Diagnostic Strategies in CEREBRAL ISCHEMIA

The future of therapy for stroke patients will be founded on multimodal and multidisciplinary care. This resource covers in succession particular topics from the onset of ischemia to prevention of recurrent events. Diagnostic modalities and innovative imaging approaches are discussed, including ultrasound, CT, MRI and angiography. All these diagnostic strategies are considered with respect to the ultimate objective of broadening current therapeutic options for ischemia. The authors also address special topics such as early diagnosis and hospitalization, “time is brain”, and refining imaging techniques.

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DIAGNOSTIC STRATEGIES
IN CEREBRAL ISCHEMIA

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# Contents

*Editor and Contributors* vii  
*Preface* ix  
1 Diagnostic challenges in cerebral ischemia  
*D. S. Liebeskind*  
2 Prehospital diagnosis and early treatment in acute ischemia  
*L. K. Ali*  
3 Time is brain – revisited  
*D. S. Liebeskind*  
4 Symptomatic versus asymptomatic cerebrovascular disease  
*M. S. Goyal, C. P. Derdeyn*  
5 Stroke or TIA? Risk of cerebral ischemia  
*A. Y. Poppe, N. Sanossian, S. B. Coutts, A. M. Demchuk*  
6 Multimodal computed tomography in acute ischemic stroke  
*C. J. Ledezma, M. Wintermark*  
7 Multimodal magnetic resonance imaging in acute ischemic stroke  
*B. H. Buck, R. I. Aviv*  
8 Implementing novel magnetic resonance imaging features of acute ischemia to refine therapy: from mismatch to deoxygenation, permeability and beyond  
*O. Y. Bang*  
9 Transcranial Doppler ultrasonography: diagnosis to thrombolysis in acute ischemic stroke  
*A. V. Alexandrov*  
10 Cerebral angiography for definitive diagnosis and treatment  
*T. N. Nguyen, R. G. Nogueira*  

*List of abbreviations* 117  
*Index* 121
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Preface

This book on diagnostic strategies and the companion book on therapeutic strategies for cerebral ischemia encapsulate a philosophy and perspective on stroke that stand apart from other volumes on the subject. These texts embody a collective restlessness with the current impasse in reversing stroke, composed by a generation that seeks to change the next. The books are dedicated to the memory and aspirations of my family, across several generations.

As a child, I remember the devastating effects of recurrent stroke on my grandfather, Oleg, at a time before CT and MRI. My mother, Doreen, and father, Arie, both later utilized angiography, CT, MRI, and ultrasound as neuroradiologists to demystify stroke and these books are devoted to their memory. This personal history with stroke fueled my trajectory from engineering into neurology, where I could tackle stroke, one of the greatest challenges in modern medicine despite recent innovations. My love for the field is mirrored by my intense love of my family, revolving around my incredible wife and friend, Kira. I adore and seek to inspire my children, Alexander, Bernard, and Mia, who encourage me to love every minute and live for the moment.

Every day and night, my colleagues and I witness the instant terror that heralds stroke onset. Life is halted with miraculous recovery in only the lucky, yet everyone is reminded of our ephemeral status. I deeply appreciate the efforts of my co-authors on these books, who share my philosophy and friendship. I also anticipate that these books will motivate others to move forward in combating stroke, incorporating new perspectives and evolving paradigms.

David S. Liebeskind, MD
Diagnostic challenges in cerebral ischemia

D. S. Liebeskind

INTRODUCTION

After half a century of clinical trials in stroke, clinicians have a limited number of treatments for their patients with cerebral ischemia. Recent technological advances in neuroimaging offer additional insight regarding acute ischemia, yet numerous questions abound and evidence is lacking. This book on diagnostic strategies and the companion text on therapeutic strategies address current limitations in the management of patients with stroke and transient ischemic attacks (TIAs), underscoring key limitations and potential avenues for future breakthroughs in the diagnosis and treatment of cerebral ischemia. This introspective and provocative critique of current stroke research efforts and challenges at the bedside provides a potential roadmap for future innovation. From the hyperacute to chronic stages of cerebral ischemia, these texts explore critical issues in both diagnostic and therapeutic aspects of ischemia and associated vascular pathophysiology.

Cerebral ischemia, or insufficiency of blood flow to the brain leading to functional and structural compromise, is one of the most common disorders. Exhautive efforts have been directed toward lessening the impact of TIAs and ischemic stroke, yet only limited progress has been attained. As a result, cerebral ischemia continues to impose a tremendous impact on societies around the globe. Other common disorders such as heart disease and cancer have seen prominent breakthroughs in not just diagnosis, but therapy as well. The historical perspective on ischemic stroke treatment provides a rather bleak story of repeated failures punctuated by only a few celebrated exceptions. As of 2010, the entire armamentarium of proven therapeutic strategies for ischemic stroke emanating from randomized controlled trials includes only two medications: aspirin and intravenous tissue plasminogen-activator (IV tPA) [1–3]. Aspirin confers only a modest benefit and IV tPA has quite restrictive limitations on its use. The two endovascular devices sanctioned for use in clinical practice by the United States Food and Drug Administration (FDA) were not studied in randomized controlled trials and therefore remain somewhat controversial [4–7]. If one considers that these few therapies have resulted from several hundred clinical trials, it may appear that the probability of a successful or positive acute stroke trial remains incredibly low despite interim sophistication in clinical trial design and imaging technologies. Prevention trials in ischemic stroke have met different challenges over the years. Most studies have been secondary prevention trials focused on averting recurrent ischemia, based on stroke subtype or risk factor profile such as the presence of atrial fibrillation. The nature of recurrent cerebral ischemia remains difficult to predict based on the index stroke, and risk factors such as atrial fibrillation may be circumvented with anticoagulation. Practical aspects of
such studies have limited the importance of discerning specific stroke mechanisms or etiology. The complex nature of the field of vascular neurology where neurovascular disorders straddle different organ systems from vessels to neurological injury has also been a formidable challenge. Unlike in cardiology, the vascular aspects are only one piece of the entire puzzle. Many facets of stroke care have evolved or been translated from cardiology. ‘Time is brain’ and the overwhelming focus on arterial revascularization are two such examples, whilst unique aspects of neurovascular anatomy, perfusion in the brain, and the complex process of neurorepair have been relegated to subsidiary roles despite their importance [8]. Faith in the promise of large randomized controlled trials that have reaped an over-zealous reliance on statistical power despite the staggering difficulties of performing large studies in ischemic stroke. After each successive study, trialists have cited limited power to detect efficacy, but perhaps it is the considerable complexity or heterogeneity of ischemic stroke across individual cases that has plagued stroke trials to date. The design of most studies has also underscored an over-ambitious or disillusioned approach that seeks to credit one drug or device, and not supportive care, with the clinical outcome measured 90 days later. Many types of supportive care, from early hemodynamic management to systematic prevention of recurrent stroke and aggressive rehabilitation therapy, have often been overlooked [9]. Placebo arms and ‘best medical management’ strategies can no longer be considered as non-treatment approaches and, in fact, the control patients that receive solely supportive care may do as well as those receiving the putative breakthrough treatment [10]. Failure to detect differences in outcome between active and control arms may demonstrate that optimal outcomes after ischemic stroke can be assured by a multimodal approach or process rather than just one drug or device. This possible humbling realization may place ischemic stroke on an equal footing with the treatment of intracranial hemorrhage that is largely supportive in nature. So, after decades in the hunt for evidence of effective treatments for ischemic stroke, clinicians face a persistent struggle to employ rational therapy in practice when evidence is often lacking. Paradoxically, the careful selection of subjects and strict adherence to protocol in a clinical trial does not mirror expected practice once approval has been attained. For this reason, the role of registries will likely increase in coming years. Comparative effectiveness research in stroke poses an even greater challenge, given the overwhelming lack of efficacy [13].

Earlier epochs in the pursuit of effective diagnostic and therapeutic strategies for cerebral ischemia have been accentuated by the promise of specific approaches such as neuroprotection, yet we stand at a critical juncture where the future is increasingly dependent on multi-modal and multidisciplinary efforts [14]. Cerebral ischemia is actively studied across the basic sciences, in translational research and in a plethora of clinical studies. From early diagnosis to long-term treatment goals, a broad array of experts across, and beyond, the medical profession have garnered interest in ischemic stroke. The genetics, pathophysiology, pharmacology, and engineering of stroke have rapidly expanded. Not just neurologists, but paramedics, emergency physicians, nurses, radiologists, neurosurgeons, cardiologists, hospitalists, hematologists, rheumatologists, rehabilitation therapists, and more stroke care providers collaborate to help stroke patients. The process of care, from informed consent in the prehospital setting to chronic assessment of outcomes and the economic impact of stroke, is also under the spotlight. Stroke systems of care with graded levels of care from basic measures to comprehensive treatment have evolved to match the needs of particular geographic regions and telestroke has extended the reach of stroke expertise to almost anywhere in the world. Technology has produced an endless parade of novel endovascular tools that can be used to open arteries. These devices have been rapidly implemented in practice by a variety of physicians even when evidence is absent. There is now a sense of palpable enthusiasm to counter the potentially devastating
effects of cerebral ischemia, ignoring the limited success in the past. Investors, investigators, patients, and their advocates have created a sense of hope that perhaps the next decade will be different [15]. Expansive knowledge has been amassed regarding ischemic stroke, yet perhaps the current paradigm is flawed. Basic and clinical researchers must focus on translation of promising approaches, whereas academia, industry and investors must break the endless cycle of perpetual trials centered about only one therapy at a time. Most importantly, older or established preconceptions about ischemia should be challenged as the textbooks have not yielded all the answers and many gaps exist in effective management of ischemic stroke.

Against this backdrop of mounting enthusiasm and increased multidisciplinary interest in tackling the daunting challenges of cerebral ischemia, these texts provide a unique perspective on the path to eventual breakthroughs in the field. The content of these books draws upon anecdotal experiences typically noted in case reports or series, cites original research studies, provides a broader review of selected topics, and offers provocative opinions on next steps. The chapters are authored by experts on each of the respective topics, with leading opinions formulated to address the current impasse. Each successive chapter covers a particular topic from the onset of ischemia to prevention of recurrent events. In this text, novel aspects of prehospital care are followed by a reconsideration of the strict time definitions currently used to triage stroke patients. Definitions and categorizations of lesions as symptomatic or asymptomatic are considered in the light of potential treatment strategies. Triage and management of mild or transient ischemia are also considered in depth. Diagnostic modalities and innovative imaging approaches are discussed, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and angiography. All of these topics on diagnostic strategies are considered with respect to the ultimate objective of broadening current therapeutic strategies for ischemia.

The purpose of these books is to provide a broad audience with the latest advances and to underscore the limitations in the march towards realizing effective strategies to diagnose, avert, reverse, and treat cerebral ischemia. From quite philosophical aspects that may require the field to undergo a paradigm shift in longstanding concepts of pathophysiology to very practical considerations in daily management of the stroke patient, this compendium provides stimulus for novel approaches in coming years. These are not clinical handbooks with lists of items to be considered in practice, nor textbooks that summarize what is already known. In fact, unlike a standard textbook on stroke that conveys authority on a topic irrespective of whether evidence exists, these books provide more questions than simple answers to the complex problem of ischemia in the brain. After all, the most productive answers will only result from considering varied perspectives and asking the best questions.

REFERENCES

Prehospital diagnosis and early treatment in acute ischemia

L. K. Ali

INTRODUCTION

Stroke patients are an extremely heterogeneous group with respect to underlying etiology, pathophysiology, associated mechanisms, severity, premorbid status, and numerous other baseline variables that influence subsequent outcome. Each year, approximately 700,000 persons in the United States have a new or recurrent stroke; of these persons, 15–30% become permanently disabled, and 20% require institutionalization during the first 3 months after the stroke [1, 2]. The degree of stroke-related disability can be reduced if timely diagnosis is established and appropriate treatment is implemented. Advances over the past decade in hyperacute stroke care, including the introduction of thrombolytic and endovascular therapies have led to effective ways in which emergency medical services (EMS) agencies and emergency medical services systems (EMSS) can help in optimizing stroke patient evaluation and treatment [3]. Optimal management should begin in the prehospital and emergency room settings with management extending beyond these critical phases to specialized stroke units, neurointensive care when appropriate, and ultimately to neurorehabilitation programs.

PREHOSPITAL DIAGNOSIS AND TRIAGE

Despite the proven benefits of thrombolysis for patients presenting with acute ischemic stroke, fewer than 2% of patients receive thrombolytic therapy, often due to prehospital and diagnosis delay [1, 4–6]. Persistent deficiencies in recognition of stroke symptoms by patients, emergency medical services, and many healthcare providers continue to contribute to delay in diagnosis [3]. Another barrier to early treatment is the widespread lack of availability of neurological expertise on an emergent basis. Aggressive educational programs and stroke campaigns have been developed to improve public awareness of stroke and to encourage rapid recognition of, and reaction to, stroke warning signs through immediate use of the 9-1-1 system; rapid EMS assessment; priority transport with prenotification of the receiving hospital; and prompt, accurate diagnosis and treatment [7, 8]. Data from recent trials demonstrate sustained benefit of these educational interventions regarding identification and management of acute ischemic stroke, with increased thrombolytic use in patients with ischemic stroke from 2.21% to 8.65% as compared with communities that did not have such measures. In patients with ischemic stroke who were eligible for thrombolytic therapy, rates
of tissue plasminogen activator (tPA) use increased from 14% to 52% in these communities with modernized interventions [9].

Not quite half of all stroke patients use EMS access to healthcare, but those who do utilize EMS comprise the majority of patients presenting within the early thrombolytic window of 3 h [10]. In addition to bystander recognition of a medical problem, other reported predictors of EMS use by stroke patients include stroke severity, presence of intracranial hemorrhage, age, sense of urgency, unemployment, and race [11, 12]. Among the patients who arrive in a timely manner, disparities also exist in the time to receipt of brain imaging, a crucial component of stroke diagnosis and essential step before thrombolytic administration. In cases of presumed transient ischemic attack (TIA) arriving within 2 h from symptom onset, the lengthiest delays until neuroimaging have been noted. This re-emphasizes the importance of educational efforts for stroke care providers, underscoring the importance of timely diagnosis and treatment for all patients presenting with symptoms of acute cerebral ischemia [13].

As the field of acute stroke care evolves, many US states are also establishing designated stroke centers to improve acute stroke care delivery [14, 15]. The Brain Attack Coalition described two hierarchical sets of recommendations, one for primary stroke centers (PSC) and another for comprehensive stroke centers (CSC). A PSC has the personnel, programs, expertise, and infrastructure to care for many patients with uncomplicated strokes, uses many acute therapies (such as intravenous tPA), and admits such patients into a stroke unit. The CSC is designed to care for patients with complicated types of strokes, patients with intracerebral hemorrhage or subarachnoid hemorrhage, and those requiring specific interventions (e.g., surgery or endovascular procedures) or an intensive care unit type of setting [16–18]. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) has established a formal certification process for PSCs. Preferentially routing acute stroke patients to a PSC has been shown to increase the proportion of patients treated with thrombolytic therapy to 10% but only a few states have policies mandating the rerouting, partially due to the limited number of PSCs available [19]. It remains very likely that more widespread geographic implementation will evolve in the next few years.

In 2009, the American Heart Association (AHA) and the American Stroke Association (ASA) released a scientific statement that encourages all facilities which lack an onsite stroke neurologist to have teleconferencing systems in place to consult expert stroke neurologists at another facility. The group defines teleconferencing as ‘the use of dedicated, high quality, interactive, bidirectional audiovisual systems coupled with teleradiology for remote review of brain images’ [20]. Through telestroke, the application of telemedicine in stroke care, expert neurologists can remotely evaluate an acute stroke patient possibly needing thrombolytic treatment. The recommendations emphasize the goal of the stroke systems of care model to create a team of health workers involved with stroke, starting with public health advocacy to reduce stroke risk and continuing all the way to outpatient rehabilitation. Remote evaluation of stroke patients via telemedicine is increasingly utilized, particularly in neurologically underserved areas. Scientific analyses have demonstrated the reliability of neurological assessments via videoconference and improved accuracy of acute stroke treatment decisions compared to telephone-based consultation [21, 22]. Telestroke advances in coming years may extend the reach of such technologies to the field within minutes of stroke symptom onset, to ambulances, and many other settings or scenarios where acute ischemia may be encountered.

**PREHOSPITAL TREATMENT OPPORTUNITIES**

After the patient’s airway, breathing, and circulation (ABC) have been assessed and stabilized, common presenting signs of stroke should be routinely assessed. Prehospital stroke assessment tools have proved effective in identifying stroke patients in the field. The Los Angeles Prehospital Stroke Screen uses patient history, physical findings, and finger stick
Prehospital diagnosis and early treatment in acute ischemia

Glucose determination to rapidly assess stroke patients [23]. After the patient has been stabilized and assessed they should be quickly transported with cardiac monitoring to the nearest hospital or designated stroke center where applicable. It is important to establish intravenous access and deliver isotonic crystalloids (normal saline) for resuscitation. Dextrose solutions are generally avoided because the ischemic penumbra has inadequate oxygen and the presence of dextrose and lack of oxygen will drive glycolysis toward an anaerobic pathway resulting in lactic acid production as opposed to pyruvate, thereby worsening regional acidosis, further compromising cerebral blood flow and exacerbating ischemia.

Adequate tissue oxygenation is important in the setting of acute cerebral ischemia and for the prevention of hypoxia and potential worsening of the brain injury. Hypoxia can occur as a result of aspiration pneumonia, atelectasis, airway obstruction or hypoventilation. It is important to consider intervention in patients with decreased consciousness or signs of brainstem dysfunction. Pneumonia is a common complication and cause of death after stroke. Electively intubating patients with elevated intracranial pressure or malignant brain edema is advised. Patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level greater than 92% [24–26]. Inadvertent or empiric use of oxygen is unproven and should likely be subject to the same scrutiny that has covered therapeutic hyperoxia trials to date. Future prehospital studies of oxygen use may answer such basic and readily applicable strategies.

There are no established guidelines regarding prehospital management of hypertension in patients with suspected stroke and it is generally recommended that intervention be pursued solely after emergency room arrival. The management of arterial hypertension remains controversial, likely due in part to a lack of understanding regarding the cause of acute hypertension across a variety of stroke cases. Data to guide recommendations for hypertensive treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 h after onset of stroke symptoms. A relatively cautious approach to the treatment of arterial hypertension is recommended by the AHA. Pending more data, it is recommended that emergency administration of antihypertensive agents should be withheld unless the diastolic blood pressure is greater than 120 mmHg or unless the systolic blood pressure is greater than 220 mmHg. If treatment is necessary, the recommended goal is to lower blood pressure by 15–25% within the first day [27–29]. Further studies on the cause of acute hypertension in a variety of stroke cases, including detailed imaging verification of vascular status, will expand our understanding and possible treatment of blood pressure alterations.

Ischemic stroke is a potentially reversible process that depends on adequate perfusion of the brain to maintain cellular viability. Cerebral perfusion may be affected by numerous factors, including fundamental aspects such as head positioning. Patients with stroke are routinely positioned using 30° head-of-the-bed (HOB) elevation by paramedics and emergency room personnel, although this convention is not rooted in scientific evidence. Wojner-Alexander et al. [30, 31] emphasized that measures which promote blood flow during the acute phase of ischemic stroke, such as head positioning, may directly impact the subsequent development of brain infarction and associated clinical deficit. They concluded that flat HOB (0–15°) positioning to promote an increase in arterial flow to ischemic brain tissue may be beneficial in acute ischemic stroke patients. However, not all patients can tolerate 0° positioning for any length of time owing to concurrent cardiopulmonary pathology that may challenge flat positioning. Additionally, the risk of pulmonary aspiration must be considered when prescribing 0° positioning for a significant length of time. It is also unknown whether flat head positioning may be detrimental in the subacute phase of stroke when elevated intracranial pressure may rise to life-threatening levels [32]. Future studies should investigate the effects of head positioning and other related hemodynamic influences in cases of acute cerebral ischemia, carefully separating cases based on time course (acute versus subacute) and specific imaging parameters.
Eventual identification of an effective neuroprotective therapy may further expand the role of EMS in the treatment of acute cerebral ischemia. Prehospital trial conduct substantially reduces on-scene to needle time and permits hyperacute delivery of neuroprotective therapy. Neuroprotective treatments are designed to interrupt the cellular, biochemical, and metabolic elaboration of injury during or following exposure to ischemia; they encompass a rapidly expanding array of pharmacologic interventions. Various classes of neuroprotective agents have reached phase III efficacy trials in focal ischemic stroke, but no single neuroprotective agent has been shown to influence outcome after acute stroke [33, 34]. However, trials of hypothermia, magnesium and albumin are continuing. Field initiation of magnesium sulfate in acute stroke patients has been demonstrated to be feasible and safe, and a phase III randomized controlled trial is presently testing prehospital administration of magnesium sulfate [33]. The Albumin in Acute Stroke (ALIAS) trial is looking at albumin given acutely to reduce disability, yet prehospital implementation may enhance the potential yield of this investigational strategy [33, 35–38]. Citicoline (cytidine-5’-diphosphocholine or CDP-choline) is an essential precursor in the synthesis of phosphatidylcholine, a key cell membrane phospholipid, and a meta-analysis of four randomized US clinical citicoline trials concluded that treatment with oral citicoline within the first 24 h after a moderate to severe stroke is safe and increases the probability of complete recovery at 3 months [39, 40].

Fever in the setting of an acute ischemic stroke is associated with poor neurological outcome. The mechanism has been ascribed to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production [41, 42]. Measures to treat fever include antipyretic medications and cooling devices. One of the major barriers to acute hypothermia is the need for high-quality critical care to start immediately [35]. However, the feasibility of initiation of hypothermia has also been demonstrated in the prehospital setting [43, 44]. Hypothermia is a well-established neuroprotectant that reduces brain edema and intracranial pressure in patients with traumatic brain injury. It has recently been shown to improve neurological outcome following cardiac arrest and neonatal hypoxia ischemia. In the case of ischemic stroke, cooling should ideally be applied in conjunction with the re-establishment of cerebral perfusion. Endovascular cooling to 33°C seems to be feasible and safe in non-anesthetized stroke patients, even in those treated with thrombolysis [45]. However, only a few small pilot studies have evaluated hypothermia as a treatment for acute ischemic stroke, and no controlled trials of hypothermia for hemorrhagic stroke have been performed [35, 46, 47].

**EARLY THERAPEUTIC STRATEGIES**

Time is of the essence when it comes to treatment of acute cerebral ischemia. Diagnosis must be established before therapeutic strategies may be considered and rapid triage through neuroimaging evaluation is therefore critical. Developing an organized protocol and stroke team alert system allows for quick and informed decisions regarding optimal treatment and subsequent management. Once a patient arrives in the emergency room, they should be immediately evaluated with a brief history, general physical and neurological examination, enhanced with the use of a formal stroke scale such as the National Institutes of Health Stroke Scale (NIHSS). The score may influence decisions about acute treatment and can be performed with a reasonable degree of accuracy by practitioners across a broad range of specialties. Recommended routine tests include blood glucose, electrolytes, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function studies. A thorough cardiovascular examination, cardiac enzyme tests, and a 12-lead electrocardiogram (ECG) should be acquired as cardiac abnormalities are prevalent among patients with stroke [48, 49]. Additional tests may be performed as indicated by the patient’s history, symptoms, physical findings, or comorbidities.
These rapid triage elements that confirm a diagnosis to be supplemented by neuroimaging allow for earlier treatment with a broad range of therapeutic strategies.

Despite the advent of new therapies, treatment of acute ischemic stroke remains difficult. The principal drawback to thrombolytic therapy for acute ischemic stroke is a 3–6% occurrence of symptomatic cerebral hemorrhage. Intravenous thrombolytic treatment with alteplase, initiated within 3 h after the onset of symptoms, is the only approved medical therapy currently available for acute ischemic stroke. Two European trials, the European Cooperative Acute Stroke Study (ECASS) and ECASS II, investigated a time window of up to 6 h but failed to show the efficacy of thrombolytic treatment, as defined by each trial [50, 51]. Most recently, ECASS III demonstrated the potential extension of the time window to the later epoch of 3 to 4.5 h after onset of stroke symptoms, realizing a modest but significant improvement in clinical outcome without a higher rate of symptomatic intracranial hemorrhage than that reported previously among patients treated within 3 h [52]. In May 2009, the AHA/ASA issued a scientific advisory encouraging the use of tPA to treat acute ischemic stroke as late as 3 and 4.5 h after symptom onset in carefully selected cases [53].

Clinical studies have demonstrated the use of ultrasound to enhance enzymatic thrombolysis. Its use appears to increase the transport of tPA into thrombus, thus promoting the opening and cleaving of fibrin polymers, and ultimately improving the binding affinity of tPA to fibrin. In an observational pilot trial of combined therapy with 2-MHz continuous ultrasound monitoring and intravenous tPA in 55 patients with a documented middle cerebral artery (MCA) occlusion treated within 3 h of stroke onset, complete recanalization at 2 h of tPA bolus was achieved in 36% of patients. CLOTBUST, a phase II multicenter randomized trial, demonstrated that 2-h continuous monitoring transcranial Doppler ultrasound in combination with standard tPA is safe and may improve outcome [54, 55].

Endovascular methods to achieve early recanalization of an occluded artery in acute ischemic stroke encompass both pharmacological and mechanical techniques. In selective intra-arterial (IA) thrombolysis, fibrinolytic agents are infused distal to, proximal to, or directly within thrombotic occlusions using a microcatheter delivery system as part of an angiographic procedure to restore blood flow to downstream ischemic regions. IA plasminogen activators delivered directly at the clot have been shown to effectively restore perfusion and improve clinical outcomes for MCA occlusions. Although these results achieved with intra-arterial recombinant pro-urokinase demonstrated efficacy, such use of the drug has not been approved by the United States Food and Drug Administration (FDA) [56]. Endovascular thrombectomy devices for recanalization have recently expanded after the Merci Retrieval System® was unveiled as the first device for reperfusion therapy labeled specifically for use in acute ischemic stroke to extract occlusive thrombi [57]. In 2008, the Penumbra system suction thrombectomy device was also approved for use, employing vacuum aspiration to remove occlusive thrombi in acute ischemic stroke [58]. The NeuroFlo device has also been implemented as a collateral therapeutic strategy where partial aortic occlusion attempts to reverse ischemia, the principal detrimental element in stroke pathophysiology. The presumed mechanism of action of this novel device is enhancement of blood flow via cerebral collaterals to minimize infarct volume and improve clinical outcomes [59, 60]. Various drugs and multifaceted devices continue to be refined to enhance perfusion through occluded arteries or via collaterals in acute cerebral ischemia. Ongoing trials will address use of these various approaches from the earliest epochs in ischemia to later cases where benefit may be compromised by risk of adverse effects, including the use of neuroimaging to optimally select ideal candidates.

The prehospital and early phases in the care of patients with acute cerebral ischemia remain largely unexplored. These early epochs provide a tremendous opportunity to expand current diagnostic and therapeutic approaches, but numerous challenges arise. Recent transformation of prehospital care paradigms and early diagnosis and treatment algorithms will provide a framework for future advances. Telestroke also promises to extend stroke expert-
ise to vast geographic regions with incredibly short response times that will likely enhance stroke care to a larger patient population. Innovation in coming years will undoubtedly capitalize on these earliest stages of cerebral ischemia where the potential to reverse stroke is greatest.

REFERENCES

Prehospital diagnosis and early treatment in acute ischemia


