopidogrel in terms of safety (CAPRIE Steering Committee, 1996). Adverse experiences were minimal, but there was a slightly higher rate of serious hemorrhages among those patients taking aspirin (1.55% versus 1.38%). There were 10 patients in the clopidogrel group (0.10%) with significant neutropenia to $<1{,}200/mm^3$, compared to 0.17% in the aspirin group. Although no case of thrombotic thrombocytopenic purpura (TTP) was observed in the more than 30,000 patients studied in clinical trials with clopidogrel (CAPRIE Steering Committee, 1996; Steinhubl et al., 2002), 11 cases of reversible TTP have been reported in the over 3 million patients that have received this drug (Bennett et al., 1998). Adverse events associated with ticlopidine use have included neutropenia, skin rash, and diarrhea. Severe neutropenia has been seen in up to 1.0% of patients taking ticlopidine (Gent et al., 1989; Hass et al., 1989). The neutropenia occurs within several months of beginning the drug. In the TASS, serious GI adverse events (e.g., ulcers and hemorrhage) were 2.5 times more common in the aspirin group than in the ticlopidine group, despite the fact that patients with a history of GI bleeding or dyspepsia were not enrolled. Bleeding from non-GI sites was rare and approximately equal between the two groups. Diarrhea and skin rash caused drug intolerance in 4% of the patients in the ticlopidine arm. Similar results were seen in the CATS. The potential for neutropenia with ticlopidine necessitates monitoring of blood counts every 2 weeks for the first 3 months. Additionally, more than 60 cases of TTP have been reported with ticlopidine use (Bennett et al., 1998; Chen et al., 1999). These side-effects, taken with the conflicting data from the available randomized clinical trials, have seriously limited the prescription of this agent for stroke prophylaxis.

64.3.2.4. Resistance

Platelet aggregation studies have revealed the existence of clopidogrel non-responsiveness (Gurbel et al., 2003; Muller et al., 2003; Matetzky et al., 2004). Sequence alterations of the target receptor gene represent one possible mechanism for clopidogrel failure (Ziegler et al., 2005). Several mutations in platelet surface glycoprotein receptors have been identified (Quinn and Topol, 2001). Data obtained from ex-vivo studies, however, must be applied cautiously to patients. Currently the knowledge of the mechanisms that make a given patient more or less likely to respond favorably to a particular antiplatelet agent is lacking.

64.3.3. Dipyridamole

64.3.3.1. Mechanism of action

Dypyridamole's use as an antiplatelet drug follows from its inhibitory effect on the enzyme phosphodiesterase (PDE), a key molecule in the cAMP pathway (Fitzgerald, 1987). Early platelet aggregometry studies, however, showed only weak antiplatelet effects (Eisert, 2001a, b). The use of whole-blood impedance

aggregometry demonstrated that dipyridamole inhibits platelet aggregation more effectively in whole blood than in platelet rich plasma, suggesting additional antithrombotic mechanisms. Advanced laboratory techniques allow for the creation of a more realistic vascular environment. Using a subendothelial matrix covered by endothelial cells, dipyridamole was shown to enhance the indirect (near-field) antithrombotic action of the endothelium through multiple different mechanisms (Eisert, 2001a,b). First, inhibition of the cellular uptake and metabolism of adenosine leads to increased adenosine concentration at the platelet-vessel wall interface; reduced platelet aggregation and adhesion results. Second, the inhibition of cAMP PDE results in increased concentrations of intracellular cAMP and potentiation of the PGI_2 effects on platelets. Third, inhibition of cGMP PDE causes a rise in intracellular cGMP and potentiation of NO's effect on platelets. Taken together, along with the direct stimulation of prostacyclin release by the vascular endothelium, dipyridamole reversibly inhibits platelet aggregation, adhesion, and factor release (see Table 64.1). Additional mechanisms are also likely to play within the vessel wall. Increased synthesis of 13-hydroxyoctadecadienoic acid (13-HODE) decreases thrombus formation on the subendothelial matrix and vessel wall. There is an antioxidant effect of dipyridamole which results in inhibition of LDL oxygenation and reduced recognition by macrophage scavenger receptors, thus potentially reducing the development of atherosclerotic plaques. Similarly, inhibition of tissue damage reduces production of cytokines and chemotaxis of monocytes, potentially decreasing plaque formation. Lastly, dipyridamole inhibits smooth muscle cell proliferation, which could inhibit restenosis (Eisert, 2001b).

64.3.3.2. Efficacy

Studies of dipyridamole for secondary stroke prophylaxis have yielded heterogeneous results. Some of the differences may relate to the fact that many of the studies were small and underpowered; others may be due to the short half-life of dipyridamole, which requires multiple daily doses and good patient compliance. An analysis of all trials involving dipyridamole (DP) alone versus placebo, and DP combined with aspirin versus placebo, was undertaken by the Antithrombotic Trialists' Collaboration (2002). A 16% odds reduction for stroke, MI, or vascular death was seen in the 15 trials that compared DP alone to placebo. Forty-six trials compared the combination of DP and aspirin to placebo and showed a 30% odds reduction for the compound end-point, favoring the combination. Early trials of DP plus aspirin, however, were unable to detect a significant benefit for this combination therapy over aspirin alone (Guiraud-Chaumeil et al., 1982; Bousser et al., 1983; American-Canadian Co-operative Study Group, 1985; Antithrombotic Trialists' Collaboration, 2002). These trials, such as the Accidents Ischemiques Cerebraux Lies a l'Atherosclerose (AICLA) trial and the American-Canadian Cooperative Study, lacked the statistical power to detect differences in the benefit of combination versus monotherapy because of the small number of events in each treatment group. Recent meta-analyses have clearly shown a benefit for dipyridamole, both alone and in combination with aspirin, for reducing stroke recurrence in patients with prior ischemic cerebrovascular disease. Further, the combination of DP/aspirin reduces the composite end-point of stroke, myocardial infarction, and vascular death compared with aspirin alone (OR: 0.84; Leonardi-Bee et al., 2005). This benefit appears to be particularly pronounced in high-risk patients (see section 64.3.6) (Sacco et al., 2005).

An extended-release formulation of dipyridamole (ER-DP) allows for twice-daily dosing. This has currently shown efficacy in two large clinical trials. The large European Stroke Prevention Study 2 (ESPS-2) provided evidence that aspirin plus ER-DP leads to a significantly greater reduction in recurrent stroke than aspirin alone. This 6,602 patient multicenter, blinded, factorial, placebo-controlled trial randomized patients with stroke or TIA into four treatment groups: aspirin (50 mg daily) plus ER-DP (400 mg daily), aspirin alone, ER-DP alone, or placebo. There was a 2-year follow-up for all patients. The trial found that low-dose aspirin plus ER-DP more than doubled the reduction in stroke risk achieved with aspirin alone, a 37% risk reduction for the combination versus 18.1% for aspirin alone (Diener et al., 1996). There was no reduction in mortality in any treatment group. Overall, the result of the ER-DP/aspirin combination versus placebo was similar to the earlier ESPS-1 trial that used regular DP but failed to include an aspirin alone group (The ESPS Group, 1987). The relatively large number of strokes that occurred in ESPS-2, 323 non-fatal strokes versus 142 non-fatal strokes, was greater than in all previous DP/aspirin trials combined (Wilterdink and Easton, 1999). The bleeding risk of DP taken in combination with aspirin is not statistically higher than that of aspirin alone (Diener et al., 1996). Up to 40% of patients develop a transient headache when started on DP. Although the headaches are usually transient, this adverse effect leads to treatment discontinuation in about 10% of patients. Titration with an initially lower dose of ER-DP/aspirin over the first week may decrease the severity of headache, and thereby improve compliance (Lindgren et al., 2004).

The results of the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) add further evidence for the efficacy of the ER-DP/aspirin combination over aspirin alone (ESPRIT Study Group et al., 2006). In this open-label randomized trial, 2,739 patients with a recent history of a stroke or TIA were randomized to a combination of aspirin and dipyridamole (83% received ER-DP) or aspirin alone (30–325 mg/day). A 20% reduction in the primary outcomes of vascular death, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complications was seen in the group assigned to the combination treatment compared to aspirin group. The vasodilatory properties of dipyridamole have raised concern about the potential for coronary steal in vulnerable patients. In ESPRIT, the ER-DP/aspirin combination group did not show any tendency toward increased cardiac events. In fact, the rate of first cardiac events was decreased by 27% (NS). Further, many of the patients enrolled in ESPS-2 had coronary disease, yet benefited from the combination of aspirin and ER-DP (Diener et al., 2001; Albers, 2007).

64.3.4. Platelet glycoprotein IIb/IIIa inhibitors

64.3.4.1. Mechanism of action

The binding of fibrinogen to GpIIb/IIIa serves as the final common pathway for platelet aggregation, regardless of the inciting stimuli. Agents that can block this interaction are a potential pharmacologic target for stroke prophylaxis. GpIIb/IIIa receptors are unable to bind fibrinogen with high affinity when in the inactive state. A calcium-dependent conformational change occurs in the receptor when platelets are activated, allowing for high affinity fibrinogen binding. The bivalent nature of fibrinogen leads to the cross-linking of platelets when GpIIb/IIIa is bound (Coller, 1995). GpIIb/IIIa antagonists potently inhibit aggregation of platelets, with little effect on platelet activation or degranulation.

Several agents have been developed for use in the USA, each representing a different subclass of GpIIb/IIIa antagonists: abciximab, eptifibatide, and tirofiban (Agah et al., 2002). Unlike aspirin and the thienopyridines, these agents result in a reversible inhibition of platelet function. Abciximab, a chimeric monoclonal antibody 7E3 Fab fragment, dose-dependently inhibits platelet aggregation and leukocyte adhesion by binding to the GpIIb/IIIa, vitronectin ($\alpha v\beta 3$), and Mac-1 receptors. This effect is mediated through steric hindrance. The efficacy of the antiplatelet effect is directly proportional to the percentage of receptors bound. Complete inhibition of platelet aggregation requires at least 80% of GpIIb/IIIa receptors to be bound. After cessation of treatment, platelet function returns to normal over a 48-hour period. Eptifibatide is a cyclic heptapeptide based on the Lys–Gly–Asp (KGD) amino acid sequence. Tirofiban binds GpIIb/IIIa receptors with high affinity. The low-molecular-weight non-peptide tyrosine derivative mimics the RGD sequence of fibrinogen. The GpIIb/IIIa antagonists are dosed intravenously in a weight-based manner, usually as a bolus followed by a continuous infusion. The pharmacologic properties of the currently available agents, however, make them unsuitable for long-term outpatient use as antiplatelet agents for the prevention of recurrent strokes.

64.3.4.2. Efficacy and safety

Oral GpIIb/IIIa antagonists including xemilofiban (EXCITE trial), sibrafiban (SYMPHONY, Second SYMPHONY trials), and orbofiban (OPUS-TIMI 16) have been investigated (O'Neill et al., 2000; SYMPHONY Investigators, 2000; Chew et al., 2001; Second SYMPHONY Investigators, 2001). Unfortunately, not only was there no demonstrable benefit in terms of prevention of vascular events with these agents, but the vascular death rate was increased by approximately 37%. Likewise, the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial was terminated early after it failed to show a benefit of lotrafiban (30 or 50 mg twice per day) as compared to aspirin (75–325 mg/day) for the occurrence of a compound vascular end-point, but as associated with a 33% higher risk of death in GPIIb/IIa group (Topol et al., 2003). Lamifiban, roxifiban, fradafiban, lefradafiban, elarofiban, and gantofiban are newer GpIIb/IIIa antagonists (Hanson et al., 2004); ongoing investigations continue to assess the efficacy and safety of these potent agents. Whether they will be safe and effective for the prevention of atherothrombotic events in the cerebral circulation remains to be seen.

64.3.5. Other agents

Cilostazol (6-(4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy)-3,4-dihydro-2(1H)-quinolinone), a phosphodiesterase type 3 isoform inhibitor, has both antiplatelet and vasodilating effects (Tanaka et al., 1988; Ikeda et al., 2002). The phosphodiesterase type 3 is the most abundant PDE isoform in platelets (Ikeda, 1999; Oishi et al., 2000; Sudo et al., 2000). This potent quinolinone derivative decreases platelet aggregation, release, and TXA_2 formation. Endothelial production of prostacyclin, however, is not decreased by cilostazol. Limited data suggests a role for secondary stroke prevention (Gotoh et al., 2000). A recent study suggested efficacy for the prevention of progression of symptomatic intracranial stenosis with the use of cilostazol; however, the

relative contributions of antiatherogenic, antiproliferative, and antiplatelet actions are not known (Kwon et al., 2005).

Trifusal, another salicylate compound, has been investigated as a possible alternative to aspirin for stroke prophylaxis. A randomized, double-blind multicenter trial of trifusal (600 mg/day) versus aspirin (325 mg/day) failed to show a difference in the occurrence of vascular events between the groups, but the incidence of cerebral hemorrhage was less frequent in those patients who took trifusal (Matias-Guiu et al., 2003). Given the very low cost of aspirin compared to other similar compounds, it is unlikely that novel agents of the same class will supplant its use.

64.3.6. Risk-adapted stroke prevention with antiplatelet agents

Guidelines for stroke prevention have recommended either aspirin, aspirin plus extended-release dipyridamole, or clopidogrel monotherapy without accounting for the individual risk of stroke recurrence (European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Albers et al., 2004; Sacco et al., 2006). In a post-hoc analysis of the ESPS 2 data, Sacco et al. (2005) stratified subpopulations by risk factors and the risk of stroke recurrence according to validated prognostic models for first stroke (Framingham Stroke Profile [Wolf et al., 1991]) and recurrent stroke (Stroke Prognostic Instrument II [Kernan et al., 2000]). Compared with aspirin alone, aspirin plus ER-DP was more efficacious in reducing the risk of stroke and vascular events in patients with specific characteristics, including age less than 70, hypertension, prior stroke, prior TIA, prior cardiovascular disease, and current smokers. The combination of aspirin plus ER-DP also showed a higher RRR in the high-risk subgroup of the Framingham Stroke Profile and in the moderate-risk subgroup of the Stroke Prognostic Instrument II.

A predictive 10-point score (Essen Stroke Risk Score) has been developed from the CAPRIE study (Ringleb et al., 2004; Diener et al., 2005), and subsequently been validated with the ESPS II data (Diener, 2005). A post-hoc analysis of the CAPRIE data showed a more pronounced effect for clopidogrel versus aspirin in reducing the risk of stroke in patients with a recurrent stroke risk >4%/year (Diener et al., 2005). The same effect could be found for aspirin plus ER-DP versus aspirin in the ESPS 2 data (Diener, 2005). Although these retrospective analyses have yet to be validated by a prospective study, a reasonable, and cost-effective approach is to use aspirin monotherapy for patients with a recurrent stroke risk that is estimated to be less than 4% per year, and the combination of aspirin/ER-DP for patients with a recurrent stroke risk ≥4% per year. Clopidogrel is recommended for patients at high risk for recurrent events (≥4% per year) who have peripheral vascular disease or intolerance to either aspirin or dipyridamole.

64.3.7. Antiplatelet drugs in patients with carotid stenosis

Two large randomized trials and meta-analyses have clearly shown that carotid endarterectomy in patients with symptomatic high-grade (>70%) stenosis of the internal carotid artery is beneficial (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1998; Rothwell et al., 1999, 2003). In these studies, operated and medically treated patients received aspirin of various doses: 1,300 mg/day in NASCET, but not specified in ECST. No benefit of higher dose aspirin (650 mg/day or higher) was seen in the ACE trial (Taylor et al., 1999). The current recommendation is for low-dose aspirin (81–325 mg/day) before and after carotid endarterectomy to reduce the rate of stroke, myocardial infarction, and death (Chaturvedi et al., 2005). The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial investigated whether patients with recently symptomatic carotid stenosis would benefit from a combination of clopidogrel plus aspirin, in comparison with aspirin alone, in the time between the index event and a possible intervention (Markus et al., 2005). Using microemboli detected by transcranial Doppler as a surrogate marker, the combination was superior to aspirin monotherapy. Whether the combination would lead to a significant decrease in clinical end-points has yet to be shown in a larger study powered for this hypothesis. Patients who have undergone stenting of the carotid or vertebral arteries are typically treated analogously to coronary artery stent patients with a combination of clopidogrel plus aspirin for about 3 months (Yadav et al., 2004). The benefit of this approach has not been investigated in a randomized trial in cerebrovascular patients.

64.4. Anticoagulants

64.4.1. Mechanism of action

Coumarins have been used for anticoagulation for over 50 years. Warfarin (Coumadin) is derived from coumarin, a compound found in *Galium odoratum* (woodruff), licorice, lavender, and various other

plant species. Originally developed as a poisoning agent for rats, it is currently used less frequently for this indication because of the development of warfarin resistance in rodents. Vitamin K epoxide is normally reduced by epoxide reductase in the liver. This reduced form is required for the synthesis of various coagulation factors, including factors II, VII, IX, and X, as well as proteins C and S. Warfarin limits the synthesis of γ-glutamyl carboxylated forms of these factors and as a result impairs the function of these vitamin K-dependent proteins (Ansell et al., 2004).

64.4.2. Safety and efficacy

The use of warfarin for the prevention of cardio-embolic stroke in patients with non-valvular atrial fibrillation is well-established (European Atrial Fibrillation Trial Study Group, 1993; Singer et al., 2004). In this patient population, the use of anticoagulation is the most efficacious specific medical therapy for prevention of stroke, with an overall relative risk reduction of 68% (Singer et al., 2004). Similarly, anticoagulation is considered the standard of care for the prevention of strokes in patients with mechanical heart valves (Salem et al., 2004). Prevention of cardio-embolic stroke is discussed elsewhere in this volume.

There is a diminishing role for warfarin in the prevention of non-cardio-embolic strokes, as large well-designed multi-center trials have failed to demonstrate superiority over antiplatelet therapy to justify the complexity of required coagulation monitoring and the higher risk of bleeding complications. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) was stopped prematurely because of excessive bleeding in the anticoagulation group, including 27 intracranial hemorrhages (3.7%). This large randomized trial compared high-intensity anticoagulation (international normalization ratio [INR] of 3.0–4.5) to 30 mg/day of aspirin in over 1,300 patients (SPIRIT Study Group, 1997). Although the comparative efficacy of warfarin versus aspirin for prevention of ischemic events could not be determined, it was clearly demonstrated that there is a sharp increase in bleeding complications with increased intensity of anticoagulation: for each increase in 0.5 INR units, the incidence of major bleeding increased by a factor of 1.4. A more modest adjusted dose anticoagulation regimen (INR 1.4–2.8) was compared to aspirin (325 mg/day) in the Warfarin Aspirin Recurrent Stroke Study (WARSS). Patients with a history of non-cardio-embolic stroke were randomized to anticoagulation or antiplatelet therapy and followed for 2 years or until the primary endpoint of recurrent stroke or death was reached. No significant difference was found between the groups for any of the outcomes measured (Mohr et al., 2001). Additionally, patients who were taking aspirin at the time of their initial stroke did not benefit from warfarin over aspirin for recurrent stroke prophylaxis. Subgroup analyses have failed to show a benefit of warfarin over aspirin in patients with a patent foramen ovale (Homma et al., 2002) or those with antiphospholipid antibodies (Levine et al., 2004). The ongoing European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) has targeted an intermediate level anticoagulation (INR 2.0–3.0) versus the combination of aspirin (30–325 mg/day) and DP (400 mg/day) versus aspirin alone. Patients with intracranial atherosclerosis and stroke are at high risk for recurrent vascular events. The Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) study compared warfarin (INR 2.0–3.0) to high-dose aspirin (1,300 mg/day) for prevention of further strokes or death in patients with angiographically proven intracranial atherosclerotic disease. Similar to the above studies, there was no demonstrable benefit of anticoagulation over antiplatelet therapy in this patient population (Chimowitz et al., 2005). Despite the contrary evidence from large randomized trials, some physicians continue to place patients with recurrent non-cardio-embolic strokes on anticoagulation, particularly those who have "failed" antiplatelet therapy (Albers et al., 1999).

64.5. Concluding remarks

Aspirin reduces the odds of the composite outcome of stroke, myocardial infarction, or vascular death in all high-risk patients with symptomatic atherosclerosis by about 23%. The odds of stroke reduction alone are approximately 25%. A reduction of only 16% in the composite outcome is seen in trials where enrollment was limited to patients with stroke or TIA at enrollment. Clopidogrel produces a benefit that is modestly better than aspirin for prevention of stroke or a composite vascular outcome. In stroke/TIA patients, ticlopidine hydrochloride is more effective than placebo for secondary prevention, but its use is limited by frequent adverse effects and the potential for serious hematological abnormalities. The safety profile of clopidogrel is better than ticlopidine, being very similar to aspirin. The combination of DP and aspirin reduces the risk of the outcome cluster of stroke, myocardial infarction, or vascular death by as much as 30%. Both DP and ER-DP, when used in conjunction with aspirin, reduce the risk of recurrent stroke in patients with a history of stroke/TIA by approximately 37%;

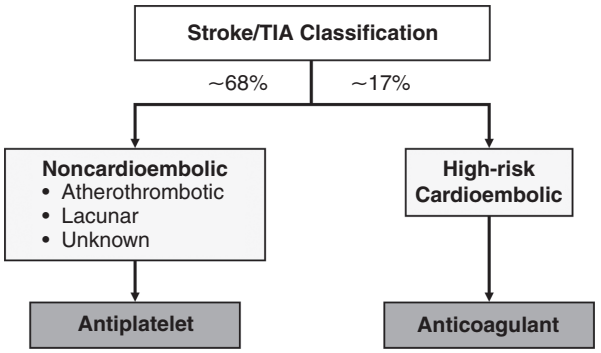

Fig. 64.4. Treatment of stroke is based upon classification of stroke subtype. More than two-thirds of stroke are presumed non-cardioembolic in nature. Antiplatelet therapy is the appropriate preventative treatment for most patients in this subtype.

ER-DP plus aspirin reduces recurrent stroke by 23% over aspirin alone. Retrospective analyses have suggested a rationale for choosing one agent over another, but ongoing prospective clinical trials, such as the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) study—comparing clopidogrel to aspirin/ER-DP—will provide information about the true advantage of one antiplatelet over another in patients with cerebrovascular disease.

Although antiplatelet agents remain the mainstay of medical treatment for preventing the majority of non-cardioembolic ischemic strokes, patients at high risk for cardioembolism should generally be treated with anticoagulants (Fig. 64.4). The perception that anticoagulation is a "stronger" therapy for non-cardioembolic stroke than antiplatelet agents has not been borne out in recent clinical trials. Typically, bleeding complications have outweighed any potential or real benefit. Whether there are specific subgroups of non-cardioembolic stroke that benefit more from anticoagulation than antiplatelet therapy remains to be determined.

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Chapter 65

Carotid endarterectomy, stenting, and other prophylactic interventions

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65.1. Introduction

Knowledge of the relationship between atheromatous disease of the extracranial carotid and vertebral arteries and the occurrence of ischemic stroke goes back to the nineteenth century. In 1856, Virchow described carotid thrombosis in a patient with sudden onset ipsilateral visual loss in whom the ophthalmic and retinal arteries were patent (Gurdjian, 1979). In 1888, Penzoldt reported a patient who developed sudden permanent loss of vision in the right eye and later sustained a left hemiplegia (Penzoldt, 1891). At post mortem she was found to have thrombotic occlusion of the right distal common carotid artery and a large area of cerebral softening in the right cerebral hemisphere. In 1905, Chiari performed a number of pathological studies which led him to suggest that emboli could break away from ulcerated carotid plaques in the neck and cause cerebral infarction (Chiari, 1905). This mechanism of stroke was re-emphasized 50 years later by M. Fisher (1951, 1954).

Several operations were developed in the 1950s and 1960s in which the aim of surgery was to restore the flow of blood to the brain in patients with stenosis or occlusion of the extracranial carotid or vertebral circulations (Thompson, 1996). One of the main contributions leading up to this was the development of cerebral arteriography by Egas Moniz in 1927 (Moniz, 1927) and the subsequent demonstration of stenosis and occlusion of the carotid arteries in life (Moniz et al., 1937). The subsequent development of extracranial/intracranial bypass surgery and carotid endarterectomy are described below. Several other surgical techniques have been tried, although unlike endarterectomy and extracranial/intracranial bypass they have not been tested in randomized controlled trials. These include various bypass procedures for occlusion of the proximal neck and aortic arch vessels, vertebral artery endarterectomy, reconstruction or bypass, and various arterial transpositions involving anastomosis of the subclavian and vertebral arteries into the common carotid artery. These procedures will not be discussed further.

The first operations on the carotid artery were ligation procedures for trauma or hemorrhage. The first report was in Benjamin Bell's *Surgery* in 1793 (Wood, 1857). However, most early ligations resulted in the death of the patient. The first successful ligation was performed by a British naval surgeon, David Fleming, in 1803 (Keevil, 1949). This operation was performed for late carotid rupture following neck trauma in an attempted suicide. The first successful ligation for carotid aneurysm was performed 5 years later in London by Astley Cooper (Cooper, 1836). By 1868, Pilz was able to collect 600 recorded cases of carotid ligation for cervical aneurysm or hemorrhage with an overall mortality of 43% (Hamby, 1952). In 1878, an American surgeon named John Wyeth reported a 41% mortality in a collected study of 898 common carotid ligations, and contrasted this with a 4.5% mortality for ligation of the external carotid artery (Wyeth, 1878).

There were relatively few developments for the next 70 years. However, in 1946, a Portuguese surgeon, Cid Dos Santos, introduced thrombo-endarterectomy for restoration of flow in peripheral vessels (Dos Santos, 1976). The first successful reconstruction of the carotid artery was performed by Carrea, Molins, and Murphy in Buenos Aires in 1951 (Carrea et al., 1955). However, this was not an endarterectomy. Rather they performed

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an end-to-end anastomosis of the left external carotid artery and the distal internal carotid artery in a man of 41 with a recently symptomatic severe carotid stenosis.

In 1954, Eastcott, Pickering and Rob published a case report detailing a carotid resection performed in May 1954 on a 66-year-old woman with recurrent left carotid TIAs and a severe stenosis on angiography (Eastcott et al., 1954). The patient made an uneventful recovery and was relieved of her TIAs. However, in 1975, DeBakey reported that he had performed a carotid endarterectomy on a 53-year-old man in August 1953 (DeBakey, 1975). However, it was the report by Eastcott and colleagues which provided the impetus for the further development of carotid surgery. Over the next 5 years there were numerous other reports of the operation being performed and several technical improvements were suggested (Thompson, 1996). Internal carotid artery occlusion generally came to be regarded as inoperable and surgical attempts to correct carotid coils, kinks, and fibromuscular dysplasia were not generally supported.

By the early 1980s there were over 100,000 procedures per year in the USA alone (Pokras and Dyken, 1988; Gillum, 1995; Tu et al., 1998). However, at this point in time, other than innumerable surgical case series and two small inconclusive randomized trials (Fields et al., 1970; Shaw et al., 1984), there was no good evidence that the operation was of any value. This prompted several eminent clinicians to question the widespread use of the operation in the early 1980s (Barnett et al., 1984; Chambers and Norris, 1984; Warlow, 1984; Jonas, 1987; Winslow et al., 1988), which led to a fall in the number of operations being performed and set the scene for a number of large randomized controlled trials. The first results in patients with symptomatic stenosis began to appear in the early 1990s (European Carotid Surgery Trialists' Collaborative Group, 1991; Mayberg et al., 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991). Surgery clearly did prevent stroke in patients with recently symptomatic severe internal carotid artery stenosis.

65.2. Carotid endarterectomy

65.2.1. The operation

The carotid bifurcation is exposed, mobilized, and slings placed around the internal, external, and common carotid arteries. After applying clamps to these arteries, away from any atheromatous plaque, the bifurcation is opened through a longitudinal incision, the entire stenotic lesion cored out, the distal intimal margin secured, the arteriotomy closed, and the clamps released to restore blood flow to the brain. Most patients should already be on antiplatelet drugs before surgery and these should be continued afterwards because the patients are still at high risk of ischemic stroke in the territory of other arteries, and of coronary events. In addition, most surgeons heparinize patients during the procedure itself. Controlling systemic blood pressure before, during, and after surgery is crucial to avoid hypotension, which will make any cerebral ischemia worse, and hypertension which may cause cerebral edema or even intracerebral hemorrhage. Operative damage to the nerve to the carotid sinus, or changes in the carotid sinus itself, may make control of post-operative blood pressure more of a problem, but in the long term has little if any effect (Eliasziw et al., 1998).

One particular variation, eversion endarterectomy, is becoming increasingly popular (Loftus and Quest, 1987; Darling et al., 1996; Cao et al., 1998; Brothers, 2005). A systematic review of five randomized control trails (RCTs) (2,590 operations) compared eversion endarterectomy versus conventional endarterectomy performed either with primary closure or patch angioplasty (Cao et al., 2004). Overall, there was no significant difference in the rates of peri-operative stroke, stroke or death, and local complication rates, but the absolute risks were rather low (risk of stroke or death was 1.7% with eversion versus 2.6% with conventional endarterectomy).

65.2.1.1. Shunting

In theory, it should be possible to prevent low cerebral blood flow (and perhaps therefore an ischemic stroke) during carotid clamping by inserting a temporary intraluminal shunt from the common carotid artery to the internal carotid artery distal to the operation site. Some surgeons routinely shunt for this reason, and to allow more time to teach trainees, but there are problems, including arterial dissection and transmission of emboli from thrombus in the common carotid artery, as well as an increase in the duration of surgery and possibly in local operation site complications. A compromise is to selectively shunt only patients likely to develop, or who actually are experiencing, cerebral ischemia as a result of low flow. However, efforts to identify the patients who need shunting have been inconclusive (Ferguson, 1986; Ojemann and Heros, 1986; Naylor et al., 1992; Belardi et al., 2003) and there is considerable variation in routine practice (Bond et al., 2002a). Unfortunately, randomized trials of different shunting policies have been too small in size and too few in number to provide reliable answers (Bond et al., 2002b). As a result, there is no standard policy for either operative monitoring or the use of shunts.

65.2.1.2. Restenosis and patch angioplasty

After carotid endarterectomy the long-term risk of ischemic stroke ipsilateral to the operated artery is so low (Cunningham et al., 2002) that recurrent stenosis cannot be of any great clinical concern in the sense of causing stroke. If stenosis does recur then a second endarterectomy is more difficult and more risky (Bond et al., 2003a), and angioplasty or stenting may be preferable, although there is no randomized evidence for either procedure in symptomatic or asymptomatic restenosis (Yadav et al., 1996). In fact, the reported rate of restenosis varies enormously depending on whether the study was prospective or retrospective, the completeness and length of follow-up, the sensitivity and specificity of the imaging method used, and the definition of restenosis (Fredricks et al., 1998). Certainly, recurrent atherothrombotic stenosis can occur, but usually not for some years, whilst early restenosis (within a year or so) is more likely to be due to neointimal hyperplasia (Hunter et al., 1987). On balance, therefore, there is little point in repeated clinical or ultrasonographic follow-up to detect asymptomatic restenosis, but if a restenosis becomes symptomatic then a repeat carotid endarterectomy or stenting is reasonable.

Many surgeons routinely use a patch of autologous vein, or synthetic material, to close the artery, enlarge the lumen and so reduce the risk of restenosis and, more importantly, of stroke. Patching increases the surgery time and there are complications, including rupture to cause a life-threatening neck hematoma, and infection if synthetic grafts are used. A meta-analysis of randomized trials of primary closure, vein patch, or synthetic patch included data on 1,127 patients undergoing 1,307 operations in several small trials (Bond et al., 2004a). Carotid patch angioplasty was associated with about a 60% reduction in the operative risks of stroke or death during the peri-operative period ($p = 0.007$) and long-term follow-up ($p = 0.004$). Patching was also associated with an 85% reduction in risk of peri-operative arterial occlusion ($p = 0.00004$), and an 80% reduction in risk of restenosis during long-term follow-up in five trials ($p < 0.00001$).

Some surgeons who use carotid patching favor using a patch made from an autologous vein, while others prefer to use synthetic materials. The most recent meta-analysis of randomized trials of different types of patch included data on 1,480 operations (Bond et al., 2004b). During follow-up for more than 1 year, no difference was shown between the two types of patch for the risk of stroke, death, or arterial restenosis. However, the number of events was small. Based on 15 events in 776 patients in 4 trials, there were significantly fewer pseudoaneurysms associated with synthetic patches than vein [OR = 0.09, 0.02–0.49; 95% confidence interval (CI)] but the clinical significance of this finding is uncertain (Bond et al., 2004b). Overall, it is likely that the differences between different types of patch material are small.

65.2.1.3. General versus regional anesthesia

Surgery has traditionally been performed under general rather than regional anesthesia, but surgery under locoregional anesthesia is becoming more widespread. With regional anesthesia, there is a much lower shunt rate because it is immediately obvious when a shunt is needed to restore blood flow distal to the carotid clamps, elaborate intraoperative monitoring is unnecessary, and hospital stay may be shorter. On the other hand, some patients will not tolerate the procedure and a quick change to general anesthesia may be required. A detailed systematic review and meta-analysis of randomized and non-randomized studies has provided some useful information (Rerkasem et al., 2004). Seven randomized trials involving 554 operations, and 41 non-randomized studies involving 25,622 operations were included. Meta-analysis of the non-randomized studies showed that the use of local anesthetic was associated with significant reductions in the odds of death (35 studies), stroke (31 studies), stroke or death (26 studies), myocardial infarction (22 studies), and pulmonary complications (7 studies), within 30 days of the operation, but these non-randomized data are potentially unreliable. Meta-analysis of the fewer and generally small randomized studies showed that the use of local anesthetic was associated with a significant reduction in local hemorrhage (OR = 0.31, 95% CI = 0.12–0.79) within 30 days of the operation, but there was only a borderline statistically significant trend towards a reduced risk of operative death and no evidence of a reduction in risk of operative stroke. A large European multicenter randomized trial (GALA) has now randomized over 3,000 patients and is expected to report its findings in 2008 (http://www.dcn.ed.ac.uk/gala).

65.2.2. Risks of carotid endarterectomy

Carotid endarterectomy is associated with a variety of potential complications (Naylor and Ruckley, 1996; Bond et al., 2002c). The most important of these are stroke and death.

65.2.2.1. Death

Death within a few days of surgery occurs in about 1–2% of patients and is generally due to stroke, myocardial infarction, or some other complication of the frequently associated coronary heart disease or (rarely) to pulmonary embolism (Rothwell et al., 1996a). Higher rates can be found in "administrative data sets"

which may be a more realistic reflection of routine practice than large randomized trials, but any comparisons are confounded by variation in casemix, particularly the proportion of patients with asymptomatic stenosis who have a lower case fatality (Rothwell et al., 1996b; Wennberg et al., 1998; Bond et al., 2003b).

65.2.2.2. Stroke

The main complication of surgery is peri-operative stroke (Naylor and Ruckley, 1996; Ferguson et al., 1999; Bond et al., 2002c). The reported risk ranges from an implausibly low 1% or less, to an unacceptably high of 20% or more (Bond et al., 2004c). This variation may be explained by differences in: the definition of stroke; whether all or only some strokes are included; the accuracy of stroke diagnosis; the completeness of the clinical details; whether the study was retrospective or prospective; whether the diagnosis of stroke was based on patient observation or just medical record review; variation in casemix, surgical, and anesthetic skills; chance variation; and publication bias (Campbell, 1993; Rothwell et al., 1996b). No more than 20% of peri-operative strokes are likely to be fatal, and so reports of less than four times as many non-fatal as fatal strokes suggest undercounting of mild strokes, a tendency which may well be due to surgeons reporting their own results without the "help" of any neurologists (Rothwell and Warlow, 1995). Despite the obvious implications for service planning, it has been all but impossible to sort out whether there really is a systematic difference in risk between surgeons. This is largely due to the problems of adjusting for casemix, as well as chance effects due to the inevitably rather small numbers operated on by each surgeon (Rothwell et al., 1999a). One might anticipate that high-volume surgeons might have lower operative risks than low-volume surgeons (Kucey et al., 1998; Killeen et al., 2007), but the data are not conclusive.

There are several causes for peri-operative stroke but these are often difficult to identify when it occurs during general anesthesia, or even afterwards. It is difficult to be sure whether any stroke is due to embolism or low flow (Steed et al., 1982; Krul et al., 1989; Riles et al., 1994; Spencer, 1997). Clearly, temporary reduction in internal carotid artery blood flow during carotid clamping may cause ipsilateral ischemic stroke if the collateral supply is inadequate, particularly if there is already maximal cerebral vasodilatation (i.e., cerebrovascular reserve is exhausted). However, embolism from the operation site is probably the most common cause of stroke *during* surgery. Atherothrombotic debris may be released while the carotid bifurcation is being mobilized, as the carotid clamps are applied, when any shunt is inserted, and when the clamps are removed. Indeed, air bubbles or particulate emboli during surgery are very commonly detected by transcranial Doppler ultrasound, although most seem to be of little clinical consequence (Gaunt et al., 1993; Jansen et al., 1994a). Post-operative ischemic stroke is usually due to embolism from residual but disrupted atheromatous plaque; thrombus forming on the endarterectomized surface or on suture lines, or more probably on a loose distal intimal flap where the lesion has been carelessly snapped off; thrombus complicating damaged arterial wall as a result of the clamps; and thrombus complicating arterial dissection starting at a loose intimal flap of the internal carotid artery or as a result of shunt damage to the arterial wall. A high rate of post-operative microembolic signals on transcranial Doppler monitoring may predict ischemic stroke (Levi et al., 1997).

65.2.2.3. Cerebral hemorrhage and hyperperfusion syndrome

Intracranial hemorrhage accounts for about 5% of peri-operative strokes (Bond et al., 2002c; Wilson and Ammar, 2005). It can occur during surgery or up to about 1 week later, almost always ipsilateral to the operated artery. It may be due to the increase in perfusion pressure and cerebral blood flow that occurs after removal of a severe internal carotid artery stenosis, particularly if cerebral autoregulation is defective as a consequence of a recent cerebral infarct (Ouriel et al., 1999). Antithrombotic drugs and uncontrolled hypertension may also play a part (Solomon et al., 1986; Hafner et al., 1987; Piepgras et al., 1988; Jansen et al., 1994b; Wilson and Ammar, 2005).

Transient cerebral hyperperfusion, ipsilateral but sometimes bilateral, lasting some days is quite common after carotid endarterectomy (Adhiyaman and Alexander, 2007), particularly if the lesion is severely stenosing and cerebrovascular reserve is already poor with impaired autoregulation. This may be the cause of the occasional case of ipsilateral transhemispheric cerebral edema, intracerebral hemorrhage, focal epileptic seizures and headache which can all occur a few days after surgery. Clearly this syndrome is different from ischemic stroke due to low flow or embolism, and is distinguished by the slower onset, as well as by brain and arterial imaging (Andrews et al., 1987; Schroeder et al., 1987; Naylor et al., 1993b; Chambers et al., 1994; Breen et al., 1996; Van Mook et al., 2005; Adhiyaman and Alexander, 2007). To complicate matters, a very similar clinical syndrome has been described as a result of cerebral vasoconstriction (Lopez-Valdes et al., 1997).

65.2.2.4. Cardiovascular and respiratory complications

Myocardial infarction during, or in the early days after surgery, occurs in 1–2% of patients (Bond et al., 2002c), more often if there is symptomatic coronary heart disease, and particularly if myocardial infarction has occurred in the previous few months or if the patient has unstable angina. Peri-operative myocardial infarction can be painless so clues to the diagnosis are unexplained hypotension, tachycardia, and dysrhythmias. Congestive cardiac failure, angina, and cardiac dysrhythmias are also occasional concerns (Riles et al., 1979; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Urbinati et al., 1994; Paciaroni et al., 1999; Bond et al., 2002c). Post-operative hypertension and hypotension may be a problem, perhaps due to operative interference with the carotid baroreceptors, but it is transient. Post-operative chest infection occurs in less than 1%.

65.2.2.5. Cranial and peripheral nerve injuries

Nerve injuries result from traction, pressure, or transection can occur in up to 20% of cases, depending on how hard one looks. However, these injuries seldom have any long-term consequence (Cunningham et al., 2004). Damage to the recurrent and superior laryngeal branches of the vagus nerve, or more probably the vagus itself, causes change of voice quality, hoarseness, difficulty coughing, and sometimes dyspnea on exertion due to vocal cord paralysis. If a simultaneous or staged bilateral carotid endarterectomy is done, and causes bilateral vocal cord paralysis, then airway obstruction can occur. Hypoglossal nerve injury causes ipsilateral weakness of the tongue which can lead to temporary or even permanent dysarthria, difficulty with mastication or dysphagia. Again, bilateral damage causes much more serious speech and swallowing problems, and sometimes even upper airway obstruction. Therefore, if a patient has symptoms referable to *both* severely stenosed carotid arteries, requiring bilateral carotid endarterectomy, it is probably safer to do the operations a few weeks apart rather than under the same anesthetic, mostly because of the dangers of bilateral hypoglossal or vagal nerve damage.

Damage to the marginal mandibular branch of the facial nerve causes rather trivial weakness at the corner of the mouth. Spinal accessory nerve injury is rare and causes pain and stiffness in the shoulder and neck, along with weakness of the sternomastoid and trapezius muscles. A high incision can cut the greater auricular nerve to cause numbness over the ear lobe and angle of the jaw, which may persist and be irritating for the patient. Damage to the transverse cervical nerves is almost inevitable and causes numbness around the scar area, which is seldom a problem. Clearly, permanent disability from a nerve injury can be as bad as a mild stroke and needs to be taken into account when considering the risks and benefits of surgery (Gutrecht and Jones, 1988; Maniglia and Han, 1991; Sweeney and Wilbourn, 1992; Cunningham et al., 2004).

65.2.2.6. Local wound complications

Local complications include: infection; hematoma, or rarely major hemorrhage, due to leakage or rupture of the arteriotomy or patch which can be life threatening if it causes tracheal compression; aneurysm formation weeks or years later; and malignant tumor in the scar. All of these are rare (Graver and Mulcare, 1986; Martin-Negrier et al., 1996; Bond et al., 2002c). Although surgeons often notice the hemostatic defect caused by preoperative aspirin, this probably does not increase the rate of reoperation for bleeding (Lindblad et al., 1993). Very rarely the thoracic duct can be damaged and cause a chyle fistula.

65.2.2.7. Headache and facial pain

Headache ipsilateral to the operation may herald cerebral hyperperfusion (Van Mook et al., 2005; Adhiyaman and Alexander, 2007), but may also be due to something akin to cluster headache due to subtle damage to the sympathetic plexus around the carotid artery (De Marinis et al., 1991; Ille et al., 1995). Very rarely, focal epileptic seizures occur as well as headache (Youkey et al., 1984; Naylor et al., 2003). Facial pain ipsilateral to surgery and related to eating is unusual and may in some way be due to disturbed innervation of the parotid gland (Truax, 1989).

65.2.3. Potential benefits of carotid endarterectomy

As a result of the large randomized controlled trials, it is now clear that endarterectomy of recently symptomatic severe carotid stenosis almost completely abolishes the high risk of ischemic stroke ipsilateral to the operated artery over the subsequent 2 or 3 years. Moreover, this effect is durable over at least 10 years (European Carotid Surgery Trialists' Collaborative Group, 1991, 1998; Mayberg et al., 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Barnett et al., 1998; Rothwell et al., 2003a). Indeed, the ipsilateral stroke risk becomes so low that presumably both embolic and low-flow strokes are being prevented (Fig. 65.1).

On average, there is an advantage to surgery when the symptomatic stenosis exceeds 80% diameter reduction of the arterial lumen using the European Carotid Surgery Trial (ECST) method, which is about the same as 70%

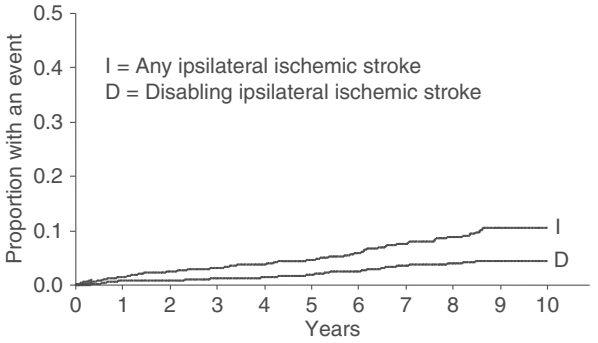

Fig. 65.1. The risk of stroke more than 30 days after successful carotid endarterectomy for recently symptomatic stenosis in patients randomized to surgery in the European Carotid Surgery Trial.

using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. The risk of surgery is much the same at all degrees of stenosis and so, because the unoperated risk of stroke in patients with less than 60% (ECST) stenosis is so low, the risk of surgery is not worthwhile for them. Because the risk of stroke in moderate stenosis patients remains low for several years, there is no point in duplex follow-up in case the stenosis becomes more severe. No doubt severe stenosis does sometimes develop but, unless there are further symptoms, the stenosis by this time is essentially asymptomatic and carries such a low risk of stroke that there is no overall advantage for surgery. It is preferable to ask the patient to return if there are any further cerebrovascular symptoms and, if the stenosis is then 80% (ECST) or more, it is reasonable to recommend carotid endarterectomy.

Carotid endarterectomy may also improve cognitive performance, perhaps by increasing cerebral blood flow or by reducing the frequency of subclinical emboli which declines after surgery (Markus et al., 1995; Van Zuilen et al., 1995). On the other hand, subtle cognitive difficulties may complicate the procedure itself (Lloyd et al., 2004; Bossema et al., 2005; Lal, 2007), and there is some evidence that previous carotid endarterectomy is associated with more rapid cognitive decline in the longer-term (Bo et al., 2006). Unfortunately, studies addressing this issue have been beset with methodological difficulties (Lunn et al., 1999) and it is difficult to imagine that this balance of cognitive benefit and risk will ever be resolved because further randomized trials will probably never be done, at least not in symptomatic stenosis patients.

It is conceivable that patients with impaired cerebral reactivity and raised oxygen extraction fraction are at particular risk of stroke without surgery, and that this impairment can be corrected by carotid endarterectomy, but the studies have been too small to be sure (Schroeder, 1988; Naylor et al., 1993a; Yonas et al., 1993; Hartl et al., 1994; Yamauchi et al., 1996; Visser et al., 1997; Silvestrini et al., 2000; Markus and Cullinane, 2001). Also, we do not know what proportion of strokes in patients with recently symptomatic severe carotid stenosis are actually due to impaired cerebral reactivity, either as a direct result of low flow or perhaps indirectly as a result of an inadequate collateral circulation to compensate for acute arterial occlusion if it should occur. Nor do we know whether the risk of surgery is higher in these patients and so whether on balance carotid endarterectomy will indeed reduce stroke risk any more than in those without impaired reactivity.

65.2.4. Selection of patients for endarterectomy for symptomatic carotid stenosis

If the surgical risk of stroke is, say, 7% in routine clinical practice rather than the more optimistic estimates of some surgeons, if the unoperated risk of stroke is 20% after 2 years which is on average the case for severe stenosis, and if successful surgery reduces this risk of stroke to zero which is not far from the truth, then doing about 15 operations would cause 1 stroke and avoid 3. The net gain would be two strokes avoided. Clearly, to reduce this number of patients that have to be operated on to prevent one having a stroke, and therefore to maximize cost-effectiveness, we need to know exactly who is at highest risk of surgical stroke, and who will survive to be at the highest risk of ipsilateral ischemic stroke if surgery is not done. It is therefore essential that safe surgery is offered to those patients who have most to gain (i.e., those at highest risk of ipsilateral ischemic stroke without surgery) and who are most likely to survive for a number of years to enjoy that gain. Ideally we must focus surgery on the small number of patients who *will* have a stroke without it, not on the larger number of patients who *might* have a stroke, because in the latter group there will be a lot of unnecessary operations.

Furthermore, the cost of identifying suitable patients for carotid surgery is high, with more than 30% of the cost attributed to the initial consultation at the neurovascular clinics. The cost of preventing one stroke by carotid endarterectomy in the UK in 1997–1998 was in the region of £100,000 if all the costs incurred in the workup of a cohort for potential carotid endarterectomy are included (Benade and Warlow, 2002a). Even excluding the cost of working up the very large number of TIA and stroke patients to find the 5–10% or so suitable for surgery, surgery is not cheap: US$4,000 and $6,000 in a private and university hospital respectively in the USA in 1985 (Green and McNamara, 1987); US$11,602 in Sweden in 1991 (Terent et al., 1994); about US$7,000 in Canada in 1996 (Smurawska et al.,

1998). The cost of surgery was mainly in the range $9,500 to $11,500 in a recent systematic review (Benade and Warlow, 2002b).

65.2.4.1. Who is at high (or low) risk of surgery?

As well as being related to the skills of the surgeon and anesthetist and aspects of the surgical technique, the operative risk of stroke and death also depends on patient age and sex, the nature of the presenting event, co-existing pathology, such as coronary heart disease, and several other factors.

65.2.4.1.1. Presenting event

The operative risk of stroke and death is lower for patients with asymptomatic stenosis than for those with symptomatic stenosis (Rothwell et al., 1996a; Bond et al., 2003a). Not surprisingly, therefore, it also varies with the nature of the presenting symptoms. In a systematic review of all studies published from 1980 to 2000 (inclusive) that reported the risk of stroke and death due to endarterectomy (Bond et al., 2003a), 103 of 383 studies stratified risk by the nature of the presenting symptoms (Table 65.1). As expected, the operative risk for symptomatic stenosis overall was higher than for asymptomatic stenosis (OR = 1.62, 95% CI = 1.45–1.81, $p < 0.00001$, 59 studies), but this depended on the nature of the symptoms, with the operative risk in patients with ocular events only tending to be lower than that for asymptomatic stenosis (OR = 0.75, CI = 0.50–1.14, 15 studies). Operative risk was the same for stroke and cerebral TIA (OR = 1.16, CI = 0.99–1.35, $p = 0.08$, 23 studies), but higher for cerebral TIA than for ocular events only (OR = 2.31, CI = 1.72–3.12, $p < 0.00001$, 19 studies). Given that the operative risk of stroke is so highly dependent on the clinical indication, audits of risk should be stratified by the nature of any presenting symptoms and patients should be informed of the risk that relates to their presenting event.

65.2.4.1.2. Age and sex

In the randomized trials of carotid endarterectomy for both symptomatic and asymptomatic carotid stenosis

Table 65.1

A systematic review of the studies reporting the operative risks of stroke or death due to carotid endarterectomy according to the nature of the presenting event and stratified according to year of publication (Bond et al., 2003a).

Presenting event	Time period	Number of studies	Number of operations	Absolute risk % & (95%CI)	*p*-heterogeneity
Symptomatic	<1995	57	17,597	5.0 (4.4–5.5)	<0.001
	≥1995	38	18,885	5.1 (4.7–5.6)	<0.001
	Total	95	36,482	5.1 (4.6–5.6)	<0.001
Urgent	<1995	9	143	16.8 (8.0–25.5)	<0.001
	≥1995	4	65	24.6 (17.6–31.6)	<0.001
	Total	13	208	19.2 (10.7–27.8)	<0.001
Stroke	<1995	27	3,071	7.3 (6.1–8.5)	<0.001
	≥1995	23	4,563	7.0 (6.2–7.9)	<0.001
	Total	50	7,634	7.1 (6.1–8.1)	<0.001
Cerebral TIA	<1995	11	4,279	4.6 (3.9–5.2)	<0.001
	≥1995	13	3,648	6.9 (6.2–7.5)	<0.001
	Total	24	8,138	5.5 (4.7–6.3)	<0.001
Ocular event	<1995	9	1,050	3.0 (2.5–3.4)	=0.9
	≥1995	9	734	2.7 (1.9–3.3)	<0.001
	Total	18	1,784	2.8 (2.2–3.4)	<0.001
Non-specific	<1995	16	1275	4.2 (3.2–5.3)	<0.001
	≥1995	8	476	4.3 (3.4–5.2)	<0.001
	Total	24	1,751	4.2 (3.2–5.2)	<0.001
Asymptomatic	<1995	29	3,197	3.4 (2.5–4.4)	<0.001
	≥1995	28	10,088	3.0 (2.5–3.5)	<0.04
	Total	57	13,285	2.8 (2.4–3.2)	<0.001
Redo surgery	<1995	9	215	3.8 (2.7–4.9)	<0.001
	≥1995	3	699	4.4 (3.1–5.8)	=0.9
	Total	12	914	4.4 (2.4–6.4)	<0.001

benefit was decreased in women (Rothwell, 2004; Rothwell et al., 2004a), due partly to a higher operative risk than in men, but operative risk was independent of age. However, because these trial-based observations might not be generalizable to routine clinical practice, a systematic review of all publications reporting data on the association between age and/or sex and procedural risk of stroke and/or death from 1980 to 2004 was done (Bond et al., 2005). Females had a higher rate of operative stroke and death (25 studies, OR = 1.31, CI = 1.17–1.47, $p < 0.001$) than males, but no increase in operative mortality (15 studies, OR = 1.05, CI = 0.81–0.86, $p = 0.78$). Compared with younger patients, operative mortality was increased at ≥75 years (20 studies, OR = 1.36, CI = 1.07–1.68, $p = 0.02$), at age ≥80 years (15 studies, OR = 1.80, CI = 1.26–2.45, $p < 0.001$), and in older patients overall (35 studies, OR = 1.50, CI = 1.26–1.78, $p < 0.001$). In contrast, however, operative risk of non-fatal stroke alone was not increased: ≥75 years (16 studies, OR = 1.01, CI = 0.8–1.3, $p = 0.99$); ≥80 years (15 studies, OR = 0.95, CI = 0.61–1.20, $p = 0.43$). Consequently, the overall peri-operative risk of stroke and death was only slightly increased at age ≥75 years (21 studies, OR = 1.18, CI = 0.94–1.44, $p = 0.06$), at age ≥80 years (10 studies, OR = 1.14, CI = 0.92–1.36, $p = 0.34$), and in older patients overall (36 studies, OR = 1.17, CI = 1.04–1.31, $p = 0.01$). Thus, the effects of age and sex on the operative risk in published case series are broadly consistent with those observed in the trials. Operative risk of stroke is increased in women and operative mortality but not the risk of stroke is increased in patients aged ≥75 years.

65.2.4.1.3. Other patient factors

Only a few serious attempts have been made to sort out which other patient-related factors affect peri-operative stroke risk, and then which factors are independent from each other so they can be used in combination to predict surgical risk in individuals (Sundt et al., 1975; McCrory et al., 1993; Goldstein et al., 1994; Riles et al., 1994; Golledge et al., 1996; Kucey et al., 1998; Ferguson et al., 1999). Risk factors almost certainly include hypertension, peripheral vascular disease, contralateral internal carotid occlusion, and stenosis of the ipsilateral external carotid artery and carotid siphon (Rothwell et al., 1997). Whether operating on the left carotid artery is more risky than on the right clearly needs confirmation and, if true, might be to do with the easier detection of verbal than non-verbal cognitive deficits, or with the surgical feeling that it is more difficult operating on the left side (Barnett et al., 1998; Kucey et al., 1998; Ferguson et al., 1999). The independent surgical risk factors for patients in the pooled analysis of data from ECST and NASCET were female sex, presenting event, diabetes, ulcerated plaque, and previous stroke (Rothwell et al., 2004a). Other predictors in the ECST that were not available from NASCET included systolic blood pressure and peripheral vascular disease (Bond et al., 2002c), but the predictive model derived from the ECST patients must be validated in an independent data set.

65.2.4.1.4. Timing of surgery

The optimal timing of surgery was a highly controversial topic (Pritz, 1997; Eckstein et al., 1999). However, it is increasingly clear that surgery should be performed as soon as it is reasonably safe to do so, given the very high early risk of stroke during the first few days and weeks after the presenting TIA or stroke in patients with symptomatic carotid stenosis (Lovett et al., 2004; Fairhead et al., 2005). Any increased operative risk due to early surgery must be balanced against the substantial risk of stroke occurring prior to delayed surgery (Blaser et al., 2002; Fairhead et al., 2005). If the operative risk is unrelated to the timing of surgery then urgent surgery would, of course, be indicated. The pooled analyses of data from the randomized trials of endarterectomy for symptomatic carotid stenosis showed that benefit from surgery was greatest in patients randomized within 2 weeks after their last ischemic event and fell rapidly with increasing delay (Rothwell et al., 2004a). For patients with ≥50% stenosis, the number needed to undergo surgery (NNT) to prevent one ipsilateral stroke in 5 years was 5 for patients randomized within 2 weeks after their last ischemic event versus 125 for patients randomized more than 12 weeks after. This trend was due in part to the fact that the operative risk of endarterectomy in the trials was not increased in patients operated on within a week of their last event (Rothwell et al., 2004a, 2004b). A systematic review of all published surgical case series that reported data on operative risk by time since presenting event also found that there was no difference between early (first 3–4 weeks) and later surgery in stable patients (OR = 1.13, CI = 0.79–1.62, $p = 0.62$, 11 studies). Thus, for neurologically stable patients with TIA and minor stroke, benefit from endarterectomy is greatest if performed within 1 week of the event. However, in the same systematic review (Bond et al., 2003a; Fairhead and Rothwell, 2005), emergency carotid endarterectomy for patients with evolving symptoms (stroke in evolution, crescendo TIA, "urgent cases") had a high operative risk of stroke and death (19.2%, 10.7–27.8), which was much greater than that for surgery in patients with stable symptoms in the same

studies (OR = 3.9, 2.7–5.7, $p < 0.001$, 13 studies). Some uncertainty does exist, therefore, in relation to the balance of risk and benefit of surgery within perhaps 24–72 hours of the presenting event, particularly in patients with stroke, and a randomized trial of early versus delayed surgery during this time scale would be ethical (Fairhead and Rothwell, 2005; Rantner et al., 2005; Welsh et al., 2004). However, delays to surgery in routine clinical practice in many countries can currently be measured in months (Rodgers et al., 2000; Turnbull et al., 2000; Pell et al., 2003; Fairhead et al., 2005) and so the question of by how many hours should surgery be delayed is of somewhat theoretical interest in these healthcare systems.

65.2.4.1.5. Audit and monitoring of surgical results

It is very difficult to compare surgical morbidity between surgeons or institutions, or in the same place at different times, or before and after the introduction of a particular change in the technique, without adjusting adequately for case mix—in other words, for the patient's inherent surgical risk. In addition, large enough numbers have to be collected to avoid random error (Rothwell et al., 1999a). This level of sophistication has never been achieved, and nor probably have adequate methods of routine data collection to support it, in normal clinical practice. It is clearly important, however, to have some idea of the risk of surgery in one's own hospital in the type of patients that are usually operated on. Risks reported in the literature are irrelevant because they are not generalizable to one's own institution.

65.2.4.2. Which patients have most to gain from surgery for symptomatic carotid stenosis?

Not all patients with even extremely severe symptomatic stenosis go on to have an ipsilateral ischemic stroke—far from it. In the ECST, although about 30% with 90–99% stenosis had a stroke in 3 years, 70% did not and these 70% could only have been harmed by surgery, never helped. Both the ECST and NASCET have shown very clearly the importance of increasing severity of carotid stenosis ipsilateral to the cerebral or ocular symptoms in the prediction of ischemic stroke in the same arterial distribution, although even this relationship is not straightforward in that if the internal carotid artery "collapses" distal to an extreme stenosis the risk of stroke is substantially reduced (Morgenstern et al., 1997; Rothwell et al., 2000b) (Fig. 65.2). Angiographically demonstrated "ulceration" or "irregularity" increases the stroke risk even more, but it is unclear whether this can be translated to the appearances on ultrasound (Eliasziw et al., 1994; Rothwell et al., 2000a). These and other determinants of benefit are reviewed below. To complicate matters further one also must avoid offering surgery to patients unlikely to survive long enough to enjoy any benefit of stroke prevention and so for whom the immediate surgical risks would not be worthwhile. These include the very elderly and patients with advanced cancer. It would also seem sensible to avoid surgery in patients with severe symptomatic cardiac disease who are likely to die a cardiac death within a year or two.

65.2.4.2.1. Which range of stenosis?

To target carotid endarterectomy appropriately, it is first necessary to determine as precisely as possible how the overall average benefit from surgery relates to the degree of carotid stenosis. The analyses of each of the main trials of endarterectomy for symptomatic carotid stenosis were stratified by the severity of stenosis of the symptomatic carotid artery, but different methods of measurement of the degree of stenosis on prerandomization angiograms were used, the NASCET method underestimating stenosis as compared with the ECST method (Rothwell et al., 1994). Stenoses reported to be 70–99% in the NASCET were equivalent to 82–99% by the ECST method, and stenoses reported to be 70–99% by the ECST were 55–99% by the NASCET method (Rothwell et al., 1994).

In 1998, the ECST (European Carotid Surgery Trialists' Collaborative Group, 1998) showed that there was no benefit from surgery in patients with 30–49% ECST stenosis or 50–69% ECST stenosis, but that there was major benefit in patients with 70–99% ECST stenosis. When the results of the ECST were stratified by decile of stenosis, endarterectomy was only beneficial in patients with 80–99% ECST stenosis. The 11.6% absolute reduction in risk of major stroke or death at 3 years was consistent with the 10.1% reduction in major stroke or death at 2 years reported in the NASCET (Barnett et al., 1998) in patients with 70–99% NASCET stenosis. However, in contrast to the ECST, the NASCET reported a 6.9% ($p = 0.03$) absolute reduction in risk of disabling stroke or death in patients with 50–69% NASCET stenosis (65–82% ECST stenosis).

Given this apparent disparity between the results of the trials, the ECST group reanalyzed their results such that they were comparable with the results of the NASCET (Rothwell et al., 2003b). This required that the original ECST angiograms be remeasured by the method used in the NASCET and that outcome events be re-defined. Reanalysis of the ECST showed that endarterectomy had reduced the 5-year risk of any stroke or surgical death by 5.7% (95% CI 0–11.6) in patients with 50–69%

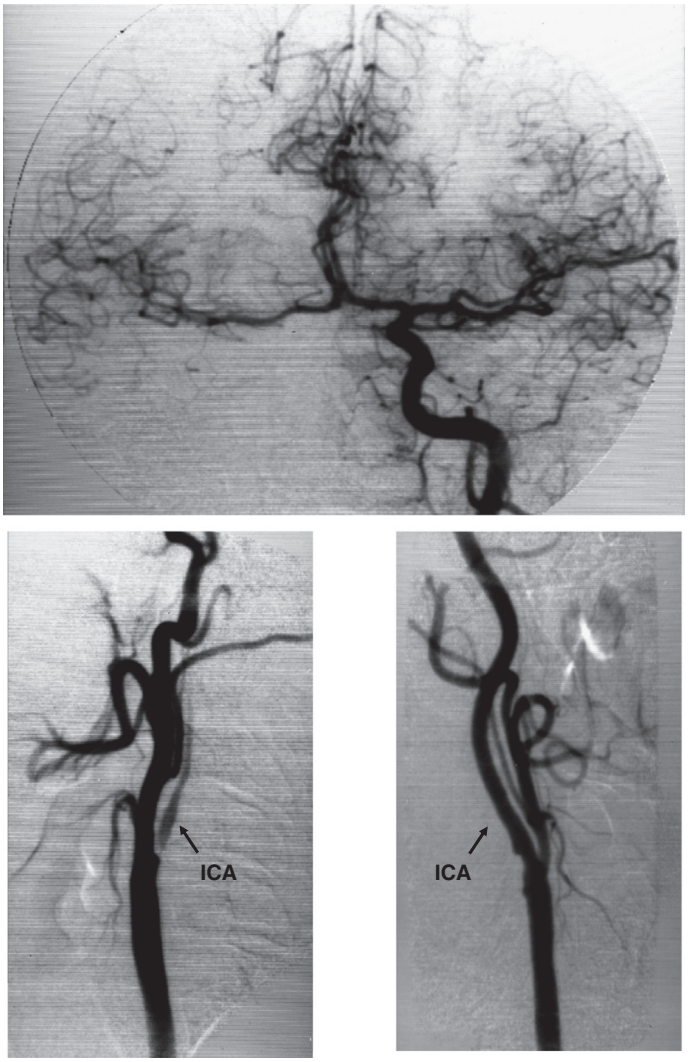

Fig. 65.2. Selective arterial angiograms of both carotid circulations in a patient with a recently symptomatic carotid "near occlusion" (left), and a mild stenosis at the contralateral carotid bifurcation (right). The near-occluded internal carotid artery is markedly narrowed, and flow of contrast into the distal internal carotid artery is delayed. After selective injection of contrast into the contralateral carotid artery significant collateral flow can be seen across the anterior communicating arteries with filling of the middle cerebral artery of the symptomatic hemisphere (top).

NASCET stenosis ($n = 646, p = 0.05$) and by 21.2% (95% CI 12.9–29.4) in patients with 70–99% NASCET stenosis without "near occlusion" ($n = 429$, $p < 0.0001$). Surgery was harmful in patients with < 30% stenosis ($n = 1{,}321$, $p = 0.007$) and of no benefit in patients with 30–49% stenosis ($n = 478, p = 0.6$). Thus, the results of the two trials were therefore consistent when analyzed in the same way. This allowed a pooled analysis of data from the ECST, NASCET and VA#309 trials (Mayberg et al., 1991), which included over 95% of patients with symptomatic carotid stenosis ever randomized to endarterectomy versus medical treatment (Rothwell et al., 2003a)

The pooled analysis showed that there was no statistically significant heterogeneity between the trials in the effect of the randomized treatment allocation on the relative risks of any of the main outcomes in any of the stenosis groups. Data were therefore merged on 6,092 patients with 35,000 patient years of follow-up (Rothwell et al., 2003a). The overall operative mortality was 1.1% (95% CI 0.8–1.5), and the operative risk of stroke and death was 7.1% (95% CI 6.3–8.1). The effect of surgery on the risks of the main trial outcomes is shown by stenosis group in Fig. 65.3. Endarterectomy reduced the 5-year absolute risk of any stroke or death in patients with 50–69% NASCET stenosis (ARR = 7.8%, 95% CI 3.1–12.5) and was highly beneficial in patients with 70–99% NASCET stenosis (ARR = 15.3%, 95% CI 9.8–20.7), but was of no benefit in patients with near occlusion. The

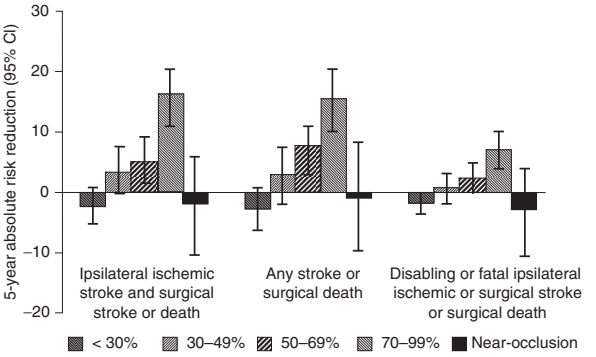

Fig. 65.3. The effect of endarterectomy on the 5-year risks of each of the main trial outcomes in patients with <30% stenosis, 30–49% stenosis, 50–69% stenosis ≥70% stenosis without near occlusion, and in near occlusions, in an analysis of pooled data from the three main randomized trials of endarterectomy versus medical treatment for recently symptomatic carotids stenosis (Rothwell et al., 2003a).

confidence intervals around the estimates of treatment effect in the near occlusions were wide, but the difference in the effect of surgery between this group and patients with ≥70% stenosis without near occlusion was statistically highly significant for each of the outcomes. Qualitatively similar results were seen for disabling stroke.

The results of these pooled analyses show that with the exception of near occlusions, the degree of stenosis above which surgery is beneficial is 50% NASCET (equivalent to about 65% ECST stenosis). Given the confusion generated by the use of different methods of measurement of stenosis in the original trials, it has been suggested that the NASCET method be adopted as the standard in future (Rothwell et al., 2003a). There are several arguments in favor of the continued use of selective arterial angiography in the selection of patients for endarterectomy (Johnston and Goldstein, 2001; Norris and Rothwell, 2001). However, if non-invasive techniques are used to select patients for surgery, then they must be properly validated against catheter angiography within individual centers (Rothwell et al., 2000c). More work is also required to assess the accuracy of non-invasive methods of carotid imaging in detecting near occlusion (Bermann et al., 1995; Ascher et al., 2002).

65.2.4.2.2. What about near-occlusions?

Near occlusions (Fig. 65.2) were identified in the NASCET, because it is not possible to measure the degree of stenosis using the NASCET method in cases in whom the post-stenotic internal carotid artery is narrowed or collapsed due to markedly reduced post-stenotic blood flow. Patients with "abnormal post-stenotic narrowing" of the internal carotid artery were also identified in the ECST (Rothwell and Warlow, 2000b). In both trials, these patients had a paradoxically low risk of stroke on medical treatment. The low risk of stroke is most likely due to the presence of a good collateral circulation, which is visible on angiography in the vast majority of the patients with narrowing of the internal carotid artery distal to a severe stenosis. The benefit from surgery in near occlusions in the NASCET had been minimal, and both the reanalysis of the ECST (Rothwell et al., 2003b) and the pooled analysis (Rothwell et al., 2003a) suggested no benefit at all in this group in terms of preventing stroke. Some patients with near occlusion may still wish to undergo surgery, particularly if they experience recurrent TIAs. In the reanalysis of the ECST (Rothwell et al., 2003b), endarterectomy did reduce the risk of recurrent TIA in patients with near occlusion (absolute risk reduction 15%, $p = 0.007$). However, patients should be informed that endarterectomy does not prevent stroke.

65.2.4.2.3. Which subgroups benefit most?

The overall trial results are of only limited help to patients and clinicians in making decisions about surgery. Although endarterectomy reduces the relative risk of stroke by about 30% over the following 3 years in patients with a recently symptomatic severe stenosis, only 20% of such patients have a stroke on medical treatment alone. The operation is of no value in the other 80% of patients who, despite having a symptomatic stenosis, are destined to remain stroke-free without surgery and can only be harmed. It would, therefore, be useful to be able to identify in advance, and operate on, only those patients with a high risk of stroke on medical treatment alone, but a relatively low operative risk. The degree of stenosis is a major determinant of benefit from endarterectomy, but there are several other clinical and angiographic characteristics that might influence the risks and benefits of surgery.

NASCET published 11 reports of different univariate subgroup analyses, which are summarized elsewhere (Rothwell, 2005). Although interesting, the results are difficult to interpret because several of the subgroups contain only a few tens of patients, with some of the estimates of the effect of surgery based on only one or two outcome events in each treatment group, the 95% confidence intervals around the absolute risk reductions in each subgroup have generally not been given, and there have been no formal tests of the interaction between the subgroup variable and the treatment effect. It is, therefore, impossible to be certain whether differences in the effect of surgery between subgroups are real or due to chance.

Subgroup analyses of pooled data from ECST and NASCET have greater power to determine subgroup–treatment interactions reliably and several clinically important interactions were reported (Rothwell et al., 2004a). Sex ($p = 0.003$), age ($p = 0.03$), and time from the last symptomatic event to randomization ($p = 0.009$) modified the effectiveness of surgery (Fig. 65.4). Benefit from surgery was greatest in men, patients aged ≥75 years, and patients randomized within 2 weeks after their last ischemic event and the benefit from surgery decreased rapidly with increasing delay. For patients with ≥50% stenosis, the number of patients needed to undergo surgery (NNT) to prevent one ipsilateral stroke in 5 years was 9 for men versus 36 for women, 5 for age ≥75 versus 18 for age <65 years, and 5 for patients randomized within 2 weeks after their last ischemic event versus 125 for patients randomized more than 12 weeks after the event. The corresponding absolute risk reductions are shown separately for patients with 50–69% stenosis and 70–99% stenosis in Fig. 65.5. These observations were consistent across the 50–69% and ≥70% stenosis groups and similar trends were present in both ECST and NASCET.

Women had a lower risk of ipsilateral ischemic stroke on medical treatment and a higher operative risk in comparison to men. For recent symptomatic carotid stenosis, surgery is very clearly beneficial in women with ≥70% stenosis, but not in women with 50–69% stenosis (Fig. 65.4). In contrast, surgery reduced the 5-year absolute risk of stroke by 8.0% (3.4–12.5) in men with 50–69% stenosis. This sex difference was statistically significant even when the analysis of the interaction was confined to the 50–69% stenosis group. These same patterns were also shown in both of the large published trials of endarterectomy for asymptomatic carotid stenosis (Rothwell, 2004).

Benefit from carotid endarterectomy increased with age in the pooled analysis of trials in patients with recently symptomatic stenosis, particularly in patients aged over 75 years (Fig. 65.4). Although patients randomized in trials generally have a good prognosis, and there is some evidence of an increased operative mortality in elderly patients in routine clinical practice, as discussed above a recent systematic review of all published surgical case series reported no increase in the operative risk of stroke and death in older age groups. There is therefore no justification for withholding carotid endarterectomy in patients aged over 75 years who are deemed to be medically fit to undergo surgery. The evidence suggests that benefit is likely to be greatest in this group because of their high risk of stroke on medical treatment. Benefit from surgery is probably also greatest in patients with stroke, intermediate in those with cerebral TIA and lowest in those with retinal events (Fig. 65.4). There was also a trend in the trials towards greater benefit in patients with irregular plaque than a smooth plaque.

65.2.4.2.4. Which individuals benefit most?

There are some clinically useful subgroup observations in the pooled analysis of the endarterectomy trials, but the results of univariate subgroup analysis are often of only limited use in clinical practice. Individual patients frequently have several important risk factors, each of which interacts in a way that cannot be described using univariate subgroup analysis, and all of which should be taken into account in order to determine the likely balance of risk and benefit from surgery (Rothwell and Warlow, 1999b). For example, what would be the likely benefit from surgery in a 78-year-old (increased benefit) female (reduced benefit) with 70% stenosis who presented within 2 weeks (increased benefit) of an ocular ischemic event (reduced benefit) and was found to have an ulcerated carotid plaque (increased benefit)?

One way in which clinicians can weigh the often-conflicting effects of the important characteristics of an individual patient on the likely benefit from treatment is to base decisions on the predicted absolute risks of a poor outcome with each treatment option using prognostic models. A model for prediction of the risk of stroke on medical treatment in patients with recently symptomatic carotid stenosis has been derived from the ECST (Rothwell et al., 1999b, 2005) (Table 65.2). The model was validated using data from the NASCET and showed very good agreement between predicted and observed medical risk (Mantel-Haenszel $x^2_{\text{Trend}} = 41.3$, $p < 0.0001$), reliably distinguishing between individuals with a 10% risk of ipsilateral ischemic stroke after 5 years follow-up and individuals with a risk of over 40% (Fig. 65.6). Importantly, Fig. 65.6 also shows that the operative risk of stroke and death in patients who were randomized to surgery in NASCET was unrelated to the medical risk (Mantel-Haenszel $x^2_{\text{Trend}} = 0.98$, df $= 1$, $p = 0.32$). Thus, when the operative risk and the small additional residual risk of stroke following successful endarterectomy were taken into account, benefit from endarterectomy at 5 years varied significantly across the quintiles ($p = 0.001$), with no benefit in patients in the lower three quintiles of predicted medical risk (ARR = 0–2%), moderate benefit in the fourth quintile (ARR = 10.8%, 95% CI = 1.0–20.6), and substantial benefit in the highest quintile (ARR = 32.0%, 95% CI = 21.9–42.1).

Prediction of risk using models requires a computer, a pocket calculator with an *exponential* function, or Internet access (the ECST model can be found at www.stroke.ox.ac.uk). As an alternative, a simplified

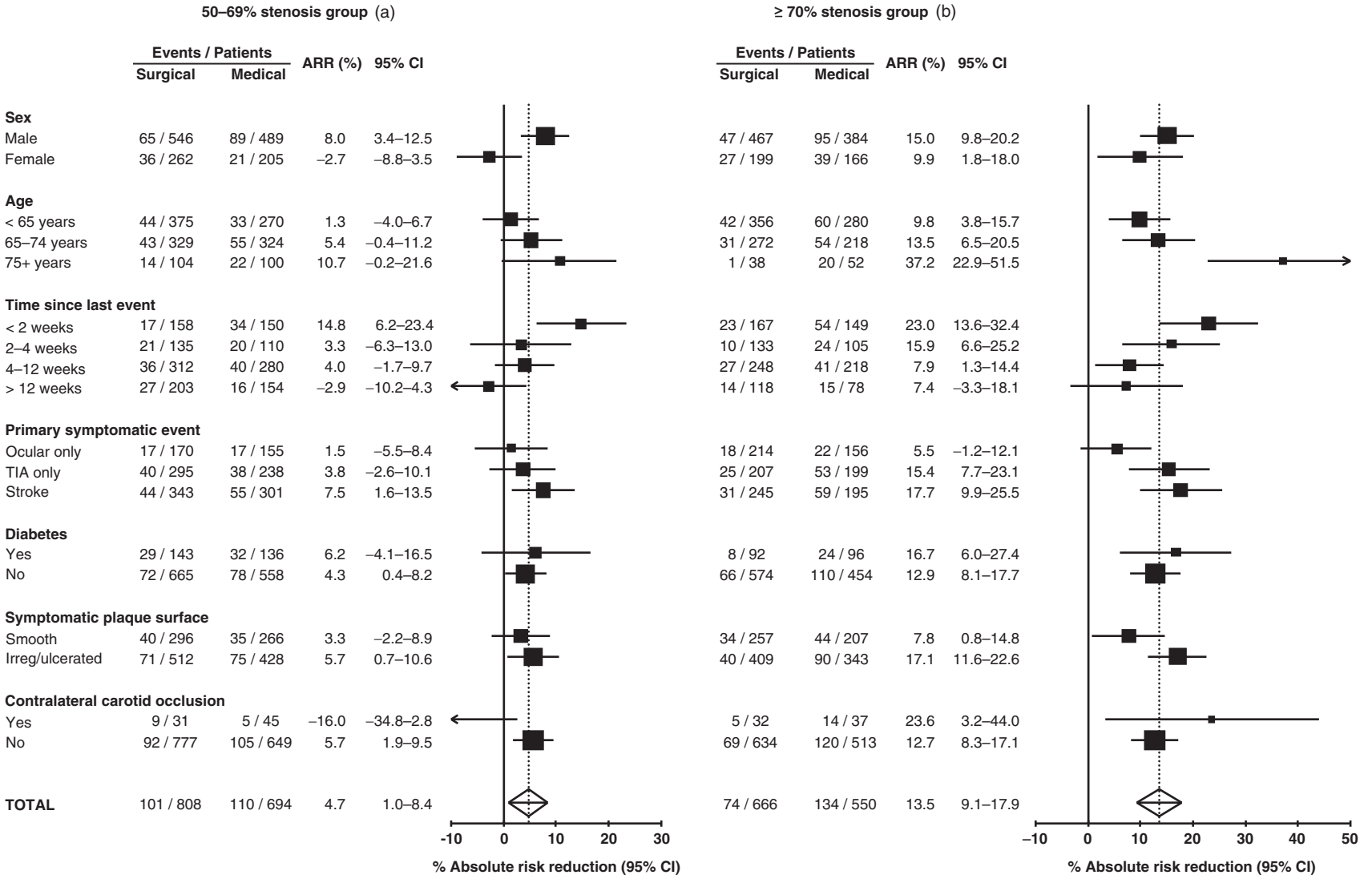

Fig. 65.4. Absolute reduction with surgery in the 5-year risk of ipsilateral carotid territory ischemic stroke and any stroke or death within 30 days after trial surgery according to predefined subgroup variables in an analysis of pooled data from the two largest randomized trials of endarterectomy versus medical treatment for recently symptomatic carotid stenosis (derived from Rothwell et al., 2004a) in: (a) patients with 50–69% stenosis; (b) patients with ≥70% stenosis.

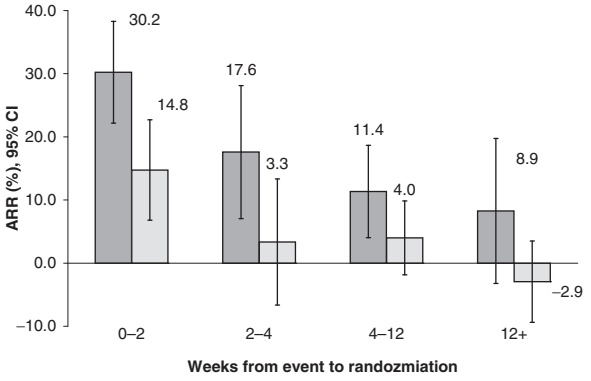

Fig. 65.5. Absolute reduction with surgery in the 5-year risk of ipsilateral carotid territory ischemic stroke and any stroke or death within 30 days after trial surgery in patients with 50–69% stenosis and ≥70% stenosis without near occlusion stratified by the time from last symptomatic event to randomization in an analysis of pooled data from the two largest randomized trials of endarterectomy versus medical treatment for recently symptomatic carotid stenosis (Rothwell et al., 2004a). The numbers above the bars indicate the actual absolute risk reduction.

risk score based on the hazard ratios derived from the relevant risk model can be derived. Table 65.2 shows a score for the 5-year risk of stroke on medical treatment in patients with recently symptomatic carotid stenosis derived from the ECST model. As is shown in the example, the total risk score is the product of the scores for each risk factor. Fig. 65.7 shows a plot of the total risk score against the 5-year predicted risk of ipsilateral carotid territory ischemic stroke derived from the full model, and is used as a nomogram for the conversion of the score into a risk prediction.

Alternatively, risk tables allow a relatively small number of important variables to be considered and have the major advantage that they do not require the calculation of any score by the clinician or patient. Fig. 65.8 shows a risk table for the 5-year risk of ipsilateral ischemic stroke in patients with recently symptomatic carotid stenosis on medical treatment derived from the ECST model. The table is based on the five variables that were both significant predictors of risk in the ECST model (Table 65.2) and yielded clinically important subgroup–treatment effect interactions in the analysis of pooled data from the relevant trials (sex, age, time since last symptomatic event, type of presenting event(s), and carotid plaque surface morphology).

One potential problem with the ECST risk model is that it might over-estimate risk in current patients because of improvements in medical treatment, such as the increased use of statins. However, such improvements in treatment pose more problems for interpreta-

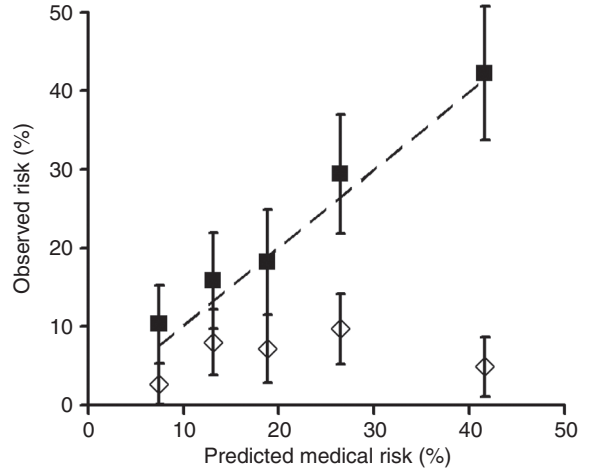

Fig. 65.6. Validation of the ECST model (Table 65.2) for the 5-year risk of stroke on medical treatment in patients with 50–99% stenosis in NASCET (Rothwell et al., 2005). Predicted medical risk is plotted against observed risk of stroke in patients randomized to medial treatment in NASCET (squares) and against the observed operative risk of stroke and death in patients randomized to surgical treatment (diamonds). Groups are quintiles of predicted risk. Error bars represent 95% confidence intervals.

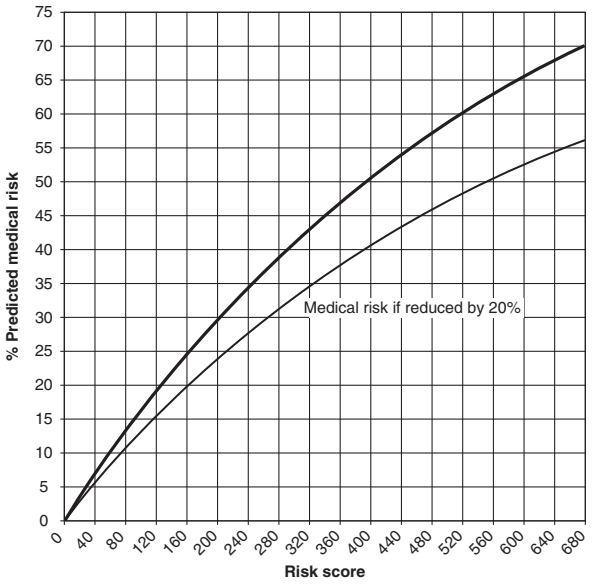

Fig. 65.7. A plot of the total risk score derived from the table against the 5-year predicted risk of ipsilateral carotid territory ischemic stroke derived from the full model in the table in patients in the ECST (thick line). This should be used as a nomogram for the conversion of the score into a prediction of the percentage risk (Rothwell et al., 2005). The thin line represents a 20% reduction in risk as might be seen with more intensive medical treatment than was available in the ECST in the late 1980s and 1990s.

Table 65.2

A predictive model for 5-year risk of ipsilateral ischemic stroke on medical treatment in patients with recently symptomatic carotid stenosis (Rothwell et al., 2005). Hazard ratios derived from the model are used for the scoring system. The score for the 5-year risk of stroke is the product the individual scores for each of the risk factors present. The score is converted into a risk with Fig. 65.7.

MODEL			SCORING SYSTEM		
Risk factor	Hazard ratio (95% CI)	*P* value	Risk factor	Score	Example
Stenosis (per 10%)	1.18 (1.10, 1.25)	<0.0001	Stenosis (%)		
			50–59	2.4	2.4
			60–69	2.8	
			70–79	3.3	
			80–89	3.9	
			90–99	4.6	
Near occlusion	0.49 (0.19, 1.24)	0.1309	Near occlusion	0.5	No
Male sex	1.19 (0.81, 1.75)	0.3687	Male sex	1.2	No
Age (per 10 years)	1.12 (0.89, 1.39)	0.3343	Age (years)		
			31–40	1.1	
			41–50	1.2	
			51–60	1.3	
			61–70	1.5	1.5
			71–80	1.6	
			81–90	1.8	
Time since last event (per 7 days)	0.96 (0.93, 0.99)	0.0039	Time since last event (days)		
			0–13	8.7	8.7
			14–28	8.0	
			29–89	6.3	
			90–365	2.3	
Presenting event		0.0067	Presenting event		
Ocular	1.000		Ocular	1.0	
Single TIA	1.41 (0.75, 2.66)		Single TIA	1.4	
Multiple TIAs	2.05 (1.16, 3.60)		Multiple TIAs	2.0	
Minor stroke	1.82 (0.99, 3.34)		Minor stroke	1.8	
Major stroke	2.54 (1.48, 4.35)		Major stroke	2.5	2.5
Diabetes	1.35 (0.86, 2.11)	0.1881	Diabetes	1.4	1.4
Previous MI	1.57 (1.01, 2.45)	0.0471	Previous MI	1.6	No
PVD	1.18 (0.78, 1.77)	0.4368	PVD	1.2	No
Treated hypertension	1.24 (0.88, 1.75)	0.2137	Treated hypertension	1.2	1.2
Irregular/ulcerated plaque	2.03 (1.31, 3.14)	0.0015	Irregular/ulcerated plaque	2.0	2.0
Total risk score					263
Predicted medical risk using nomogram					37

In cases of near-occlusion, enter degree of stenosis as 85%. Presenting event is coded as the most severe ipsilateral symptomatic event in the last 6 months (severity is as ordered above i.e., ocular events are least severe and major stroke is most severe). Major stroke is defined as stroke with symptoms persisting for at least 7 days. Treated hypertension included previously treated or newly diagnosed.

tion of the overall trial results than for the risk-modeling approach. For example, it would take only a relatively modest improvement in the effectiveness of medical treatment to erode the overall benefit of endarterectomy in patients with 50–69% stenosis. In contrast, very major improvements in medical treatment would be required in order to significantly reduce the benefit from surgery in patients in the high predicted-risk quintile in Fig. 65.6. Thus, the likelihood that ancillary treatments have improved, and are likely to continue to improve, is an

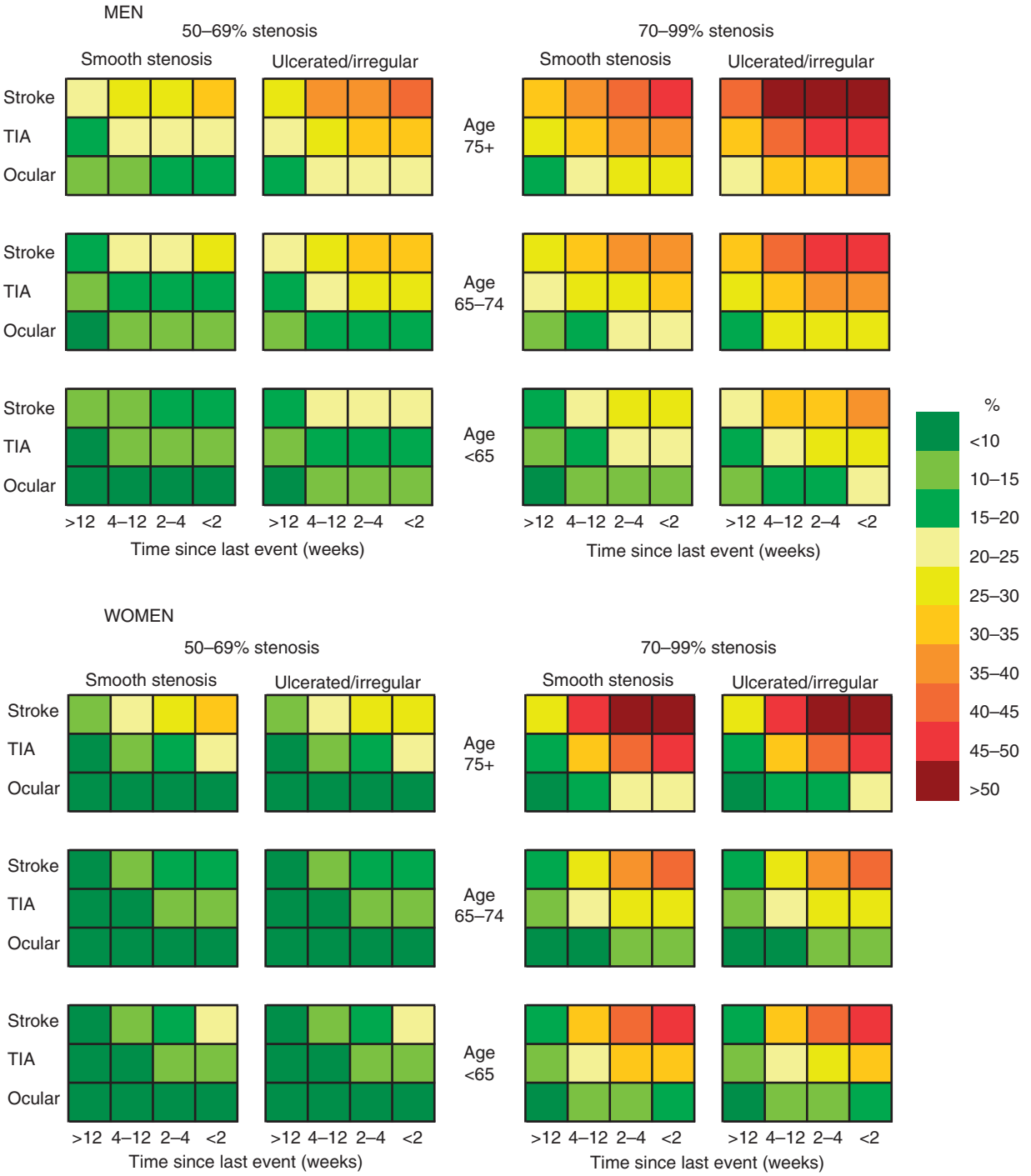

Fig. 65.8. A table of the predicted 5-year absolute risk of ipsilateral ischemic stroke on medical treatment in ECST patients with recently symptomatic carotid stenosis derived from a Cox model based on six clinically important patient characteristics (Rothwell et al., 2005).

argument in favor of a risk-based approach to targeting treatment. However, it would be reasonable in a patient on treatment with a statin, for example, to reduce the risks derived from the risk model by 20% in relative terms. Other prognostic tools, such as measurements of cerebral reactivity and emboli load on transcranial Doppler (Molloy and Markus, 1999; MacKinnon et al., 2005; Markus and MacKinnon, 2005) are not widely used in clinical practice and it is unclear to what extent they are likely to add to the predictive value of the ECST model.

65.2.4.2.5. Patients with multiple potential causes of stroke

Patients often have multiple possible causes for their TIA or stroke. For example, patients with a lacunar ischemic stroke or TIA may have ipsilateral severe carotid stenosis. The question then arises whether the stenosis is "symptomatic" (i.e., a small deep lacunar infarct has, unusually, been caused by artery-to-artery embolism or low flow) or "asymptomatic" (i.e., the stenosis is a coincidental bystander and the infarct was really due to intracranial small vessel disease). Unfortunately, but not surprisingly, the number of such patients in the randomized trials is so small and there are only limited published data (Boiten et al., 1996; Inzitari et al., 2000a), although pooled analysis of the individual patient data shows that surgery is beneficial for patients with severe stenosis ipsilateral to a lacunar TIA or stroke (Rothwell, unpublished data). The observational studies mostly show that severe stenosis is approximately equally rare in the symptomatic and contralateral carotid arteries, which rather supports the notion of the stenosis being coincidental (Mead et al., 2000), but does not mean that surgery would not still be beneficial. In practice, most clinicians would recommend surgery, particularly if the stenosis is very severe, because even if the artery was in truth asymptomatic there is some evidence that the risk of ipsilateral ischemic stroke is high enough to justify the risk of surgery. The same arguments probably apply if there is also a major coexisting source of embolism from the heart (such as non-rheumatic atrial fibrillation), in which case the patient may reasonably be offered surgery as well as anticoagulation. With the more widespread use of diffusion-weighted imaging it is, of course, often possible now to infer the likely etiology of stroke from the distribution of acute ischemic lesions.

65.3. Endarterectomy for asymptomatic carotid stenosis

Less than 20% of ischemic stroke patients have had any preceding transient ischemic attacks (TIAs), even when the stroke is likely to have been due to the embolic or low-flow consequences of severe carotid stenosis. Until the moment of stroke, any stenosis is "asymptomatic." If these asymptomatic stenoses could be detected before the stroke, then unheralded (by TIA) stroke might be preventable by carotid endarterectomy, particularly as surgery is beneficial in patients whose stenosis has revealed itself by becoming "symptomatic."

Asymptomatic carotid stenosis can be identified: during screening programs of apparently healthy people when a carotid bruit is heard and/or carotid ultrasound is being used routinely; as a result of hearing a carotid bruit or doing an ultrasound examination during the course of working up patients with angina, claudication, or non-focal neurological symptoms; when bilateral carotid imaging is done in patients with unilateral carotid symptoms (i.e., the patient is symptomatic but one carotid artery is asymptomatic); and when patients are being worked up for major surgery below the neck and a carotid bruit is heard or an ultrasound reveals carotid stenosis. When asymptomatic carotid stenosis comes to attention, four questions arise: What is the risk of operating on it? What is the risk (of stroke) if the stenosis is left unoperated? Does surgery reduce the risk of stroke? What is the balance of immediate surgical risk versus long-term benefit?

65.3.1. Evidence of benefit

Whether the benefits of carotid endarterectomy in patients with asymptomatic stenosis justify the risks and cost is still unclear (Chambers and Donnan, 2005; Chaturvedi et al., 2005), particularly in an era of improved medical treatments. Until relatively recently, guidelines on endarterectomy for asymptomatic stenosis were largely based on the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995) and a few other smaller trials (Chambers and Donnan, 2005). ACAS reported a 47% relative reduction in the risk of ipsilateral stroke and peri-operative death in the surgical arm despite a 5-year risk of ipsilateral stroke without the operation of only 11%. However, even in this optimal trial environment, the absolute reduction in risk of stroke with endarterectomy was only about 1% per year. In addition, the very low operative risks in ACAS may not be matched in routine clinical practice. ACAS only accepted surgeons with an excellent safety record, rejecting 40% of initial applicants and subsequently barring from further participation some surgeons who had adverse operative outcomes during the trial (Moore et al., 1996).

The more pragmatic Medical Research Council Asymptomatic Carotid Surgery Trial (ACST) has probably produced more widely generalizable results (Halliday et al., 2004). Between 1993 and 2003, ACST randomized 3,120 patients with >60% mainly asymptomatic carotid stenosis (12% had symptoms at least 6 months previously) to immediate endarterectomy plus medical treatment versus medical treatment alone or until the operation became necessary. Surgeons were required to provide evidence of an operative risk of 6% or less for their last 50 patients having an endarterectomy

for asymptomatic stenosis, but none were excluded on the basis of his/her operative risk during the trial. Selection of patients was based on the "uncertainty principle," with very few exclusion criteria.

Despite the differences in methods of ACST and ACAS, the absolute reductions in 5-year risk of stroke with surgery were similar (5.3%, 95% CI = 3.0–7.8% versus 5.1%, 95% CI = 0.9–9.1%, respectively). In addition, whereas ACAS had reported only a non-significant 2.7% reduction ($p = 0.26$) in the absolute risk of disabling or fatal stroke with surgery, ACST reported a significant 2.5% (95% CI = 0.8–4.3%, $p = 0.004$) absolute reduction, although the number needed to treat to prevent one disabling or fatal stroke after 5 years remains about 40. The main differences between the trials were in the 30-day operative risks of death (0.14%, 95% CI = 0–0.4% in ACAS versus 1.11%, 95% CI = 0.6–1.8% in ACST; $p = 0.02$) and in the combined operative risk of stroke and death (1.5%, 95% CI = 0.6–2.4% in ACAS versus 3.0%, 95% CI = 2.1–4.0% in ACST; $p = 0.04$).

65.3.2. Selection of patients for endarterectomy for asymptomatic stenosis

As discussed above, the decision to perform carotid endarterectomy should not be taken lightly, given the inevitable anxiety and risks faced by patients undergoing surgery. Applying the same arithmetical approach used above for symptomatic stenosis, if the surgical risk of stroke is, say, 4% in routine clinical practice, if the unoperated risk of stroke is 10% after 5 years on intensive medical treatment, and if successful surgery reduces this risk of stroke to almost zero, then doing about 100 operations would cause four strokes and avoid up to 10. To maximize cost-effectiveness, it is essential that we know who is at highest risk of surgical stroke, and who will survive to be at highest risk of ipsilateral ischemic stroke if surgery is not done. Furthermore, given the high cost of surgery for symptomatic carotid stenosis (Benade and Warlow, 2002a,b), we need to be aware of the health-economic and public health issues related to surgery for asymptomatic stenosis.

65.3.2.1. Risk of carotid endarterectomy for asymptomatic carotid stenosis

There are a large number of case series with very different reported surgical stroke risks for the same reasons as in symptomatic carotid stenosis. Although the risk is about half that for symptomatic carotid stenosis (Rothwell et al., 1996b; Bond et al., 2003a), there is still some risk. Indeed, the risk may not necessarily be low in, for example, patients with angina whose carotid stenosis was discovered during preparation for coronary artery surgery, or in patients who have already had an endarterectomy on one side and are at risk of bilateral vagal or hypoglossal nerve palsies if both sides are operated on.

As for symptomatic stenosis, the risk of surgery cannot be generalized from the literature to one's own institution, a risk that should be known locally. For example, ACAS reported an operative mortality of 0.14% and a risk of stroke and death of 1.5%. However, a systematic review of all studies published during 1990–2000 that reported the risks of stroke and death due to endarterectomy for asymptomatic stenosis found much higher risks (Bond et al., 2003b). The overall risk of stroke and death was 3.0% (2.5–3.5) in 28 studies published post-ACAS (1995–2000). The risk in 12 studies in which outcome was assessed by a neurologist (4.6%, 3.6–5.7) was three times higher than in ACAS (risk ratio = 3.1, 1.7–5.6, $p = 0.0001$). Operative mortality during 1995–2000 (1.1%, 0.9–1.4) was eight times higher than in ACAS (risk ratio = 8.1, 1.3–58, $p = 0.01$). In studies that reported outcome after endarterectomy for symptomatic and asymptomatic stenosis in the same institution, operative mortality was no lower for asymptomatic stenois (OR = 0.80, 0.6–1.1). The proportion of patients operated for asymptomatic stenosis in these studies increased from 16% during 1990–1994 to 45% during 1995–2000. Thus, published risks of stroke and death due to surgery for asymptomatic stenosis are considerably higher than in ACAS, particularly if outcome was assessed by a neurologist. Operative mortality is eight times higher than in ACAS, and suggests that endarterectomy might even increase mortality in patients with asymptomatic carotid stenosis in routine clinical practice. Even after community-wide performance measurement and feedback, the overall risk for stroke or death after endarterectomy performed for asymptomatic stenosis in 10 states in the USA was 3.8% (including 1% mortality) (Kresowik et al., 2004).

65.3.2.2. Who benefits most from surgery for asymptomatic carotid stenosis?

Given the surgical risk (which to some extent must depend on the type of patient under consideration as well as surgical skill), the added risk of any preceding catheter angiography unless non-invasive vascular imaging is deemed sufficiently accurate, and what appears to be a remarkably low risk of stroke in unoperated patients

(even when they have major surgery below the neck), there is clearly no reason to recommend *routine* carotid endarterectomy for asymptomatic stenosis. It follows that deliberately screening apparently healthy people for carotid stenosis is also unwise. What is needed is a prognostic model to pick out those very few patients whose asymptomatic stenosis is particularly likely to cause stroke, and then operate only on them.

Which range of stenosis? Although there is evidence that the risk of ipsilateral ischemic stroke on medical treatment increases with degree of angiographic carotid stenosis, in contrast to trials of endarterectomy in patients with symptomatic carotid stenosis, neither ACST nor ACAS showed increasing benefit from surgery with increasing degree of stenosis within the 60–99% range. There are several possible explanations for this. First, ultrasound may be less accurate than catheter angiography in measuring the degree of stenosis. In ACAS, only patients randomized to surgery underwent catheter angiography, and in ACST all imaging was by Doppler ultrasound without any centralized audit (Halliday et al., 1994). The importance of the precise methods used to measure stenosis was highlighted in a study of patients randomized to the medical arm of the ECST which demonstrated that angiographic measures of stenosis were most reliable in predicting recurrent stroke when selective carotid contrast injections had been given, biplane views were available and when the mean of measurements made by two independent observers was used. (Cuffe and Rothwell, 2006). Second, patients with carotid near-occlusion, which is not readily detectable on ultrasound, were not identified in the randomized trials of endarterectomy for asymptomatic stenosis. In the ECST, for example, the proportion of near-occlusions was 0.6% at 60–69% stenosis, 2.3% at 70–79% stenosis, 9.2% at 80–89% stenosis, and 29.5% at 90–99% stenosis (Rothwell and Warlow, 2000b), and only when near-occlusions were removed was the increased benefit of CEA with increasing stenosis between 70% and 99% clearly apparent (Rothwell et al., 2003a). This issue is further complicated by the findings of recent study of 1,115 patients with asymptomatic stenosis, in which increasing stenosis on ultrasound was positively associated with risk of ipsilateral hemispheric ischemic events at mean 38 months follow-up when stenosis was measured using ECST criteria, but not when NASCET criteria were used (Nicolaides et al., 2005a). Third, the rate of stenosis progression may determine the risk of stroke in patients with asymptomatic stenosis, which is potentially very important considering the longer time frame over which strokes occur in patients with asymptomatic versus symptomatic stenosis. In the ECST, a strong association between the risk of ipsilateral stroke and the degree of carotid stenosis was only seen for strokes that occurred during the first year after randomization, and no relationship was seen between initial stenosis and strokes occurring more than 2 years later (European Carotid Surgery Trialists' Collaborative Group, 1998; Rothwell et al., 2000b). While this could have been partly due to plaque "healing," it is conceivable that in some patients, the degree of stenosis had progressed and the rate of this progression rather than the degree of stenosis at baseline, was the important determinant of stroke risk.

Which subgroups benefit most? Although some subgroup analyses were reported in ACAS, the trial had insufficient power to reliably analyze subgroup–treatment effect interactions. Because of its larger sample size, ACST had greater power to evaluate subgroups, although no analyses were prespecified in the trial protocol (Halliday et al., 1994). ACST did perform some subgroup analyses, but only reported results for the reduction in risk of non-peri-operative stroke (i.e., the benefit) and the peri-operative risk (i.e., the harm) separately (Halliday et al., 2004). The overall balance of hazard and benefit, which is of most importance to patients and clinicians was not reported, although the data could be extracted from the web tables that accompanied the ACST report (Halliday et al., 2004).

ACAS reported a statistically borderline sex–treatment effect interaction, with no benefit from endarterectomy in women (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995). The same trend was seen in ACST (Halliday et al., 2004). A meta-analysis of the effect of endarterectomy on the 5-year risk of any stroke and peri-operative death in ACAS and ACST (Rothwell, 2004) (Fig. 65.9) showed that benefit from surgery was greater in men than in women (pooled interaction $p = 0.01$), and that it remained uncertain whether there is any worthwhile benefit in women at 5 years follow-up, although some benefit may accrue with longer follow-up in ACST.

In patients with symptomatic 70–99% carotid stenosis, the surgical complication rate is higher in the presence of contralateral occlusion, although the evidence still favors endarterectomy in these patients (Rothwell et al., 2004a). However, a post-hoc analysis from ACAS found that patients with contralateral occlusion derived no long-term benefit from endarterectomy, largely due to a lower long-term risk on medical treatment (Baker et al., 2000) but this analysis was under-powered (163 patients) and there was no significant heterogeneity

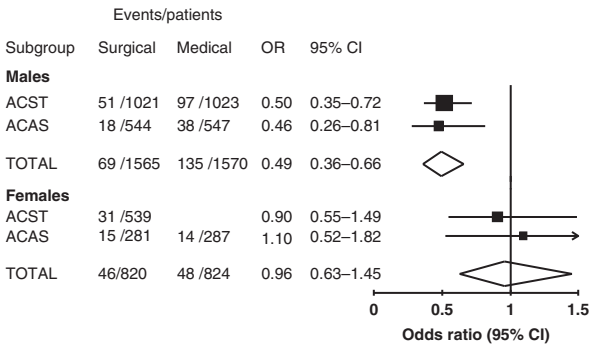

Fig. 65.9. The effect of endarterectomy for asymptomatic carotid stenosis on the risk of any stroke and operative death by sex in the Asymptomatic Carotid Surgery Trial (ACST) and the Asymptomatic Carotid Surgery Trial (ACAS).

according to presence of contralateral occlusion in ACST (Halliday et al., 2004).

Which individuals benefit most? Given the small absolute reductions in the risk of stroke with CEA in ACST and ACAS, there is an urgent need to identify which individual patients are at highest risk of stroke and which individuals are at such low risk of stroke that the risks of surgery cannot be justified. A risk-modeling approach similar to that used in symptomatic carotid stenosis is required, perhaps combining patient clinical features with the results of potentially prognostic investigations, such as transcranial Doppler-detected emboli, impaired cerebral reactivity, the nature of the stenotic plaque on imaging and the rate of plaque progression.

Rates of micro-embolic signals (detected on transcranial Doppler ultrasound scanning might well provide prognostically useful information. A study of 200 patients with $\geq$50% recently symptomatic carotid stenosis found that micro-embolic signals detected on a 1-hour transcranial Doppler (TCD) recording predicted the 90-day risk of recurrent stroke (Markus et al., 2005). In another study of 319 patients with asymptomatic $\geq$60% stenosis (19% had symptoms $>$18 months previously), patients with micro-embolic on 2 $\times$ 1-hour TCD recordings were more likely to have stroke within the first year of follow-up than patients with no micro-embolic signals (adjusted OR for stroke and TIA combined = 4.72 [1.99–11.19, $p < 0.001$]) (Spence et al., 2005). However, a multicenter study of 202 patients with asymptomatic stenosis, in which a variable number (mean 4.3) of 1-hour TCD recordings were made, found only a non-significant trend for more ipsilateral events in micro-embolic-signal-positive arteries (Abbott et al., 2005). Further data will soon be available from the ongoing ACES study (Markus and Cullinane, 2000).

Several observational studies have suggested that increased plaque echolucency (a marker of plaque lipid and hemorrhage content) on ultrasound is associated with higher risks of stroke and TIA distal to a carotid stenosis. However, most of these studies were in patients with symptomatic stenosis and included TIA in the primary end-point. In a recent analysis of imaging data from a cohort study of 1,115 patients with asymptomatic stenosis with a mean of 37 months follow-up, patients were categorized according to the presence of echolucency on baseline ultrasound (Nicolaides at al., 2005b). The cumulative stroke rate was 2% per year in patients with plaques that were uniformly or partly echolucent and 0.14% per year in the remaining patients. However, plaque echolucency on ultrasound was not associated with benefit from carotid endarterectomy in ACST (Halliday et al., 2004) and further research is therefore required to clarify the significance of plaque lipid content in patients with asymptomatic stenosis.

Other methods of plaque imaging might also be of prognostic value. In a study of 154 patients with asymptomatic carotid stenosis imaged with multi-contrast-weighted MRI and followed up for a mean of 38 months, thin or ruptured fibrous cap, intra-plaque hemorrhage, and large lipid core on MRI were all associated with ipsilateral TIA and stroke on follow-up (Takaya et al., 2006). With gadolinium enhancement, the fibrous cap can be visualized more easily on MRI which may allow accurate quantification of fibrous cap thickness (Cai et al., 2005).

There is also good evidence that inflammation has a causal role in carotid plaque instability (Van der Wal et al., 1994; Redgrave et al., 2006). Magnetic resonance visualization of plaque macrophages after their uptake of ultra-small particles of iron oxide is now possible (Trivedi et al., 2004; Tang et al., 2006). However, large prospective studies are required to determine whether these imaging characteristics predict the risk of stroke.

65.4. Carotid angioplasty and stenting

Endovascular treatment was first used in the limbs in the 1960s and subsequently in the renal and coronary arteries (Dotter et al., 1967), but was introduced more cautiously for treatment of carotid bifurcation stenosis in the early 1990s because of the procedural risk of stroke. If endarterectomy of a recently symptomatic severe carotid stenosis more-or-less abolishes the risk of ipsilateral ischemic stroke, then percutaneous transluminal balloon angioplasty, particularly with stenting to maintain arterial patency, could also do so as well (Mathur et al., 1998) (Fig. 65.10). The endovascular approach is now widely used when carotid pathology makes endarterectomy difficult (e.g., high bifurcation

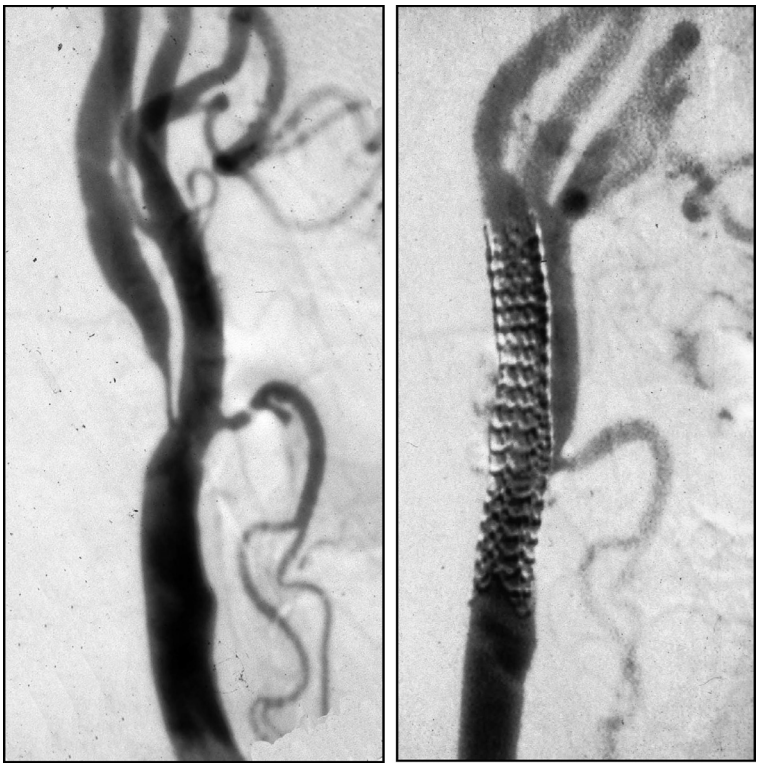

Fig. 65.10. Arterial contrast angiography of a severe carotid stenosis before and after stenting.

or post-radiation stenosis), although it is not always feasible because of contrast allergy, difficult vascular anatomy, or lumen thrombus.

Angioplasty and stenting is usually less unpleasant and less invasive than carotid endarterectomy, and generally more convenient and quicker. Being done under local anesthetic, there may be less perioperative hypertension although cerebral hemorrhage and hyperperfusion have been reported (McCabe et al., 1999; Qureshi et al., 1999). It is less likely to cause nerve injuries, wound infection, venous thrombo-embolism or myocardial infarction, and hospital stay may be shorter, but there are also some potential disadvantages of stenting. The angioplasty balloon may dislodge atherothrombotic debris which then embolizes to the brain or eye, although use of protection devices might help to reduce the risk of stroke due to peri-procedural embolization (Reimers et al., 2001). The procedure may cause arterial wall dissection at the time or afterwards and late embolization might occur due to thrombus formation on the damaged plaque. The angioplasty balloon may obstruct carotid blood flow for long enough to cause low-flow ischemic stroke and dilatation of the balloon may cause bradycardia or hypotension due to carotid sinus stimulation, or aneurysm formation and even arterial rupture due to over-distension of the arterial wall. Hematoma and aneurysm formation may also occur at the site of arterial cannulation in the groin. Rarely the stent may erode through the arterial wall or fracture. In the longer-term, restenosis might be more problematic after stenting than after endarterectomy.

Data on the complication rates of carotid angioplasty/stenting are available from published case series and registries, but as was demonstrated for endarterectomy, such studies tend to underestimate risks. Formal randomized comparisons of endarterectomy and angioplasty/stenting are therefore required to reliably determine the overall balance of risks and benefits. Prior to 2006 only five relatively small RCTs (1,269 patients) had been reported (Naylor et al., 1998; CAVATAS Investigators, 2000; Alberts et al., 2001; Brooks et al., 2001; Yadav et al., 2004). The largest of these trials suggested that the procedural stroke complication rate of angioplasty and stenting was similar to carotid endarterectomy (albeit with wide confidence intervals) and that there are few strokes in the long term (with even wider confidence intervals) (CAVATAS Investigators, 2001). Taken together, the five trials suggested that angioplasty/stenting might have a higher procedural risk of stroke and death than

endarterectomy (OR = 1.33, 95% CI = 0.86–2.04) and a higher rate of restenosis (Coward et al., 2005b).

However, improvements in endovascular techniques and cerebral protection might have reduced the procedural risks (Reimers et al., 2001), and so several larger trials were done, two of which reported initial results in 2006. The SPACE trial is the largest trial of carotid stenting versus endarterectomy to date, doubling the number of randomized patients. It was intended that 1,900 patients with 50–99% (NASCET method) recently symptomatic carotid stenosis be recruited based on a non-inferiority design, but randomization was stopped at 1,200 patients, partly due to a shortage of funding. The procedural 30-day risk of stroke and death was non-significantly higher in the angioplasty/stenting group (OR = 1.1, 95% CI = 0.7–1.7, $p = 0.09$), with 37 (6.3%) strokes and deaths among 584 (6.3%) patients randomized to surgery versus 41 (6.8%) in 599 patients randomized to stenting, and a similar trend for disabling ipsilateral stroke (4.01% versus 2.91%).

The Endarterectomy versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial also reported initial results in 2006 (Mas et al., 2006). EVA-3S was an RCT of angioplasty/stenting versus endarterectomy for 60–99% (NASCET method) recently symptomatic carotid stenosis. The trial stopped early after a higher 30-day procedural risk of stroke and death was found after angioplasty/stenting at a planned interim analysis with 527 randomized patients: 9.6% versus 3.9% (RR = 2.5, 1.2–5.1, $p = 0.01$). There were also more local complications after angioplasty/stenting.

In both of these recent trials, participating clinicians had to demonstrate competence and a good safety record prior to joining, with a quarter of potential centers rejected by SPACE, and there was no evidence that more experienced interventionists had a lower procedural risk than average. The results of further follow-up are awaited and other large trials are currently ongoing (Featherstone et al., 2004; Hobson et al., 2004; CaRESS Steering Committee, 2005; CREST, 2006). Another important issue that is currently being addressed in a large RCT (www.galatrial.com) is whether endarterectomy might have a lower operative risk with local versus general anesthetic, for which there is some evidence (Rerkasem et al., 2004). Any advantage for local anesthetic would have implications for comparisons with stenting since existing RCTs have mainly compared with endarterectomy under general anesthetic.

Taking all the currently available randomized evidence from trials comparing carotid endarterectomy and stenting, stenting appears to be associated with a higher procedural risk of stroke and death, but there is still sufficient uncertainty to justify continuation of ongoing trials. Pending the results of these trials, carotid stenting should be confined to RCTs or to cases in which endarterectomy is technically difficult. Whichever intervention is used, early intervention and selection of patients based on predicted risk of stroke without intervention remain the key to effective stroke prevention.

65.5. Carotid intervention before, during, or after coronary artery surgery

If patients with recently symptomatic carotid stenosis also have symptomatic coronary heart disease requiring surgery, it is unclear whether coronary bypass should be done before the carotid endarterectomy (and risk a stroke during the procedure), after the carotid endarterectomy (and risk cardiac complications during carotid endarterectomy) or simultaneously under the same general anesthetic (and risk both stroke and cardiac complications all at once) (Graor and Hertzer, 1988; Akins, 1995; Davenport et al., 1995). The apparently high risk of the last option may well be unacceptable, although a small quasi-randomized trial suggests otherwise (Hertzer et al., 1989; Borger et al., 1999).

Although carotid endarterectomy or stenting are increasingly recommended before coronary surgery, there is little evidence to support this practice. In an attempt to determine the role of carotid artery disease in the etiology of stroke after coronary artery bypass (CABG), Naylor et al. (2002) performed a systematic review of published case series. The risk of stroke during the first few weeks after CABG was about 2% and remained unchanged from 1970 to 2000. Two-thirds of strokes occurred after day 1 and 23% died. Ninety-one percent of screened CABG patients had no significant carotid disease. Stroke risk was about 3% in predominantly asymptomatic patients with a unilateral 50–99% stenosis, 5% in those with bilateral 50–99% stenoses, and 7–11% in patients with carotid occlusion. Significant predictive factors for post-CABG stroke included carotid bruit (OR 3.6, 95% CI = 2.8–4.6), prior stroke/TIA (OR 3.6, CI = 2.7–4.9) and severe carotid stenosis/occlusion (OR 4.3, CI = 3.2–5.7). However, the systematic review indicated that 50% of stroke sufferers did not have significant carotid disease and 60% of territorial infarctions on CT scan/autopsy could not be attributed to carotid disease alone. Thus, although carotid disease is an important etiological factor in the pathophysiology of post-CABG stroke, even assuming that prophylactic carotid endarterectomy carried no additional risk, it could only ever prevent about 40% of procedural strokes at most.

In a subsequent systematic review, Naylor et al. (2003) aimed to determine the overall cardiovascular

risk for patients with coronary and carotid artery disease undergoing synchronous CABG and carotid endarterectomy, staged endarterectomy then CABG, and reverse staged CABG then endarterectomy. In a systematic review of 97 published studies following 8,972 staged or synchronous operations, mortality was highest in patients undergoing synchronous endarterectomy plus CABG (4.6%, 95% CI = 4.1–5.2). The risk of death or stroke was highest in patients undergoing synchronous CEA plus CABG (8.7%, 95% CI = 7.7–9.8) and lowest following staged endarterectomy then CABG (6.1%, 95% CI = 2.9–9.3). The risk of death/stroke or MI was 11.5% (95% CI = 10.1–12.9) following synchronous procedures. Thus, about 10–12% of patients undergoing staged or synchronous procedures suffer death or major cardiovascular morbidity (stroke, myocardial infarction) within 30 days of surgery.

In summary, the available data suggest that only about 40% of strokes complicating CABG could be attributable to ipsilateral carotid artery disease. The rate of death and stroke following staged or synchronous carotid surgery in published series is high, but a large randomized trial is necessary to determine whether a policy of prophylactic carotid endarterectomy reduces the risk of stroke after cardiac surgery. However, in the absence of any randomized evidence of benefit, the available data do not support a policy of routine intervention for carotid stenosis in patients undergoing CABG (Naylor, 2004).

65.6. Extra-to-intracranial bypass surgery

About 10% of patients with minor carotid ischemic events have occlusion of the internal carotid artery, or stenosis of the internal carotid artery well distal to the bifurcation, or middle cerebral artery occlusion or stenosis. All these lesions are inoperable, or out of reach of the vascular surgeon, if not of the angioplasty enthusiast's balloon. These lesions can all be bypassed by anastomosing a branch of the external carotid artery (usually the superficial temporal) via a skull burr hole to a cortical branch of the middle cerebral artery. This "surgical collateral" was reckoned to improve the blood supply in the distal middle cerebral artery bed and so reduce the risk of stroke, and to reduce the severity of any stroke that did occur. However, there are several reasons why the procedure might not work: the artery feeding the anastomosis can take months to dilate into an effective collateral channel; many patients have good collateral flow already from orbital collaterals or via the circle of Willis; not all strokes distal to internal carotid artery/middle cerebral artery occlusion or inaccessible stenosis are due to low flow; the risk of stroke in patients with internal carotid artery occlusion is not that high compared with severe and recently symptomatic internal carotid artery stenosis (less than 10% per year) and in any case not all of these strokes are ipsilateral to the occlusion; neither resting cerebral blood flow nor cerebral reactivity are necessarily depressed in these patients; and the risk of surgery may outweigh the benefit (Latchaw et al., 1979; Hankey and Warlow, 1991; Karnik et al., 1992; Klijn et al., 1997; Powers et al., 2000).

The risk–benefit relationship has been evaluated in only one completed randomized trial and this failed to show any benefit from routine surgery (EC–IC Bypass Study Group, 1985). However, it has been argued that patients with impaired cerebrovascular reactivity, or with maximal oxygen extraction, were not identified and perhaps it is these patients who might benefit from surgery (Warlow, 1986; Derdeyn et al., 2005). But to show whether stroke is prevented, and not just that pathophysiology is improved, would require another randomized trial in this specific subgroup, not a series of anecdotes, however persuasive (Karnik et al., 1992).

In fact, a trial is now ongoing that will test the hypothesis that superficial temporal artery–middle cerebral artery anastomosis, when combined with the best medical therapy, can reduce ipsilateral ischemic stroke by 40% at 2 years in patients with symptomatic internal carotid artery occlusion and increased oxygen extraction fraction on PET scanning (Grubb et al., 2003). The primary end-point will be all strokes and death occurring between randomization and the 30-day post-operative cut-off (with an equivalent period in the non-surgical group), as well as subsequent ipsilateral ischemic stroke developing within 2 years. It is estimated that 186 patients will be required in each group.

65.7. Surgery and angioplasty for vertebrobasilar ischemia

There is no good evidence (i.e., there are no large randomized trials) (Coward et al., 2005b) that surgery improves the prognosis for patients with vertebrobasilar ischemia. There is, however, no shortage of ingenious, if technically demanding, techniques that are far from risk free: endarterectomy of severe carotid stenosis to improve collateral blood flow, via the circle of Willis, to the basilar artery distal to severe vertebral or basilar artery stenosis or occlusion; resection and anastomosis, resection and reimplantation, bypass or endarterectomy of proximal vertebral artery stenosis; release of the vertebral artery from compressive fibrous bands or osteophytes; various extra-to-intracranial procedures to

bypass vertebral artery stenosis or occlusion; and angioplasty of the vertebral and basilar arteries (Diaz et al., 1984; Harward et al., 1984; Thevenet and Ruotolo, 1984; Hopkins et al., 1987; Spetzler et al., 1987; Terada et al., 1996; Malek et al., 1999).

There are no randomized trials of surgical procedures for posterior circulation disease and therefore data are only available from case series. For proximal vertebral reconstruction peri-operative mortality in published case series is 0–4%, with rates of stroke and death of 2.5–25% (Eberhardt et al., 2006). For distal vertebral reconstruction a 2–8% mortality rate has been reported.

Several case series have described angioplasty and stenting of symptomatic vertebral and basilar stenosis (Cloud et al., 2003). A recent review (Eberhardt et al., 2006) of more than 600 cases published up to 2005 provides useful information on peri-operative complication rates, particularly the difference in complication rates in treatment of proximal versus distal vertebrobasilar artery lesions. In early studies, proximal lesions were treated primarily with angioplasty but this was associated with restenosis in 15–31% of cases after 15–30 months of follow-up. More recently stenting has been used for the proximal vertebral system, especially ostial lesions. Several series have reported low peri-procedural or post-interventional stroke rates (Eberhardt et al., 2006). Pooling data from 20 reports in 313 patients, there was a peri-operative stroke risk of 1.3% and death rate of 0.3%. However, the rate of restenosis during a mean of about 14 months follow-up was still about 25%, albeit usually asymptomatic.

The complication rate for distal vertebrobasilar lesions treated with angioplasty and stenting is higher. In the review by Eberhardt et al. (2006), data from 170 angioplasties for distal vertebrobasilar disease were pooled. Peri-interventional complications rates were 7.1% for stroke and 3.7% for death. Data from 45 reports, including 280 patients undergoing stenting (as opposed to angioplasty alone) of the distal vertebrobasilar arteries, were available. This included information from the prospective multicenter stenting of symptomatic atherosclerotic lesions in the vertebral or intracranial arteries (SSYLVIA) study, which included 61 vertebral and intracranial lesions (SSYLVIA Study Investigators, 2004). The pooled estimates of peri-procedural risk were 3.2% for death and 10.6% for stroke, suggesting that complication rates do not differ much between angioplasty and stenting in the distal vertebrobasilar system.

One randomized trial of stenting for vertebral artery disease was started (Coward et al., 2005b). The CAVATAS trial included both carotid and vertebral stenosis. However, only 16 patients were randomized between vertebral angioplasty or stenting and best medical treatment. Therefore, there is no robust data from randomized trials providing data on the safety and efficacy of vertebral artery stenting.

Subclavian (and innominate) steal, although commonly detected with ultrasonography, very rarely causes neurological symptoms and does not seem to lead to ischemic stroke. However, incapacitatingly frequent vertebrobasilar TIAs in the presence of demonstrated unilateral or bilateral retrograde vertebral artery flow distal to severe subclavian or innominate disease may sometimes be relieved by endarterectomy or angioplasty of the subclavian artery; carotid-to-subclavian or femoral-to-subclavian bypass; transposition of the subclavian artery to the common carotid artery; transposition of the vertebral artery to the common carotid artery; and axillary-to-axillary artery bypass grafting. All these procedures carry a risk and it is not clear which is the most sensible. Irrespective of the neurological situation, some kind of vascular surgical procedure may be needed if the hand and arm become ischemic distal to subclavian or innominate artery disease.

65.8. Other surgical procedures

Aortic arch atheroma is now increasingly diagnosed by transesophageal echocardiography in patients with TIAs or ischemic stroke, but so far there are no surgical, or indeed medical, treatment options over and above controlling vascular risk factors and antiplatelet drugs. One trial has been started, the ARCH trial (MacLeod et al., 2004).

Innominate or proximal common carotid artery stenosis or occlusion is quite often seen on angiograms in symptomatic patients but, unless very severe, does not influence the decision about endarterectomy for any internal carotid artery stenosis. Although it is possible to bypass such lesions it is highly doubtful whether this reduces the risk of stroke unless, perhaps, several major neck vessels are involved and the patient has low-flow cerebral or ocular symptoms. This very rare situation can be due to atheroma, Takayasu's disease, or aortic dissection. Clearly, close consultation between physicians and vascular surgeons is needed to sort out, on an individual patient basis, what to do for the best.

Coronary artery bypass surgery (or angioplasty) may of course be indicated for patients presenting with cerebrovascular events who also happen to have cardiac symptoms. But, in addition, because asymptomatic coronary artery disease is so often associated with symptomatic cerebrovascular disease, would coronary intervention also be worthwhile even if there were no cardiac symptoms or signs? Given the high risk of

cardiac events which might be reduced in the long term, this is a perfectly reasonable question, but one which could only be answered by a randomized controlled trial, perhaps first in patients who are thought to be at particularly high risk of coronary events on the basis of clinical features, or non-invasive cardiac investigation.

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Chapter 66

Stroke recovery and rehabilitation

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66.1. Introduction

The World Health Organization previously categorized the effects of neurological disease into several domains, each evaluating its impact from a different perspective. The term "impairments" referred to specific physiologic deficits such as those affecting language, strength, coordination, and sensation. "Disability" reflected the impact of these impairments on specific activities (i.e., "activities of daily living" such as eating, dressing, and grooming). "Handicaps" indicated functional consequences at a societal level (i.e., loss of employment). The International Classification of Functioning and Disability-2 again organizes this same information into three dimensions (World Health Organization, 2001): The "body dimension" corresponds to impairment-level deficits and refers to the structure and function of body systems. The "activities dimension" corresponds to disability and reflects the complete range of activities performed by an individual. The "participation dimension" corresponds to handicap and indicates areas of life in which an individual is involved, has access, and has societal opportunities or barriers.

For stroke survivors, the process of recovery begins as soon as the sequelae of the acute injury have subsided. For most, stroke is a life-changing event. Although 50–70% regain functional independence despite having persistent neurological impairments, 15–30% are permanently disabled (American Heart Association, 2004). Most stroke survivors improve over time, albeit to varying degrees (Newman, 1972; Kinsella and Ford, 1980; Wade et al., 1983, 1985; Loewen and Anderson, 1990; Duncan et al., 1992). The pattern of recovery is similar regardless of the type and severity of the initial deficit. Using the example of post-stroke motor impairments, the most rapid period of recovery is over the first 30 days and continues to a great degree over the ensuing 60 days. Individuals may continue to improve over longer periods of time, even over years.

The goal of post-stroke rehabilitative interventions is to shift the recovery curve upwards so that patients achieve higher levels of function than they would have "spontaneously." Spontaneously is placed in quotes in this context because stroke patients, even those who do not receive formal physiotherapeutic interventions, may be exposed to a variety of activities and experiences that have the potential to influence outcome.

66.2. Experience and training—experimental studies

Numerous studies in laboratory animals show that environmental complexity can have a direct impact on anatomical brain plasticity (Rose et al., 1993a; Grabowski et al., 1995). Housing animals in complex environments is associated with overall and regionally specific increases in brain weight, cortical depth, hippocampal thickness, callosal size, and cortical glial density (Rose et al., 1993a), and has effects on both neuronal morphology (Rose et al., 1993a; Kolb et al., 1998) and connectivity (Beaulieu and Colonnier, 1988). It has also long been recognized that even housing animals in complex environments as compared to a standard cage either before or after brain injury can lead to less severe neurological deficits and more favorable outcomes (Will and Kelche, 1992; Hamm et al., 1996; Johansson, 1996; Schallert et al., 2003), although some debate remains as to whether this represents true recovery or an enhancement of compensatory behavioral strategies (Rose et al., 1993a, 1993b). Housing animals in a typical laboratory cage is equivalent to keeping stroke patients in a non-stimulating

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environment isolated from contact with friends or family, yet laboratory-based studies have largely continued to consider housing in complex environments to represent an experimental intervention rather than standard conditions. This needs to be recognized as it may have direct implications for the translation of the results of animal model studies to the design and interpretation of human clinical trials.

In addition to general environmental factors, laboratory studies show the important impact of post-brain injury training on functional motor recovery (Kolb et al., 1998; Cotman and Berchtold, 2002; Kleim et al., 2003; Will et al., 2004). As summarized in these detailed reviews, exercise can increase levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), enhance neurogenesis, and improve learning. Rehabilitative training is associated with specific improvements in motor function after cortex injury in several behavioral paradigms (Goldstein and Davis, 1990a, 1990c; Delay and Rudolph, 1994; Nudo et al., 1996; Jones et al., 1999; Biernaskie and Corbett, 2001; Biernaskie et al., 2004), particularly when this training is coupled with housing in complex environments (Biernaskie and Corbett, 2001; Biernaskie et al., 2004).

66.3. Environmental factors and standard physiotherapy

Based on the data from animal model studies, it is not surprising that premorbid level of functioning and general environmental factors would have an effect on post-stroke recovery. For example, prestroke social isolation contributes to poorer outcome after stroke (Glass et al., 1993; Boden-Albala et al., 2005).

The site of rehabilitation (rehabilitation hospital, subacute nursing home, traditional nursing home) can affect the rate and degree of recovery (Kramer et al., 1997). However, in the USA, where a patient resides may be as important, if not more important, than clinical and social factors in determining the setting in which rehabilitative care is provided. Over 70% of stroke survivors receive either post-acute institutional or ambulatory rehabilitative services over the first 6 months after stroke (Lee et al., 1996). Nearly one-third of this care takes place in rehabilitation hospitals, 25% in skilled nursing facilities, 16% in acute care hospitals, and 11% through home health agencies with wide variations across the country. For example, the percentage of stroke survivors admitted to a rehabilitation hospital varies from as low as 10% in some regions to as high as 31% in others. Discharge to a skilled nursing facility varies from 14% to 41% and the use of home health services varies from 19% to 57% in different cities. Stroke patients living in rural areas are 25% less likely to be admitted to a rehabilitation hospital and 10% less likely to receive home health services.

Participation in multidisciplinary post-stroke rehabilitation programs can have a profound effect on functional outcome and are associated with a reduction in mortality, institutionalization, and dependency (Langhorne and Duncan, 2001). Improved levels of function occur with adherence to rehabilitation guidelines developed by the US Agency for Healthcare Policy and Research (Post-Stroke Rehabilitation Guidelines Panel, 1995) as reflected in the Functional Independence Measure (FIM) motor score, Instrumental Activities of Daily Living (IADL) and the Stroke Impact Scale (quality of life) (Duncan et al., 2002). As reflected in a meta-analysis, stroke unit care that includes multidisciplinary rehabilitation is associated with reduced mortality and increased independence one year after the stroke (Cochrane Stroke Group, 2005).

Although receiving multidisciplinary rehabilitative interventions improves post-stroke outcomes, the relative impact of different components of rehabilitation therapy is not certain. Different therapists may approach the same type of patient differently. Traditional physiotherapeutic techniques can focus on improving compensatory strategies (Wescott, 1967) or on regaining lost functions (Wolf and Binder-Macleod, 1983; Basmajian et al., 1987). Some approaches discourage excessive effort because of concern of increasing abnormal tone whereas others do the opposite (encourage maximal effort to facilitate movement) (Duncan, 1997). A systematic analysis of studies evaluating these seemingly contradictory approaches failed to find that one was superior to the other or that one led to better outcomes than standard care (Duncan, 1997). This lack of difference has led to the perception that the benefit of standard physiotherapy is due to a placebo effect. However, many of the studies evaluating physiotherapeutic interventions have methodological limitations that preclude meaningful conclusions.

66.4. Intensity of therapy

Experimental studies in laboratory animals indicate that more intensive physiotherapeutic interventions result in increased plasticity and improved recovery after brain injury (Schallert et al., 2000; Kleim et al., 2003). For example, repetitive use of the impaired hand after motor cortex infarction in squirrel monkeys is required to maintain the spared portion of the hand cortical representation (Friel et al., 2000). However, there is some concern that overuse during vulnerable periods after brain injury could both exacerbate the underlying brain damage, and in some cases lead to

poorer functional outcomes (Kozlowski et al., 1996; Humm et al., 1998, 1999; Risedal et al., 1999; Bland et al., 2000; Jones et al., 2003; Leasure and Schallert, 2004). However, in animal ischemia models, despite exacerbation of injury, with exercise begun immediately after the injury, functional outcome is still improved (Risedal et al., 1999; Farrell et al., 2001). Intensive training after the first 3–5 days after focal brain injury does not exacerbate lesion size or negatively affect outcome (Nudo et al., 1996; Jones et al., 1999). Delaying training can diminish its beneficial effect (Biernaskie et al., 2004).

In humans, repetitive training of a synchronized movement is associated with plastic changes in the contralateral somatosensory cortex (Schwenkreis et al., 2001). Over the short term, more intensive training after stroke is associated with improved basic hand movements and functional abilities as compared to standard physiotherapy (Bütefisch et al., 1995). Another study found that those treated with more intensive physiotherapy had less disability after 3 months despite having greater initial deficits (Sivenius et al., 1985). A more versus less intensive physiotherapeutic regimen led to a small but statistically significant improvement in arm strength, and range and speed of movement 6 months after stroke (Sunderland et al., 1992). A preliminary trial found greater improvements in arm motor function with "forced use" intensive therapy started within the first 14 days after stroke as compared to standard rehabilitation in humans (Dromerick et al., 2000). In contrast, a program which added arm sensorimotor stimulation to standard therapy resulted in an improvement in motor impairment, but no effect on disability after 6 weeks (Yekutiel and Guttman, 1993). Another trial found no effect of an additional 10 hours of arm physiotherapy given over 5 weeks when assessed after 3 weeks or 6 months (Lincoln et al., 1999).

The timing and characteristics of the intensive physiotherapeutic intervention may be critical. Although the principle that patients benefit more from intensive as compared to less intensive physiotherapy is generally held, definitive studies proving that this is true are limited, and whether this benefit impacts on disability and handicap remains uncertain.

66.5. Robot-assisted therapy

"Robot-assisted therapy" uses a computerized mechanism to provide reproducible limb movements having specified force and velocity (Aisen et al., 1997). Passive exercise of even paralyzed limbs can be provided that can be modified as the patient recovers. A randomized study including 20 stroke patients found some improvement in accuracy of proximal arm movements with robotic training, but no significant improvement in disability as measured by the FIM score or in motor function as assessed with the Fugl–Meyer scale (Aisen et al., 1997). Twelve of the 20 patients were evaluated 3 years later at which time the motor status scores for shoulder/elbow function were significantly better in those who had robot-assisted therapy, but there were no differences between the treatment groups based on Fugl–Meyer motor scores (Volpe et al., 1999). Definitive conclusions regarding clinical efficacy cannot be made owing to the small sample size, but these data suggest that at least some early gains may be sustainable.

A second trial of robot-assisted therapy included 56 patients with stroke-related motor deficits (Volpe et al., 2000a). The addition of robot-assisted training to standard physiotherapy was associated with greater reductions in motor impairments and improved motor performance. The use of robot-assisted therapy may also lead to functional gains after normal recovery has reached a plateau (Ferraro et al., 2003). Whether this benefit persists and whether it translates into a long-term reduction in disability remains uncertain.

66.6. Supported treadmill training

Impaired gait is a major cause of stroke-related disability with gait being a crucial determinant of stroke-related handicaps as measured with scales such as the Rankin index (Rankin, 1957). Partial weight-supported treadmill training allows otherwise non-ambulatory stroke patients to practice patterned walking movements. In a preliminary study, seven non-ambulatory stroke patients were first treated with supported treadmill training, then crossed over to standard physiotherapy, and then crossed back to treadmill training (Hesse et al., 1995). There were improvements in walking velocity during the periods of treadmill training with the patients regaining the ability to ambulate by the end of the study. Another study reported improvements in gait symmetry after treadmill training (Hassid et al., 1997). These studies were followed by a trial in 100 gait-impaired stroke patients in which partial body weight supported treadmill training was compared to treadmill training without body weight support (Visintin et al., 1998). By the end of the 6-week intervention period, those in the body weight support group had better functional balance, mobility, walking speed, and endurance. Benefits in voluntary movement, mobility and walking speed persisted as long as 3 months after the completion of training. A further study compared body-weight-supported treadmill gait training with the use of an electromechanical gait trainer (Werner et al., 2002). The two approaches were generally equivalent with

less therapist time required for the electromechanical trainer. In another study, 61 adults with a persistent hemiparetic gait at least 6 months after stroke were randomized to progressive treadmill exercise or a program of stretching plus low-intensity walking with the hypothesis that an improvement in cardiovascular fitness would lead to functional gains (Macko et al., 2005). The intensive exercise was associated with better functional mobility as well as improved cardiovascular function showing that gait can be improved even long after stroke.

66.7. Constraint-induced movement therapy

Constraint-induced movement therapy is based on laboratory observations that animals with paretic limbs can regain function if the normal limb is restrained and they are forced to use the paretic limb (Ostendorf and Wolf, 1981; Taub et al., 1993, 1994). This type of training has been associated with cortical reorganization after stroke in humans as reflected in transcranial magnetic stimulation (Liepert et al., 2000). In a study of 16 stroke and 5 traumatic brain injury patients with some volitional hand movement more than 1 year after injury, restraining the non-involved hand for 2 weeks led to significant improvements in timed tasks (Wolf et al., 1989). Benefits were sustained over 2 years of follow-up (Taub et al., 1993). Other initial small studies also suggested that chronic stroke patients may benefit from the approach (Kunkel et al., 1999; Miltner et al., 1999). A single-blind study including 66 chronic stroke patients found improvements in two of four parameters of arm function 1 week after treatment, with a persistent benefit as measured by one of the parameters reflecting dexterity after 1 year (Van Der Lee et al., 1999). A preliminary study also suggests that there may be benefit from constraint-induced movement therapy beginning within 2 weeks of stroke (Dromerick et al., 2000). A multicenter, randomized trial sponsored by the National Institutes of Health (Extremity Constraint-Induced Therapy, EXCITe) evaluating constraint-induced movement therapy found that this approach led to clinically relevant improvements in arm motor function in patients who had a stroke in the prior 3-9 months with the benefit persisting for at least 1-year. (Wolf et al., 2006).

66.8. Adjunctive therapies

Meta-analyses of the effects of biofeedback on post-stroke recovery have had conflicting results. One suggested that biofeedback added to usual therapy might lead to an improvement of motor function (Schleenbaker and Mainous, 1993) whereas the second found it provided no advantage (Glanz et al., 1995a). Visual biofeedback in addition to standard physiotherapy did not further improve post-stroke functional balance (Geiger et al., 2001). In contrast, auditory biofeedback improved some measures of functional reach in patients with chronic stroke-related deficits (Maulucci and Eckhouse, 2001). Overall, the impact of biofeedback is at best inconsistent and there remains no evidence that reported improvements in impairment level measures lead to reductions in disability or handicap.

Functional electrical stimulation (FES) applies electrical current to paretic muscles or to peripheral nerves. Two separate meta-analyses reported that FES leads to overall improvements in strength and coordination (Glanz et al., 1995b; Chae and Yu, 2000). As with biofeedback, there is no clear evidence that this improvement in impairments leads to better functioning in daily activities.

Transcranial magnetic stimulation (TMS) has been used extensively as a research tool in studies evaluating cortical reorganization and plastic changes in the brain after injury (Caramia et al., 2000; Trompetto et al., 2000; Bütefisch et al., 2002; Werhahn et al., 2003; Baron et al., 2004). In addition, TMS may be helpful in determining prognosis for recovery with some evidence that it may be useful therapeutically (Liepert, 2005; Takeuchi et al., 2005).

66.9. Pharmacotherapy—experimental studies

Numerous experimental studies provide evidence supporting the role of norepinephrine as a modulator of the recovery process. The administration of a single dose of d-amphetamine the day following a unilateral sensorimotor cortex injury in the rat results in an enduring enhancement of motor recovery (Feeney et al., 1982). Post-injury treatment with amphetamine also enhances motor recovery in cats that had unilateral or bilateral frontal cortex ablations (Hovda and Feeney, 1984; Sutton et al., 1989) and reinstates stereoscopic vision in cats with bilateral visual cortex lesions (Feeney and Hovda, 1985; Hovda et al., 1989). These effects have replicated in several other laboratories (Dunbar et al., 1989; Dietrich et al., 1990; Goldstein, 1999).

The impact of amphetamine and other adrenergic agonists and antagonists on post-brain injury recovery can be predicted based on their effects on the release of norepinephrine from noradrenergic terminals. Both yohimbine and idazoxan (centrally acting α_2-adrenergic receptor antagonists) increase norepinephrine release and enhance motor recovery (Weaver et al., 1987; Goldstein, 1989; Goldstein et al., 1989; Sutton and Feeney, 1992) whereas clonidine, a centrally acting α_2-adrenergic receptor agonist that decreases norepinephrine release, has a prolonged detrimental effect on motor recovery in rats and reinstates motor deficits when given to animals that had recovered motor

function (Stephens et al., 1986; Goldstein and Davis, 1990b; Sutton and Feeney, 1992). Prazosin and phenoxybenzamine, centrally acting α_1-adrenergic receptor antagonists, are also harmful (Hovda et al., 1983; Feeney and Westerberg, 1990; Sutton and Feeney, 1992).

Co-administration of the butyrophenone haloperidol blocks amphetamine-promoted motor recovery in rats and impairs motor recovery when given alone (Feeney et al., 1982). When given to recovered rats, haloperidol as well as other butyrophenones (fluanisone, droperidol), transiently reinstate the animals' motor deficits (Van Hasselt, 1973). Haloperidol also blocks amphetamine-facilitated recovery of stereopsis in visually decorticated cats (Hovda and Feeney, 1985; Hovda et al., 1989). Although a dopamine receptor antagonist, haloperidol also has antagonist effects at noradrenergic receptors. Dose-effect experiments confirm that haloperidol has a detrimental impact on post-brain-injury recovery, but clozapine, an atypical antipsychotic and a potent dopamine receptor antagonist, does not have this effect (Goldstein and Bullman, 2002). Radioligand binding studies show that haloperidol is a marginally more potent α_1-adrenergic receptor antagonist than clozapine (K_D 6.1 versus 9 nM, respectively) whereas clozapine is a significantly more potent α_2-adrenergic receptor antagonist than haloperidol (K_D 160 versus 3,800 nM, respectively). Thus, haloperidol's detrimental effects are likely to be noradrenergically mediated.

Consistent with the pharmacological data, pretreatment with a neurotoxin that depletes central norepinephrine (N-(2-Chloroethyl)-N-ethyl-2-bromobenzylamine; DSP-4) impairs motor recovery after a subsequent injury to the cerebral cortex (Goldstein et al., 1991; Boyeson et al., 1992). Selective lesions placed in the locus coeruleus, the major source of central noradrenergic projection fibers, result in poorer behavioral recoveries after sensorimotor cortex lesions as compared to controls that had sham locus coeruleus lesions (Goldstein, 1997).

Classes of centrally acting drugs affecting other neurotransmitters may also affect the recovery process. Antidepressants affect the serotonergic system. A single dose of trazodone slows motor recovery, and a single dose of desipramine facilitates motor recovery in rats with cortical injury (Boyeson and Harmon, 1993). In contrast, fluoxetine and amitriptyline have no demonstrable effect on motor recovery after experimental focal brain injury (Boyeson et al., 1994).

Intracortical infusion of γ-aminobutyric acid (GABA) increases the hemiparesis produced by a small motor cortex lesion in rats (Brailowsky et al., 1986a). Diazepam, an indirect GABA agonist, blocks recovery from the sensory asymmetry caused by anteromedial neocortex damage in rats (Schallert et al., 1986). In addition to being anxiolytics, benzodiazepines are potent anticonvulsants. The deleterious effect of GABA on motor recovery after motor cortex injury is increased by the systemic administration of phenytoin (Brailowsky et al., 1986b), which may act through a GABA-mediated mechanism. Phenobarbital also delays behavioral recovery after cortical injury (Hernandez and Holling, 1994) whereas carbamazepine has no effect (Schallert et al., 1992). Anxiolytics that do not act through the GABA/benzodiazepine receptor complex such as gepirone do not have detrimental effects (Schallert et al., 1992).

66.10. Pharmacotherapy—clinical studies

Similar to animal model studies, α_2-adrenergic receptor agonists, α_1-adrenergic receptor antagonists, dopamine receptor antagonists, benzodiazepines, phenytoin and phenobarbital may impair post-stroke recovery in humans (Goldstein et al., 1990; Goldstein, 1995).

Several small clinical studies suggest that it may be possible to pharmacologically enhance recovery. In one of the first such studies, eight patients with stable motor deficits were randomized to receive a single dose of either 10 mg of d-amphetamine or placebo within 10 days of ischemic stroke (Crisostomo et al., 1988). Within 3 hours of drug administration, all of the patients had intensive physical therapy. The amphetamine-treated group had a significant improvement in motor performance as compared to baseline whereas there was little change in the placebo-treated group when assessed the next day.

A second double-blind, placebo-controlled compared the recoveries of 12 patients given 10 mg of d-amphetamine daily for 14 days followed by 5 mg for 3 days with the recoveries of 12 patients who received placebo (Reding et al., 1995). Interventions began more than 1 month after stroke and the administration of the drug/placebo was not tightly linked with physical therapy. Disappointingly, there was no benefit of treatment, possibly attributable to the different dosing regimen, longer treatment window, and/or a lack of a tightly coupled drug/physical therapy regimen.

A third double-blind, placebo-controlled trial included 5 amphetamine-treated and 5 placebo-treated patients with treatment given once every 4 days for 10 sessions beginning 15 to 30 days after stroke (Walker-Batson et al., 1995), a schedule based on data from experiments in cats (Hovda and Feeney, 1984). Patients treated with amphetamine had significantly greater improvements in motor scores compared to placebo-treated patients 1 week after drug treatment

was completed. The benefit further increased at the 1-year follow-up evaluation.

In contrast, dl-amphetamine was tested in a group of elderly stroke patients (Sonde et al., 2001). These patients were treated beginning 30–45 days after stroke with 10 mg of dl-amphetamine on a twice-weekly regimen that was tied to physical therapy with outcomes measured after 30 days. There was no effect of treatment, possibly because the l-stereoisomer of amphetamine is less potent than the d-stereoisomer.

Another negative trial randomized 30 patients with impaired consciousness within 96 hours of stroke to 5 10 mg of d-amphetamine once or twice daily (depending on alertness) plus 30 45 minutes of non-specific physiotherapy twice daily or placebo plus a maximum of 15 minutes of physiotherapy each day (Martinsson et al., 2003). Therapy sessions were conducted for 5 consecutive days. No benefit was found. In addition to using a different dosing regimen, treatment interval and duration, treatment began sooner after stroke, included only the most severely affected patients, and lacked a tightly coupled drug/physical therapy regimen.

In the largest study reported to date, 71 stroke patients were randomized to 10 sessions of physiotherapy coupled with either d-amphetamine or placebo twice per week beginning 5–10 days post-stroke (Gladstone et al., 2006). To limit inter-therapist variability, a single therapist provided the physiotherapy. Although there was no overall difference in those with severe baseline deficits, the addition of d-amphetamine accelerated recovery of arm motor function among those with moderate deficits. A preliminary study combining intensive robot-assisted arm physiotherapy with or without d-amphetamine found early benefit only with d-amphetamine (Volpe et al., 2000b). The Amphetamine-Enhanced Stroke Recovery (AESR) is in progress and is evaluating the impact of several factors related to the timing and duration of therapy (Goldstein, 2003).

66.11. Polypeptide growth factors

As summarized in several reviews, experimental studies show that a variety of polypeptide growth factors have the capacity to support neural outgrowth, synaptogenesis, and neurogenesis after stroke and other brain injuries (Kawamata et al., 1997; Zhang and Chopp, 2002; Ren and Finklestein, 2005). These include basic fibroblast growth factor (bFGF), vascular endothelial growth factor (Veg-f), osteogenic protein-1 (OP-1), erythropoietin (EPO), and granulocyte colony stimulating factor (G-CSF) (Kawamata et al., 1997; Ren and Finklestein, 2005). In addition, Veg-f and the angiopoietins (e.g. Ang-1) mediate angiogenesis in the adult brain (Zhang and Chopp, 2002). Importantly, administration of several of these polypeptide growth factors after ischemic brain injury have each been associated with improved behavioral outcomes that are not related to a reduction in infarct size, suggesting an impact on neuronal rearrangements underlying the recovery process (Ren and Finklestein, 2005).

At least two of these growth factors have come to clinical trials in humans. There have been two completed trials of bFGF given after acute ischemic stroke. The first, published only in abstract form, enrolled 302 patients at 58 centers and was halted early because of poorer outcomes in the active treatment group (Clark et al., 2000). The second bFGF trial planned to enroll 900 patients and was also stopped early after 286 patients were randomized because of futility (Bogousslavsky et al., 2002). A pilot safety and efficacy trial of intravenous erythropoietin randomizing 40 patients found it was well-tolerated and associated with improved outcomes at 1 month (Ehrenreich et al., 2002). A large-scale clinical trial is in progress.

66.12. Transplants

An extensive literature beyond the scope of this review suggests that neural precursor cell transplantation might improve recovery after brain injury. A variety of possible mechanisms might underlie these potential benefits including release of trophic or tropic factors that could stimulate and guide endogenous post-injury neural rearrangements as well as direct formation of neuronal circuitry to replace connections that were damaged by stroke. Regardless of mechanism of action, studies in laboratory animals indicate that any of a variety of transplant strategies might be helpful. Rat fetal hippocampal cell suspensions stereotactically injected into rat adult ischemic hippocampus become structurally integrated into the host brain, appear to establish nerve connections, and may lead to cognitive improvement (Nunn and Hodges, 1994). Similarly, suspensions of fetal neocortex grafted into infracted adult cortex can be functionally integrated with neural circuits of the host (Grabowski et al., 1993) and be associated with functional improvements (Plumet et al., 1993). As with pharmacological interventions, there may be complex relationships between the grafted and host tissue that depend on an animal's physical environment and training (Kelche et al., 1995; Mattsson et al., 1997; Dobrossy and Dunnett, 2003).

A particularly exciting approach to transplantation is the use of marrow stromal cells. When injected intra-arterially in rats with middle cerebral artery infarctions, the cells localize to the damaged tissue

with the transplantation associated with improved functional outcomes (Li et al., 2001). In rats, behavioral improvements occur if human stromal cells are given intravenously, possibly through an increase in growth factors, reduction of apoptosis, and proliferation of endogenous cells in the subventricular zone (Li et al., 2002). Similar to marrow stromal cells, intravenous infusion of human umbilical cord blood reduces behavioral deficits after stroke in rats (Chen et al., 2001; Vendrame et al., 2004).

One preliminary study suggested that stereotactic transplantation of precursor cells induced to differentiate neurons, basal ganglion infarctions in humans might be feasible and lead to functional improvements (Stilley et al., 1320; Kondziolka et al., 2000). A second feasibility study randomized patients with middle cerebral artery distribution infarctions to receive autologous bone marrow mesenchymal stem cells given intravenously ($n = 5$) 5–7 weeks after stroke or to act as controls (Bang et al., 2005). There were no adverse effects of the treatment, but no significant differences in functional outcomes between the groups after one year. Much work needs to be done to determine whether this or another transplantation approaches are safe and feasible in the clinical setting.

66.13. Conclusion

Improving post-stroke recovery beyond what can be achieved with standard physiotherapy may be possible. Patients can benefit now from participation in multidisciplinary rehabilitative interventions. Optimization of functional benefits may be achieved through combinations of new physiotherapeutic approaches aimed at providing more intensive practice, along with pharmacological treatments, avoidance of potentially harmful centrally acting drugs, and possibly incorporation of a progenitor cell transplantation strategy.

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Index

Page numbers in italic, e.g. *65*, refer to figures. Page numbers in bold, e.g. **64**, denote tables.