PROCEEDINGS OF
NEUROCritical CARE 2003: HERE COMES THE SUN
A GLOBAL SUMMIT ON CRITICAL CARE FOR CEREBROVASCULAR DISEASE

SEPTEMBER 5–6, 2003, CLEVELAND, OHIO

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The Cleveland Clinic

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Welcome to Neurocritical Care 2003: Here Comes the Sun—A Global Summit on Critical Care for Cerebrovascular Disease. This supplement to the Cleveland Clinic Journal of Medicine contains the proceedings of the summit, which took place September 5 and 6, 2003, in Cleveland, Ohio.

Critical care medicine developed in the 1970s and 1980s at the same time that tremendous advances were being made in our understanding and treatment of myocardial ischemia. Neurocritical care developed in the 1980s and 1990s during the decade of the brain, concurrent with great progress in cerebrovascular neurology and neurosurgery. Today, there is a convergence of vascular neurology, vascular neurosurgery, and neurocritical care to the point where brain ischemia can be diagnosed with stunning precision and reperfusion therapy started immediately. Patients today can be managed by a team of specialists in the neurological intensive care unit, where blood flow and hemodynamics can be optimized to achieve the best possible outcome.

The success of our neurocritical care conferences illustrates this convergence. Our first international conference, Neurocritical Care 2001: Returning from the Dark Side of the Brain, focused on multimodal monitoring and hypothermia. Despite occurring just 2 weeks after the tragic events of September 11, Neurocritical Care 2001 was well attended by people from around the world and was met with great enthusiasm. With Neurocritical Care 2003, we broadened the scope of topics, reviewing intracranial pressure, in many ways the raison d’être for neurocritical care, as well as hemorrhagic stroke, the fundamentals of neurocritical care, and acute ischemic stroke.

We hope you will share our enthusiasm in learning about new areas of study and discovery in critical care for cerebrovascular disease and plan on joining us at this year’s conference, Neurocritical Care 2004: Imagine.

Michael DeGeorgia, MD
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* In addition to the presentations represented here, The Cleveland Clinic’s Neurocritical Care 2003 Summit also included the following talks, which were not accompanied by written syllabus submissions for publication:
  - Impact of vascular disease on world health care—Marc Mayberg, MD (Introductory Presentation)
  - Blood pressure: Do we raise it or lower it? CPP protocol vs Lund protocol—Randall Chestnut, MD (Intracranial Pressure)
  - Decompressive craniectomy: Back to the future—Jeffrey Frank, MD (Intracranial Pressure)
  - Subarachnoid hemorrhage: From clip to coil—Neil Martin, MD (Hemorrhagic Stroke)
  - Cerebral vasospasm: Which H is the most important H?—Stephan Mayer, MD (Hemorrhagic Stroke)
  - Intracerebral hemorrhage: To evacuate or not to evacuate—A.D. Mendelow, MB, Bch, PhD (Hemorrhagic Stroke)
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The development of neurologic intensive care

ALLAN H. ROPPER, MD

The primary drivers for the existence of a critical care unit have been (1) concentration of patients who require clinical surveillance that is more intensive than can be provided on a normal ward; (2) a need for efficient deployment of specially trained staff to provide this surveillance, along with the sophisticated technology that they manage; and (3) a need to apply solutions to disordered cerebral and systemic physiology.

Following this model, the progenitors of neurologic intensive care units (ICUs) grew from several streams of medical endeavor:

- The respiratory care units designed to service patients with polio following the development of mechanical ventilators by Ibsen in Copenhagen, and the evolution from these of Spalding and Crampton’s respiratory ICUs at Radcliffe Infirmary
- The growth of cardiac care units following the demonstration by Killup in Indiana that provided a model for the application of a special technology (continuous ECG monitoring) and a focused treatment (lidocaine), and the modern medical-surgical ICU with special capability to monitor and treat wedge pressure
- Postoperative neurosurgical wards that promoted specific neurologic examination surveillance by special nurses and the application of intracranial pressure monitoring.

In all these circumstances, the ability to monitor and treat a physiologic change was the fulcrum on which special units were opened, and, just as importantly, the existence of these units was the basis for the establishment of a medical field.

■ EARLY FORCES THAT SHAPED THE FIELD

In addition to the training of neurologic nurses, the special physiologic measurement that truly created neurologic intensive care was the ability to measure intracranial pressure, beginning in the 1960s with the work of Lundberg. There was a presumption not only that intracranial pressure could be measured in humans but that it could be treated and that this would benefit patients.

Certain hospital social forces also contributed to the growth of the field, particularly the expansion of neurosurgical work that required postoperative beds for patients with trauma, brain tumors, aneurysmectomy, etc. It was only after momentum was created by neurosurgeons in large institutions that neurologists began to cull critically ill patients or patients with complex cases of status epilepticus and neuromuscular respiratory failure in the same or similar units.

This configuration set up a natural competitiveness in these units between neurosurgeons, neurologists, and the anesthesiologists who had been administering neuroanesthesia. Neurosurgeons soon lagged in involvement for a number of reasons, mainly because of their special surgical abilities, which offered a more sensible career path. Anesthesiologists, who initially took the lead in respiratory management and in cerebral physiology relating to blood flow and intracranial pressure, were largely displaced from critical care units by medical intensivists who had a wider range of skills, although their major limitation was (and continues to be) airway management.

■ MARKING MILESTONES

Certainly milestones are worth noting. Large neurologic ICUs with an academic mission began opening in the late 1970s, including those at the Massachusetts General Hospital, Johns Hopkins, and Columbia-Presbyterian. Spinal cord units with a
focus on central nervous system sparing also appeared at this time, particularly in Miami. In 1978, David Jackson from Cleveland began giving an organized course in neurologic intensive care for the American Academy of Neurology. A textbook devoted to the subject appeared in 1983, and a number of pedagogic courses emerged afterwards. Board certification in critical care began in 1987 through the American Board of Internal Medicine and the American Board of Anesthesiology. An interest group arose at the American Academy of Neurology, but attempts at creating an identity through a subspecialty examination in neurology failed.

Through the 1980s, the number of neurologic ICUs proliferated greatly and fellows were trained, initially about four per year. Stroke units, often appended to a neurologic ICU, began to appear in the mid- to late 1980s. European units opened, notably in Heidelberg, and took the lead in critical stroke problems.

An intense period of investigation in brain sparing occurred in the 1990s but left little of value. Attempts at widening the use of electrophysiologic measurements met with mixed success.

Among the many accomplishments of the field have been the development of postprocedure care of interventional neuroradiology, subarachnoid hemorrhage fluid management, treatment of status epilepticus, refinements of treatment for Guillain-Barré syndrome and myasthenia gravis, codification and study of brain death, and hemicraniectomy for stroke swelling. This year, a journal devoted to the field was initiated with Eelco Wijdicks as its editor.

**CHALLENGES OF MATURITY**

The field is now fairly mature. Neurointensivists have been successful at extracting aspects of practices from other specialties and incorporating them into a coherent specialty. However, there have been few fundamental changes since the early 1980s and almost no advancement of the neuroscience aspects of the field. The table of contents of a textbook from 1983 reflects the main themes presented in the current era. Looking back, it would appear that another novel physiologic measurement or treatment may be needed to stimulate the field.
The contribution of brain edema to brain swelling in cases of traumatic injury, ischemia, and tumor remains a critical problem for which there is currently no effective clinical treatment. It is well documented that in head injury, swelling leads to an elevation in intracranial pressure (ICP), which is a frequent cause of death, and to very poor prognosis in survivors. This swelling process has been classified into four distinct degrees of severity based on studies of the Traumatic Coma Data Bank. Of great importance is the fact that the degree of swelling assessed on the first CT scan, obtained soon after injury, is highly correlated with outcome ($P < .0002$).

**BRAIN SWELLING—EDEMA OR VASCULAR ENGORGEMENT?**

Our experimental and clinical studies provide strong evidence that edema is primarily responsible for the swelling process. For the past several decades, it has been generally accepted that the swelling process accompanying traumatic brain injury is mainly due to vascular engorgement, with blood volume providing the increase in brain bulk and subsequent rise in ICP. Edema was thought to play a minor role. However, our recent findings indicate that edema, not vascular engorgement, is responsible for brain swelling and that blood volume is actually reduced following traumatic brain injury. Thus, it is important to shift our attention to brain edema and to understand the pathophysiologic mechanisms responsible for water movement into brain.

**TRAUMATIC BRAIN EDEMA—VASOGENIC OR CELLULAR?**

By definition, edema is an abnormal accumulation of fluid within the brain parenchyma; it is subdivided into vasogenic and cytotoxic types. Vasogenic edema is defined as fluid originating from blood vessels and accumulating around cells. Cytotoxic edema is defined as fluid accumulating within cells as a result of cell injury. The most common cytotoxic edema occurs in cerebral ischemia. Neurotoxic edema is a subtype of cytotoxic edema caused by high levels of excitatory amino acids. Heretofore, the edema specific to traumatic brain injury has generally been considered to be of “vasogenic” origin, secondary to traumatic opening of the blood-brain barrier. However, all three forms of edema can coexist, and their relative contributions to brain swelling and elevated ICP have not been identified. This is a critical problem, as effective treatment will clearly depend on the type of swelling.

Our own studies in this area are in sharp contrast to the general belief that traumatic brain injury results in a predominantly extracellular edema secondary to blood-brain barrier opening. Although a vasogenic component may be present, we strongly suspect that the type of swelling in traumatic brain injury with or without associated mass lesion is predominantly a cellular edema. A lack of barrier opening in the presence of continued swelling has been noted in our clinical studies of head-injured patients in whom magnetic resonance “water maps” were obtained with gadolinium challenge. Experimentally, we have strong evidence that the type of swelling in diffuse injury is predominantly cellular.

**IONIC DYSFUNCTION IN BRAIN INJURY**

It is well documented that ionic dysfunction occurs with traumatic brain injury and that extracellular $K^+$ is transiently increased as a result of the depolariza-
tion synchronous with mechanical insult. This loss of ionic homeostasis should be accompanied by a concomitant movement of sodium. The seminal studies by Betz et al and Gotoh et al measured unidirectional movement of sodium into brain following an ischemic injury, and work by other investigators has demonstrated a clear relationship between tissue water content and sodium accumulation. As we have demonstrated a predominantly cellular swelling, the extension of our work to the study of ionic movement is fundamental to a deeper understanding of the formation of traumatic brain edema.

Traumatic brain injury triggers a cascade of events, including mechanical deformation, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization, that leads to alterations in normal ionic gradients. Excitatory amino acids released via mechanical deformation and membrane depolarization activate ligand-gated ion channels, which allow ions to move down their electrochemical gradients. In addition, membrane depolarization resulting from ionic flux and trauma triggers voltage-sensitive ion channels, providing further routes for ionic movement. These ionic disturbances are identified by an increase in extracellular potassium ([K⁺]ec) with a concomitant decrease in extracellular sodium ([Na⁺]ec), calcium, and chloride.

Restoration of ionic homeostasis is accomplished via cotransport and countertransport processes such as the Na⁺-K⁺ ATPase, Na⁺/K⁺/2Cl⁻ cotransporter, Na⁺-H⁺ transporter, and Na⁺-Ca²⁺ exchanger. However, if the injury is severe, or if secondary insults occur, disruption of ionic homeostasis persists as the cotransport and countertransport processes are impaired and become incapable of returning ion concentrations to their normal levels. Moreover, in the absence of adequate levels of ATP resulting from either an ischemic reduction in cerebral blood flow or insufficient production of ATP due to mitochondrial dysfunction, energy-dependent ion pumps and cotransport and countertransport processes are inefficient in counteracting the normal dissipative flux of ions down their electrochemical gradients.

We hypothesize that the net balance of ionic movement that accompanies brain injury results in the movement of cations out of the extracellular space into cells. The movement of sodium and calcium is passively followed by chloride to maintain electroneutrality, and is followed isosmotically by water. If sustained, ionic disturbances result in cellular swelling and cytotoxic edema, which we have shown to be the primary contributor to raised ICP. In traumatic brain injury, the initiating factors, which result in the movement of ions, may differ from those primarily responsible in ischemia. For example, ATP reduction may not be due to decreased cerebral blood flow since blood flow in traumatic brain injury persists and delivery of substrate is maintained.

LABORATORY MODELS OF TRAUMATIC BRAIN INJURY WITH BRAIN SWELLING

The study of traumatically induced swelling in the laboratory has been difficult, in part because of a lack of models that produce marked, rapid swelling and, most important, a steady rise in ICP. Fluid percussion, or direct dural impact, results in a sudden rise in blood pressure that is sufficient to breach the blood-brain barrier and is not suitable for the study of edema produced by closed head injury. Moreover, ICP increases only transiently and declines over time. Similarly, the classic model of subdural hematoma, which has been used by many investigators, also produces only a transient rise in ICP following a gradual recovery toward baseline.

For diffuse injury, we solved this problem with our development of a rat impact-acceleration model that develops marked swelling, a profound diffuse axonal injury, and a steadily rising ICP when secondary insults are superimposed upon the mechanical trauma. For mass lesions, we found that superimposing a controlled subdural hemorrhage following impact-acceleration injury resulted in similar effects. This combination, which mimics the clinical scenario better than a subdural hemorrhage alone, results in a remarkable, steady increase in ICP to greater than 50 mm Hg.

MAGNETIC RESONANCE TECHNOLOGY: DIFFUSION-WEIGHTED IMAGING TECHNIQUES AND PROTON SPECTROSCOPY

It is not possible to differentiate between vasogenic (extracellular) and cytotoxic (cellular) edema by conventional tissue water measurement. In vivo diffusion-weighted imaging is a magnetic resonance technique that, by employing strong magnetic field gradients, is sensitive to the random molecular translation of water protons. Maps of the apparent diffusion coefficient (ADC) can be derived from a series of diffusion-weighted images obtained with
different magnetic fields. Recent findings in experimental ischemia models suggest that ADC values can provide earlier and more specific information about tissue damage and characteristics of edema. Several studies have adopted this concept in distinguishing the type of edema in ischemia and traumatic brain injury. The application of such new imaging techniques can quantify the temporal changes and document the type of edema that is occurring during both the acute and the late stages of edema development.

N-ACETYLASPARTATE ASSESSED BY PROTON SPECTROSCOPY AND MITOCHONDRIAL DYSFUNCTION

We hypothesize that mitochondrial dysfunction prevents the restoration of ionic and cell volume homeostasis. Hovda’s group has clearly implicated ionic shifts as the major mechanisms for cellular and organelle swelling. Moreover, Muizelaar has recently demonstrated in rat brain suspensions that mitochondrial function was profoundly reduced after traumatic brain injury and that this was largely calcium-dependent. Povlishock has posited that the shear and tensile forces of injury induce mechanical poration of cell membranes that can cause an “excitatory amino acid storm” that leads to intracellular calcium influx with subsequent mitochondrial loading. It is envisioned that in a permissive environment, such calcium loading leads to mitochondrial permeability transition, which is linked to overt mitochondrial failure. The accuracy of this assumption is supported by several studies. More importantly, studies by Povlishock et al have shown that cyclosporin A, which blocks mitochondrial permeability transition, translates into significant neuroprotection.

N-acetylaspartate (NAA) was discovered in 1956 by Tallan, More, and Stain and is represented by the largest peak in a proton spectrum (1H MRS). It is synthesized in mitochondria from L-aspartate and acetyl-CoA in a reaction catalyzed by an N-acetyltransferase. NAA has been found histochemically to be a constituent of neurons and axons, with lesser amounts in glial cells. Large numbers of studies show NAA absent or reduced in brain tumor (glioma), ischemia, degenerative disease, and inborn errors of metabolism, and it is accepted fact that NAA levels correspond to tissue damage. Studies of NAA in severe brain injury are relatively few, and the temporal course of NAA changes in trauma in association with ADC values has not been studied. Because NAA is synthesized by the mitochondria, it is reasonable to posit that reduced tissue NAA will be associated with regions of low ADC, low ATP, ionic dysfunction, and brain edema. This report describes the most recent information available on NAA reduction in human head injury.
Cerebral edema and elevated intracranial pressure (ICP) are important and frequent problems in the neurocritically ill patient. They can both result from various insults to the brain. Improving cerebral edema and decreasing ICP has been associated with improved outcome. However, all current treatment modalities are far from perfect and are associated with serious adverse events: indiscriminate hyperventilation can lead to brain ischemia; mannitol can cause intravascular volume depletion, renal insufficiency, and rebound ICP elevation; barbiturates are associated with cardiovascular and respiratory depression and prolonged coma; and cerebrospinal fluid (CSF) drainage via intraventricular catheter insertion may result in intracranial bleeding and infection.

Other treatment modalities have been explored, and hypertonic saline (HS) solutions particularly appear to be an appealing addition to the current therapeutic avenues for cerebral edema. This article succinctly reviews some of the basic concepts and mechanisms of action of HS and discusses some of its possible clinical applications.

**Physiologic Context**

**The blood-brain barrier**

The blood-brain barrier (BBB) represents both an anatomic and a physiologic structure. The BBB is made up of tight junctions between the endothelial cells of the cerebral capillaries. Various mechanisms exist for compounds to cross the BBB, including active transport, diffusion, and carrier-mediated movements. Because transport through the BBB is a selective process, the osmotic gradient that a particle can create is also dependent on how restricted its permeability through the barrier is. This restriction is expressed in the osmotic reflection coefficient, which ranges from 0 (for particles that can diffuse freely) to 1.0 (for particles that are excluded the most effectively and therefore are osmotically the most active).

The reflection coefficient for sodium chloride is 1.0 (mannitol's is 0.9), and under normal conditions sodium (Na⁺) has to be transported actively into the CSF. Animal studies have shown that in conditions of an intact BBB, CSF Na⁺ concentrations increase when an osmotic gradient exists but lag behind plasma concentrations for 1 to 4 hours. Thus, elevations in serum Na⁺ will create an effective osmotic gradient and draw water from brain into the intravascular space.

**Cerebral edema and intracranial dynamics**

Cerebral edema is defined as an increase in brain water leading to an increase in total brain mass. There are three major categories of brain edema:

- **Vasogenic edema**, which is caused by increased permeability of the endothelial cells of brain capillaries and is seen in patients with brain neoplasms
- **Cytotoxic edema**, which results from the influx of water into cells. This type of edema may be caused by energy depletion with failure of the ATP-dependent Na⁺-K⁺ pump (ie, cerebral infarction) or low extracellular Na⁺ content (ie, hyponatremia).
- **Interstitial edema**, in which CSF diffuses through the ependymal lining of the ventricles into the periventricular white matter. This type of edema is seen with hydrocephalus.

It is important to point out that different types of edema can coexist in the same patient. For instance, brain ischemia is associated with both cytotoxic and vasogenic edema.

The presence of cerebral edema, with the subse-
quent increase in brain mass, alters the intracranial contents (brain, blood, and CSF). Small increases in brain volume can be compensated by changes in CSF volume and venous blood volume. Beyond that, changes in intracranial volume (ΔICV) will result in changes in ICP (ΔICP), which has been termed compliance (ΔICV/ΔICP). When brain compliance decreases, such as when intracranial volume rises, ICP rises. However, it is important to realize that focal cerebral edema can create ICP gradients and cause tissue shifts in the absence of a global increase in ICP.8

**HYPERTONIC SALINE: MECHANISMS OF ACTION**

HS solutions can possibly affect the volume of the intracranial structures through various mechanisms. All or several of them are likely to be interacting to achieve the end result of HS therapy: reduction of cerebral edema and elevated ICP. These mechanisms are summarized below:

- **Dehydration of brain tissue** by creation of an osmotic gradient, thus drawing water from the parenchyma into the intravascular space. As mentioned above, this would require an intact BBB. Experimental evidence suggests that the brain water–reducing properties of HS are accomplished at the expense of the normal hemisphere.
- **Reduced viscosity.** HS solutions enhance intravascular volume and reduce viscosity.9 The autoregulatory mechanisms of the brain vasculature have been shown to respond not only to changes in blood pressure but also to changes in viscosity.10 Thus, a decrease in blood viscosity results in vasoconstriction in order to maintain a stable cerebral blood flow (CBF).
- **Increased plasma tonicity.** It has been postulated, based on experimental animal data, that increased plasma tonicity, such as that seen after HS administration, favors more rapid absorption of CSF.11
- **Increased regional brain tissue perfusion,** possibly secondary to dehydration of cerebral endothelial cells and erythrocytes, facilitating flow through capillaries.12
- **Increased cardiac output and mean arterial blood pressure,** with resultant augmentation of cerebral perfusion pressure, most likely due to improvement of plasma volume and a positive inotropic effect.7,13
- **Diminished inflammatory response to brain injury,** which has been demonstrated with HS administration.14
- **Restoration of normal membrane potentials through normalization of intracellular sodium and chloride concentrations.**13
- **Reduction of extravascular lung volume,** leading to improved gas exchange and improved PaO2.15

**EXPERIMENTAL SUPPORT FOR THE EFFICACY OF HYPERTONIC SALINE**

**Animal studies**

HS solutions have been studied extensively in a variety of animal models, as thoroughly detailed in a recent review.1 The literature suggests that fluid resuscitation with an HS bolus after hemorrhagic shock prevents the ICP increase that follows resuscitation with standard colloid and crystalloid fluids for 2 hours or less. This effect can be maintained for longer periods by using a continuous HS infusion. HS may be superior to colloid solutions with regard to ICP response during the initial period of resuscitation.1,16 In animal models of cerebral injury, the maximal ICP-reducing effect of HS is appreciated with focal lesions, such as cryogenic injury or intracerebral hemorrhage. Again, the ICP reduction may be caused by reduction in water content in areas of the brain with the BBB intact, such as the nonlesioned hemisphere and the cerebellum. HS has also been compared with mannitol and was found to have equal efficacy in reducing ICP but to have a longer duration of action and to yield greater improvement in cerebral perfusion pressure.13

**Human studies**

Despite the numerous studies in animal models, most of the evidence in humans is based on the publication of case series and a few randomized studies. Some of the published studies are briefly reviewed here. Readers are referred to a recent review13 for a more detailed description.

**Acute ischemic stroke.** HS in two different concentrations, 7.5% and 10%, has been used to reduce ICP in patients after large cerebral infarcts.18,19 Schwarz et al18 compared the effect of 100 mL of 7.5% HS hydroxyethyl starch (osmolarity 2,570 mosm/L) and 200 mL of 20% mannitol (osmolarity 1,100 mosm/L) in 9 patients with stroke randomized to one of the two treatments. HS hydroxyethyl starch caused a greater and earlier peak reduction in ICP, although mannitol caused more improvement in cerebral perfusion pressure. These same researchers studied the effect of 10% saline bolus
infusions in 8 patients in whom mannitol had failed. HS reduced ICP by at least 10% in all the instances it was used, and the maximal effect was noted at 20 minutes after the end of the infusion. Even though ICP rose subsequently, it did not reach pretreatment values during the 4 hours of data recording.

**Intracranial hemorrhage.** There has been one report of 2 patients with nontraumatic (presumably hypertensive) intracranial hemorrhage who were treated with continuous HS infusion. Both patients improved clinically after 24 hours of treatment but deteriorated at 48 and 96 hours despite continued HS infusion. Repeat CT scanning showed extension of edema. These findings were attributed to a rebound effect similar to that described with mannitol.

**Subarachnoid hemorrhage.** Two studies have been published on the effect of HS on clinical improvement and CBF in patients with subarachnoid hemorrhage. Suarez et al retrospectively studied 29 patients with symptomatic vasospasm and hyponatremia who received continuous infusions of 3% saline. They found that a positive fluid balance was achieved, and there was short-term clinical improvement without adverse effects. Tseng et al studied the effect of 23.5% saline bolus infusions on CBF, ICP, and cerebral perfusion pressure in 10 patients with poor-grade subarachnoid hemorrhage. They found that HS caused a significant decrease in ICP and a significant rise in blood pressure with a subsequent increase in cerebral perfusion pressure. These effects were accompanied by a significant elevation in CBF as determined by transcranial Doppler ultrasonography and xenon CT. The ICP-lowering effect occurred immediately after the infusion and continued for more than 200 minutes. The increase in blood flow velocities lasted 175 to 450 minutes.

**Traumatic brain injury.** Most of the human studies have been in patients with traumatic brain injury. Although there is no agreement on the appropriate concentration, dose, or duration of treatment, HS has been reported to have a beneficial effect on elevated ICP in patients after traumatic brain injury. Most of the reported studies are limited by small sample size and the use of various concentrations of HS. The use of HS in patients with traumatic brain injury deserves more attention, and well-designed studies are needed.

**Miscellaneous conditions.** Other investigators have reported on the use of HS in patients with various intracranial pathologies.

Gemma et al performed a prospective, randomized comparison of 2.5 mL/kg of 20% mannitol and 7.5% saline in patients undergoing elective supratentorial procedures. They found that the two treatments had similar effects on CSF pressure and on clinical assessment of brain bulk. However, the administered solutions used were not equiosmolar.

In a retrospective study, Qureshi et al determined the effect of continuous 3% saline/acetate infusion on ICP and lateral displacement of the brain in patients with cerebral edema and a variety of underlying cerebral lesions. The authors found a reduction in mean ICP within the first 12 hours, correlating with an increase in serum sodium concentration, in patients with traumatic brain injury and postoperative edema, but not in patients with nontraumatic intracranial hemorrhage or cerebral infarction. This beneficial effect was not apparent at later intervals.

In a retrospective review of 8 patients with intracranial hypertension refractory to hyperventilation, mannitol, and furosemide, Suarez et al showed that bolus administration of 23.4% saline was effective in reducing ICP and raising cerebral perfusion pressure. The effect was still present at 3 hours after administration of the HS solution.

Horn et al reported on the administration of 7.5% saline boluses in patients with subarachnoid hemorrhage or traumatic brain injury and refractory intracranial hypertension. The authors demonstrated an increase in cerebral perfusion pressure and a decrease in ICP. The maximal drop in ICP was observed at a mean of 100 minutes after the bolus was given.

**ADVERSE EFFECTS**

The administration of HS has been associated with potential adverse effects, both theoretical and real, as summarized below.

**Intracranial complications**

- Rebound edema can occur as a result of continuous infusion.
- Disruption of the BBB (“osmotic opening”) may be due to the shrinking of endothelial cells and a loosening of the tight junctions that form the BBB, or to an increase in pinocytotic activity and possibly an opening of transendothelial channels.
- The possibility of excess neuronal death has been postulated after continuous infusion of 7.5% saline.
saline in a rat model of transient ischemia.\textsuperscript{40} This has not been proven.

- Alterations in the level of consciousness associated with hypernatremia.\textsuperscript{6} Also, other intracranial alterations have been reported in children with fatal hypernatremia, including capillary and venous congestion; intracerebral, subdural, and subarachnoid bleeding; and sagittal sinus and cortical vein thrombosis with hemorrhagic infarction. Severe hypernatremia (>375 mosm/L) has been found to cause similar changes in animal models.\textsuperscript{6}

- Central pontine myelinolysis is a syndrome typically associated with too-rapid correction of (in most cases chronic) hyponatremia.\textsuperscript{41} Such grave complications have not been reported in association with the use of HS in humans.

### Systemic complications

- Congestive heart failure can be precipitated secondary to volume expansion.\textsuperscript{45}

- Transient hypotension is possible after rapid intravenous infusions, but it is followed by an elevation in blood pressure and cardiac contractility.\textsuperscript{32}

- Decreased platelet aggregation and prolonged prothrombin times and partial thromboplastin times have been reported with large-volume infusion of HS.\textsuperscript{34}

- Hypokalemia and hyperchloremic metabolic acidosis can be seen with infusion of large quantities of HS solutions but can be avoided by adding potassium and acetate, respectively, to the infusion.\textsuperscript{40}

- Phlebitis can be avoided by infusing HS solutions through a central venous catheter.

- Renal failure was reported to occur with increased incidence in a single study.\textsuperscript{44}

### SUMMARY

The use of HS solutions has been shown to reduce ICP both in animal models and in human studies in a variety of underlying disorders, even in cases refractory to treatment with hyperventilation and mannitol. There are several possible mechanisms of action, and important complications such as central pontine myelinolysis and intracranial hemorrhage have not been reported in the human studies. Different types of HS solutions with different methods of infusion (bolus and continuous) have been used in the past, and so far there are not enough data to recommend one concentration over another. Many issues remain to be clarified, including the exact mechanism of action of HS, the best mode of administration and HS concentration to be given, and the relative efficacy of HS vis-à-vis available treatments, particularly mannitol.

### REFERENCES


Hyperventilation is one of the most effective methods available for the rapid reduction of intracranial pressure (ICP). The CO2 reactivity of intracerebral vessels is one of the normal mechanisms involved in the regulation of cerebral blood flow (CBF). Experimental studies using a pial window technique clearly demonstrate that the action of CO2 on cerebral vessels is exerted via changes in extracellular fluid pH. Molecular CO2 and bicarbonate ions do not have independent vasoactivity on these vessels. Although even a mild traumatic brain injury (TBI) can reduce the ability of cerebral vessels to react to changes in pCO2, most patients with moderate or severe TBI retain at least some global CO2 reactivity. As a result, hyperventilation consistently lowers ICP.

**THE MAIN DRAWBACK:**

**REDUCED CEREBRAL BLOOD FLOW**

Despite the effectiveness of hyperventilation in lowering ICP, use of this treatment modality has fallen out of favor, primarily because of the simultaneous effect on CBF. Current guidelines for the management of TBI recommend avoiding hyperventilation during the first 24 hours after injury, when CBF is generally lowest, and recommend that moderate hyperventilation may be used subsequently, but only as a treatment for an elevated ICP.

The effect of a reduction in pCO2 on CBF in a normal subject is approximately 3% per mm Hg. Early studies in normal subjects using the Kety Schmidt technique for measuring global CBF demonstrated that reducing pCO2 from 37 to 19 mm Hg resulted in a decrease in global CBF from 45 to 25 mL/100 g/min. Cerebral oxygen extraction was increased, but cerebral oxygen consumption (CMRO2) remained unchanged. Only when pCO2 was further reduced to an average value of 10 mmHg was CMRO2 significantly reduced, suggesting that ischemia may have resulted from the reduction in CBF.

Studies in patients with TBI follow this same pattern, with hyperventilation resulting in a consistent decrease in global CBF and increasing global cerebral oxygen extraction, but no reduction in CMRO2 until very extreme levels of pCO2 are reached. However, patients with TBI often have areas of brain that are hypoperfused as a result of their brain injury, and these patients may be more vulnerable to regional effects of hyperventilation on CBF.

Recently, studies using positron emission tomography have clearly shown that reduction in pCO2 to levels of 25 to 30 mm Hg does reduce regional CBF, even in areas of the brain that are hypoperfused at baseline. Furthermore, hyperventilation increases the volume of the brain that is marginally perfused, but no significant reduction in regional CMRO2 has been observed at these levels of pCO2. The conclusion of these recent studies seems to be that hyperventilation regularly reduces CBF and increases the proportion of the brain that is critically hypoperfused, but does not result in ischemia at the levels of pCO2 that are commonly used in clinical practice.

The consequences of these hemodynamic effects of hyperventilation on outcome after severe TBI have been studied multiple times, and there is no consistent neuroprotective effect. One randomized clinical trial has shown an adverse effect of chronic hyperventilation in TBI patients. Experimental studies using the cortical impact injury model demonstrate that hyperventilation for 5 hours after TBI increased CA3 hippocampal neuron loss.
EFFECTS ARE TRANSIENT

Another characteristic of hyperventilation that limits its usefulness as a treatment modality for intracranial hypertension is the transient nature of its effect. Because the extracellular space of the brain rapidly accommodates to the pH change induced by hyperventilation, the effects on CBF and on ICP are transient. In fact, after a patient has been hyperventilated for more than 6 hours, rapid normalization of arterial pCO₂ can cause a significant rebound increase in ICP.

SUMMARY

Hyperventilation can rapidly lower ICP, but because it induces a consistent reduction in CBF and because the effects on ICP are transient, the only role that hyperventilation plays in the management of intracranial hypertension is in the management of acute elevations in ICP. In these circumstances, hyperventilation can be life-saving and can temporize until more definitive treatment of the intracranial hypertension can be undertaken.

REFERENCES

For many years, monitoring in the intensive care unit was limited to clinical examination, heart rate, and blood pressure. In 1970, the Swan-Ganz pulmonary artery catheter was introduced, and the specialty of critical care medicine was born. For the first time, clinicians could guide therapy based on physiologic parameters.

In the neurologic intensive care unit, monitoring has also been limited to the clinical exam and intracranial pressure. In the 1980s, much was learned about the importance of the cerebral perfusion pressure and cerebrovascular autoregulation. In the 1990s, the concept of “multimodal monitoring” was introduced—namely, cerebral blood flow monitoring, brain tissue oxygenation, and intracerebral microdialysis. Multimodal monitoring to assess metabolic function provides the neurointensivist with crucial information at the cellular level. This information can be used to detect potentially reversible secondary insults and to target therapy more precisely.

### CEREBRAL BLOOD FLOW

Although we have been able to measure cerebral blood flow for decades, beginning in 1948 with Kety and Schmidt and more recently with xenon-enhanced CT scanning, these methods give only snapshots of cerebral blood flow and do not allow for continuous monitoring. Two methods are used for continuous monitoring at the bedside:

- With laser Doppler flowmetry, a qualitative estimate of regional cerebral blood flow, based on the Doppler shift principle, is displayed (in arbitrary units).
- With thermal diffusion, a quantitative estimate of regional cerebral blood flow, based on the tissue’s ability to dissipate heat, is displayed in mL/100 g/min.

Cerebral blood flow monitoring can be useful for determining the state of autoregulation.

### BRAIN TISSUE OXYGENATION

Brain tissue oxygen tension, or tissue partial pressure of oxygen (PtiO₂), can be measured using a small flexible probe that is inserted directly into the brain parenchyma, most commonly in the frontal white matter. The normal brain PtiO₂ varies depending on location, but it averages approximately 40 mm Hg. Several studies have shown that cerebral oxygenation is strongly correlated with cerebral perfusion pressure. Low brain PtiO₂ has also been associated with poor outcome. Zauner and coworkers showed that in patients who had a good recovery, the brain PtiO₂ was greater than 35 mm Hg. In patients with moderate to severe disability, the brain PtiO₂ was 26 to 35 mm Hg; in those with a poor outcome, it was 25 mm Hg or less. Though intuitive, whether improving brain PtiO₂ improves patient outcome is inconclusive at this point. Further studies are needed.

### INTRACEREBRAL MICRODIALYSIS

Introduced more than 25 years ago, microdialysis is a technique for monitoring the chemistry of the extracellular space in living tissue. The microdialysis probe is designed to mimic a “blood capillary.” When a physiological salt solution is slowly pumped through the microdialysis probe, the solution equilibrates with the surrounding extracellular tissue fluid. After a while, it will contain a representative proportion of the tissue fluid’s molecules. The microdialysate can then be extracted and analyzed.
in the laboratory or by the bedside.

The first human studies of microdialysis in the brain were published in the 1990s. Subsequent studies have shown the potential of intracerebral microdialysis for monitoring in the neurologic intensive care unit. This technique has been used to show early impaired cerebral blood flow after severe head injury, which was found to result in poor brain tissue oxygen delivery, lactate accumulation, and massive release of glutamate. Unterberg and coworkers have demonstrated changes in microdialysis in patients who develop vasospasm following subarachnoid hemorrhage.

■ CONCLUSION

Multimodal monitoring that includes cerebral blood flow monitoring, brain tissue oxygenation, and intracerebral microdialysis appears to have a unique potential for providing critical basic physiologic information about brain function in patients with brain ischemia. This approach, along with a new system for integrating these parameters in the neurologic intensive care unit, may revolutionize the way in which patients with brain injury are monitored and treated.

■ REFERENCES

Endovascular coiling: The end of conventional neurosurgery?

PETER A. RASMUSSEN, MD

The mainstay of therapy for cerebral aneurysm has been microsurgical clipping. Microsurgery offers a high rate of initial aneurysm cure coupled with a low rate of aneurysm recurrence or recurrent hemorrhage. At present, it continues to be the gold standard for cerebral aneurysm therapy.

Recently, however, endovascular management of cerebral aneurysms has become a viable alternative to surgical clipping. Initial attempts at endovascular management focused on the use of balloons to occlude either the aneurysm itself or the parent vessel giving rise to it. These initial attempts proved unsatisfactory, and in the early 1990s the GDC detachable coil became available. For the first time, a satisfactory solution for the endovascular treatment of at least a subset of intracranial cerebral aneurysms (those with narrow necks) became available. Subsequent technological advances have allowed for a greater scope of aneurysms to be treated.

TWO KEY ADVANCES FOR ENDOVASCULAR THERAPY

The past year has seen two important developments that have strengthened the argument for endovascular therapy and broadened the types and sizes of aneurysms that can be treated by endovascular means.

ISAT results

First, the results of the International Subarachnoid Aneurysm Trial (ISAT) have been published, demonstrating an increased likelihood of good outcome following aneurysmal subarachnoid hemorrhage when the patient is treated by endovascular means as compared with craniotomy. ISAT was a randomized, multicenter clinical trial comparing a policy of endovascular treatment to a policy of microsurgical treatment of ruptured intracranial aneurysms. More than 2,100 patients were enrolled at 44 centers in Europe. The primary outcome measure was the rate of death or disability at 1 year. Interestingly, most patients were classified in Hunt and Hess grades 1 or 2 and had small aneurysms located in the anterior circulation. Clinical outcomes showed that 76% of patients treated by endovascular means had a modified Rankin score of 2 or less at 1 year, compared with 69% of patients treated with microsurgery (P = .0019).

Stent for wide-neck intracranial aneurysms

Second, an intracranial stent has been approved by the US Food and Drug Administration specifically for the treatment of wide-neck intracranial aneurysms. These aneurysms had previously been considered “uncoilable,” as the risk of parent vessel occlusion and/or thromboembolic events was too high. The new Neuroform Stent (Boston Scientific, Fremont, Calif.) allows for the treatment of these previously uncoilable aneurysms by placing a scaffolding or buttress over the face of the aneurysm to prevent coil herniation into the parent vessel. The introduction of this device thus corrects a previous deficiency in endovascular treatment.

Future developments and advances in catheter, coil, and device design promise to continue to broaden the indications for endovascular aneurysm treatment.

REFERENCES

Lessons from the medical and surgical ICU

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s the field of neurologic intensive care has become better defined and more independent from medical and surgical intensive care, there has been a trend to focus on the neurologic aspects of care. This approach has allowed many of the recent advances in neurocritical care, including research into hemicraniectomy for malignant stroke syndromes and cooling for brain injury. As we continue to improve our therapies to protect brain function and augment recovery, it is increasingly important to look at the advances in medical and surgical critical care to evaluate both the new therapies that they test and the processes employed to study fundamental issues.

This review discusses three trends in research and care in medical and surgical intensive care units (ICUs) that may impact the care of patients in the neurointensive care unit (neuroICU). Although many of the studies behind these trends are important landmarks in critical care, it is important to note that they were conducted in patients with illnesses and injuries that are distinct from what is normally seen in the neurointensive care setting. These results may not be applicable in different ICU settings. As a specialty, we need to validate these promising studies in our patient population before we fully endorse a change in standard of care. For now, they serve as examples of current thinking on research into the problems of critically injured patients.

A SYSTEMS APPROACH TO INTENSIVE CARE RESEARCH

In the past 10 years, protocols have been developed and validated in many aspects of critical care. Arguably the biggest impact has been on the liberation of patients from mechanical ventilation. A number of studies have directly compared protocol-driven weaning programs with physician-run weaning and liberation from mechanical ventilation (reviewed by Ely et al3). In two of the four randomized controlled trials comparing these weaning methods, there was a statistically significant decrease in the number of days of weaning with protocol-driven programs compared with physician-directed weaning. The other two studies showed a trend toward significance for a reduction in the time of mechanical ventilation or weaning time with protocol-driven programs. Interestingly, the protocols used in these four trials were very different in two aspects: the type of practitioner who determined which patients were ready for extubation, and how that practitioner determined who was ready for liberation from mechanical ventilation. The conclusion that can be drawn is that regardless of the protocol used, the systematic approach to weaning is a more successful paradigm than physician-based decision-making.

This heralds a new type of research in intensive care: systems evaluation. The typical research done in the ICU has been to directly compare one intervention with another. This new approach, which evaluates groups of interventions based on a common premise, is proving to be a powerful tool for assessing the effect of complicated interventions such as ventilator liberation. A study by Bulger et al8 exemplifies how this tool can be used in the neuroICU. In this retrospective review, the group aimed to determine if adherence to the Brain Trauma Foundation guidelines was associated with improved outcome for patients with severe head injuries. Instead, what they found was that “aggressive care,” and not close adherence to the guidelines, was associated with improved outcome (no center adhered tightly to the guidelines).

REEVALUATION OF ROUTINE INTERVENTIONS

A second approach to research that has become important in the medical and surgical ICU is the reevaluation of currently held beliefs about routine
interventions. Many tests and orders, such as blood glucose monitoring and blood pressure assessment, are ordered routinely at admission per the custom of the ICU. These aspects of critical care management are seldom part of the patient’s admission problem. A current area of active research is the evaluation of the standard sliding scale of insulin coverage for hyperglycemia in the ICU. Interestingly, much of the rationale for this type of study comes from work done in rats subjected to cerebral ischemia.9,10

A landmark paper published in the New England Journal of Medicine by van den Berghe et al11 showed that an aggressive protocol for controlling serum blood glucose in critically ill surgical patients yielded a 42.5% decrease in mortality compared with the standard sliding-scale practice (4.6% vs 8%). This reduction in mortality is impressive considering that none of the patients in the study had been admitted to the ICU expressly for hyperglycemia. Unfortunately, this study was not able to determine if blood glucose control or insulin therapy alone was the driving force for the mortality benefit. Although it is difficult to extrapolate these findings to the patient population in the neuroICU, if a similar magnitude of mortality benefit is seen in neurologic patients, it will be a more beneficial intervention for stroke patients, in terms of mortality, than intravenous tissue-plasminogen activator (t-PA) was in the NINDS t-PA Stroke Trial.12 A trial involving the stroke population is currently under way in Europe.13

■ CRITICAL EVALUATION OF OLDER STUDIES USING NEW TECHNIQUES

Much of the information we use to make decisions in the ICU is based on studies done before the advent of more powerful research tools and the implementation of standards for statistical analysis. Consequently, much of the information we pass on to future intensive care physicians is suspect. Unfortunately, repetition is often used as a substitute for hard evidence, and information written in textbooks becomes irrefutable.

No better example of this can be found than the current reevaluation of blood transfusion policy in the ICU. The traditional teaching in the ICU is that the optimal hemoglobin level for a vascular patient in the ICU is 10 g/dL, based on physiologic studies showing that the optimal combination of oxygen carrying capacity and blood viscosity is in this range (reviewed by Chapler and Cain14). This has led to a protocol to give transfusions to all patients who are anemic, to maintain a hemoglobin level around 10 g/dL.

Although the studies done on the rheology of blood flow were quite elegant in their day and accurate, they didn’t address the question of whether the risk of allographic transfusion of blood is sufficiently large to obscure the benefit of an increased hemoglobin level. The Canadian Critical Care Trials Group conducted a study, published in 1999, to address this question.15 Despite the limitations of the study, they showed convincingly that in younger patients, a strategy of transfusions to keep the hemoglobin level above 10 g/dL was associated with a higher mortality. The population of patients in which the data were less convincing was in the cardiac ischemia group.

This study shows that our previous belief that transfusions of blood products to maintain a predesignated hemoglobin level will improve outcome is not necessarily true for all patients and is likely false for the young and those without severe illness. More importantly, it showed that blood transfusions, like many interventions in the ICU setting, have become a tradition without the scrutiny of rational science. It is important to reevaluate all of our interventions, whether old or new, so that we are not tainted by the traditions of the past.

■ CONCLUSIONS

Research into intensive care management has grown enormously over the last 30 years. Whereas there used to be only a handful of journals and journal articles dedicated to the care of critically ill patients, now there are hundreds of journals and many subspecialties in the field, including neurointensive care. As each of the subspecialized fields becomes more independent and develops research strategies of its own, individual practitioners and researchers become more enveloped by their own subspecialty and sequestered from many interesting advances in other areas.

As the examples cited for the first of our three trends illustrate, the complexity of interactions in the ICU makes direct comparisons of single interventions or medications statistically challenging. A systems approach allows researchers to buffer the effects of individual patient and physician variables that have vexed many critical care studies. Unfortunately, it also reduces the precision with which we can deter-
mine which individual interventions are most useful.

The studies cited in support of our second and third trends show how seemingly insignificant changes in care can have important effects. Looking critically at established intensive care management is not inherently interesting to most practitioners. It is more intellectually appealing to try to find as-yet-undiscovered therapies for neurologic diseases. It is also unfortunate that there is little financial incentive to study clinical practice unrelated to primary disease management, as it is seldom associated with a marketable product that brings with it pharmaceutical company funding. In the future, this type of research may very well improve patient outcome more profoundly than the high-profile studies directed at neurologic injuries.

The three trends highlighted here are interesting because they use techniques not usually seen in intensive care research. In developing these tools to look more closely at practice, these trends open the door for a host of other research projects that can employ similar techniques geared more closely to the problems of neurointensive care patients.

REFERENCES

If clinicians are to understand where they are now and where they are headed, they must know where they and their predecessors have been. History adds a broadening dimension to knowledge, including knowledge of cerebrovascular disease. Here is a quick survey of progress in cerebrovascular disease, from the earliest days.

**THE PAST**

400 BC–1700 AD: Emphasis on prognosis, early exploration of brain and vascular structures

Hippocrates wrote aphorisms (circa 400 BC) related mostly to prognosis. Galen (131–201 AD) dissected animals, and he related diseases and prognosis to various body humors. Andreas Vesalius (1514–1564) based his *De Humani Corporis Fabrica* on dissections of human cadavers. His work contained 15 diagrams of the brain. Johann Jakob Wepfer (1620–1695) wrote a popular treatise on apoplexy and showed that bleeding into the brain was an important cause. He described occlusive disease of intracranial arteries.

Sir Thomas Willis’ (1621–1675) dissections of the brain were drawn in detail by Sir Christopher Wren in his *Cerebri Anatome*. Willis was a busy clinician who described migraine and transient ischemic attacks.

1800–1925: Emphasis on pathology and disease

Giovanni Battista Morgagni (1682–1771) was the father of clinicopathologic explorations. His *De Sedibus et Causis Morborum per Anatomam Indagatis* (On The Seats and Causes of Disease, Investigated by Anatomy), published in 1769, contained 70 letters describing necropsied cases. The first volume was *Diseases of the Head*. Morgagni described diseased arteries and “serous” and “sanguinous” apoplexies.

John Cheyne (1777–1836) published *Cases of Apoplexy and Lethargy with Observations upon the Comatose Diseases*, which emphasized the pathology in the brain, including brain softenings and subarachnoid and intracerebral hemorrhages.

Richard Bright (1759–1858) in 1831 published an atlas that included a volume on brain and nervous system disease. He collected 200 neurological cases and specimens.

Rudolph Virchow (1821–1902) described the phenomenology of arterial thrombosis and embolism and recognized the important interaction between the blood and the arterial wall. Virchow clearly showed that vascular occlusions caused infarction.

Sir William Osler (1849–1919) began as a pathologist and recognized the clinical and pathologic features of bacterial endocarditis, cerebral palsy, aphasia, and brain infarcts and hemorrhages.

1850–1950: Focus on vascular anatomy and clinical-anatomic correlations

This period focused on how the brain works as seen from vascular cases. Vascular anatomy was explored by Duret, Stopford, Foix, Duvorn, and others. Brainstem syndromes were described by Weber, Benedikt, Claude, Millard, Gubler, Babinski, Nageotte, Foville, and Wallenberg.

Jules Dejerine (1849–1919) was a master of clinic-anatomic correlations and described the clinical findings in patients with various brainstem lesions. He also described the syndrome of alexia without agraphia in a patient with a posterior cerebral artery territory infarct.

Charles Foix (1882–1927) dissected and described the clinical features and usual anatomic
distributions of ramollissements (brain softenings) caused by disease of the middle, anterior, and posterior cerebral arteries and the anterior choroidal arteries. He defined the blood supply of the brainstem and the arteries of the posterior circulation.

1927–1975: Interest in the pathology and pathophysicsology of vascular lesions begins
Charles Foix and colleagues noted in 1927 that most arteries supplying infarcted brain regions were not completely obstructed; they posited embolism, insufficiency, and vasospasm as possible explanations.

Raymond Adams and Charles Kubik in 1946 described the clinical and pathologic findings in patients with basilar artery occlusions found at necropsy. They discussed the morphologic differentiation between in situ thrombosis and embolism.

C. Miller Fisher described the pathology in arteries underlying lacunar infarcts, brain hemorrhages, and carotid artery occlusions. Fisher also clearly described the clinical features in patients with carotid artery disease, lacunar infarcts, and brain hemorrhages at various sites.

1978 to today: Stroke registries and databases begin and flourish
Computers facilitated the collection of series of patients with cerebrovascular disease. The first published prospective registry, the Harvard Stroke Registry (Mohr and Caplan, 1978), was begun before CT scanning became available. The Stroke Data Bank (Mohr, Caplan, Hier, Wolf, Price) and the Lausanne Stroke Registry (Bogousslavsky) followed and represented experience at one or more hospitals. Now large stroke registries are available in nearly every country. More recently, the German Stroke Data Bank has come to contain a wealth of cases collected in an entire country.

THE PRESENT: Technology, epidemiology, treatment, and evidence-based medicine in a managed care environment

Technology is rapidly improving and still developing. CT and MRI allow delineation of the location and type of lesion, while CTA, MRA, and extracranial and transcranial ultrasonography (TCD) allow definition of arterial lesions. Echocardiography, cardiac rhythm monitoring, and blood analysis detect cardiac, aortic, and hematologic causes of stroke.

Neurologists of today can quickly and safely define the cause and extent of cerebrovascular disease. Epidemiologic studies worldwide define stroke risk factors and factors related to prognosis.

This is the era of therapy. The introduction of thrombolysis and endovascular treatments focused attention on rapid delivery and throughput of patients. Randomized therapeutic trials are considered essential to provide a true evidence base for treatment of stroke patients. Statisticians are kings. At the same time, managed care directors and insurers control the purse strings.

THE FUTURE: Predictions and wishes

• More hospital-based cerebrovascular disease and ICU-type neurology specialists will be trained. The need for rapid evaluation and treatment means that neurologists with experience and training in cerebrovascular disease must be in the hospital and available to accomplish optimal management. Community-based practitioners and non-neurologists cannot do it because of time constraints and lack of knowledge and experience with acute stroke cases.

• Endovascular interventions will become more and more prominent.

• Stem cells and other multipotential cells and growth factors will become important therapeutic tools.

• Use of genetic information will proliferate. Physicians will be able to study individual patients’ genetic makeup to predict risks and to take measures to reduce those risks. Study of the genetics of vascular disease will identify new treatment strategies. Endovascular introduction of genetic materials may play an important role in treatment.

• The obsession of the past decades with randomized, double-blind trials as the only way to determine treatments will cool. Many conditions are too uncommon or too diverse to lend themselves to trials. In order to please statisticians, trials often lump together heterogeneous situations so that answers are not very helpful for physicians who must treat individual patients. Patients are complicated, and many psychological, social, personal, and other variables not studied in trials influence treatment decisions.

• Recovery and rehabilitation will be given more attention and will be based on a more solid sci-
Scientific foundation.

- Hopefully, the medical community will wake up to the fact that strokes are very complex. Whenever possible, stroke patients should be guided to facilities that have the following:
  1) Physicians available 7 days a week, 24 hours a day, who are trained and experienced in caring for stroke patients
  2) Advanced modern technology that can quickly and safely image the brain and causative vascular lesions

Criteria should be published for categorizing stroke care facilities in a fashion similar to the present practice for trauma centers.

- As with coronary artery and peripheral vascular disease, physicians will begin to learn that stroke is a vascular disease. To care for stroke patients, the causative cardiac–cerebrovascular–hematologic causes need to be defined. This is not possible with only a CT scan. Vascular studies are required.
A variety of pathophysiologic events occur following a stroke, and knowledge of these events can lead to potential therapeutic strategies that may reverse or attenuate injury. Events that occur following stroke include accumulation of excitatory amino acids, alterations in the genomic response, mitochondrial injury, and secondary injury, often in the setting of reperfusion. This review will focus on these areas, with an emphasis on identifying potential strategies to reverse or limit ischemic damage to the brain.

EXCITOTOXIC HYPOTHESIS AND CALCIUM TOXICITY

It is well recognized that a significant portion of ischemia-induced neuron damage is mediated by excessive accumulation of excitatory amino acids, leading to toxic increases in intracellular calcium and other ions. This increase in calcium activates various signaling pathways, ultimately leading to cell death. Soon after cessation of cerebral blood flow, energy-dependent pumps fail, resulting in the flow of ions down their concentration gradients. This results in cellular swelling and depolarization. Calcium (Ca++) enters the cell through voltage-dependent ion channels and activation of ligand-gated receptors, resulting in activation of a number of proteases, kinases, lipases, and endonucleases, ending in cell death. Glutamate, which is the major excitatory neurotransmitter in the brain, accumulates in the extracellular space and activates its receptors, some of which are also calcium-permeable.

There are four major types of glutamate receptors. The ionotropic receptors include the N-methyl-D-aspartate (NMDA), \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate (KA) receptors. The fourth receptor class is the metabotropic receptor (mGluR), which is further subdivided into eight subtypes. This latter receptor class appears to be G-protein-coupled and involves phosphoinositide hydrolysis, with some mGluR subtypes bearing protective properties and others being damaging.

EARLY GENE EXPRESSION AND CEREBRAL ISCHEMIA

Although it has long been held that protein synthesis and gene expression cease after ischemia onset, recent work has shown that quite the opposite is true. In fact, the brain has been shown to upregulate many genes and their corresponding proteins in response to injury. It is now recognized that some of these genes may actually protect the brain from a variety of stresses, including stroke. One such gene that is increased following stroke is the 70-kD inducible heat shock protein (HSP70). HSP70 performs chaperone functions by assisting in the proper folding of newly synthesized proteins. Following ischemia, it is thought to perform this function and to prevent protein aggregation. The availability of gene chips permitting the simultaneous study of thousands of genes will provide the ability to screen for other genes not previously identified, and could lead to the discovery of novel treatment strategies.

REACTIVE OXYGEN AND NITROGEN SPECIES

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been implicated in exacerbating ischemic brain injury by reacting with macromolecules, and they may activate apoptosis and inflammation.

When tissue becomes reperfused, high levels of oxygen lead to the generation of ROS and lead to direct tissue damage. ROS are thought to be generated by injured mitochondria, especially during reperfusion, but other pro-oxidant systems in the brain are activated due to increased intracellular...
calcium (eg, xanthine oxidase, cyclooxygenase). ROS can also be generated by activated microglia and peripheral leukocytes via the NADPH oxidase system. ROS are involved in activating several pathways involved in cell death, such as apoptosis and inflammation. Administration of antioxidants or genetic overexpression of endogenous antioxidants (eg, superoxide dismutase or glutathione peroxidase) can limit the extent of ischemic damage. Ebselen, a glutathione peroxidase mimic, has been studied in clinical trials with some promising results.

RNS include species such as nitric oxide (NO) and peroxynitrite (ONOO, formed from NO and superoxide, and especially damaging to DNA). NO is generated from L-arginine through one of several nitric oxide synthase (NOS) isoforms. The neuronal form (nNOS) is activated via NMDA receptor stimulation, whereas inducible NOS (iNOS) is largely produced in inflammatory cells such as microglia and monocytes. These two isoforms are, for the most part, damaging to the brain under ischemic conditions. Both pharmaceutical nNOS and iNOS inhibitors and genetic mutant mouse models have shown that inhibition of these isoforms improves outcome in experimental stroke. A third isoform found in endothelial cells (eNOS) is believed have vasodilatory properties and may play a beneficial role, as it may ultimately improve local blood flow. A class of cholesterol-lowering agents, the statins, is thought to increase local eNOS generation.

**INFLAMMATION**

During reperfusion, inflammatory cells may also gain access to necrotic regions. Although the inflammatory response accompanying ischemia has long been thought to be involved in recovery and repair, this response is also known to potentiate damage, particularly in the acute to subacute phases. This is not entirely surprising, since leukocytes are capable of producing a variety of reactive species and toxic proteases when stimulated. An endogenous inflammatory response also occurs in the brain as microglia are activated in the presence of ROS. Interfering with these processes by preventing leukocyte infiltration (anti-adhesion molecule treatments), microglial activation (minocycline), or leukocyte generation of reactive species (aminoguanidine to inhibit iNOS or apocynin to inhibit NADPH oxidase) has been shown experimentally to reduce ischemic injury. Although two anti–adhesion molecule strategies have already been studied in clinical trials, these studies were flawed or were never completed to the point of offering meaningful conclusions on whether this approach may be useful in humans.

**APOPTOSIS**

Recent studies have defined an orderly “programmed” cell death referred to as apoptosis. Apoptosis normally occurs in many organisms as a part of development, but it is now recognized to contribute to cell death in a variety of pathologic states, including stroke. Apoptosis is an energy-dependent process leading to DNA fragmentation. Although much of ischemic injury has been presumed to be necrotic, apoptosis has been detected in penumbral brain regions and after mild ischemic insults.

Central to most forms of apoptosis are the caspases, a family of proteases whose name stems from the fact that they are cysteine proteases. Caspases are proenzymes that must be cleaved to their active form and that ultimately lead to DNA cleavage and chromatin condensation (hallmarks of apoptosis). There are several classes of caspases, including the initiator (eg, caspase 8) and effector (eg, caspase 3) classes. The intrinsic, or mitochondria-dependent, pathway has been the most studied in ischemia models. This model proposes that less severe ischemic insults result in damage to the mitochondria due to prolonged depolarization, exposure to ROS, or both. This leads to the formation of a permeability transition pore that allows release of cytochrome c from its inner membrane. Cytosolic cytochrome c complexes with procaspase 9 and Apaf-1, forming the so-called apoptosome, leading to activation of caspase 9. Caspase 9 then activates effector caspases, including caspase 3, leading to DNA fragmentation and chromatin condensation, all hallmarks of apoptosis. Caspase antagonists and inhibitors of cytochrome c release (eg, cyclosporin A) have been shown to reduce cerebral ischemic injury. Apoptosis may also proceed independent of caspases via mitochondrial release of apoptosis initiating factor (AIF), which translocates from the mitochondria into the nucleus, leading to morphologic changes characteristic of programmed cell death. This latter pathway may be especially relevant in stroke, as the demonstration of caspase activity in ischemia models has been variable.
despite morphologic evidence of apoptosis.

The Bcl-2 family of proteins possess both pro- and anti-apoptotic functions. Bcl-2 and Bcl-XL are “death suppressors” that act by preventing cytochrome c and AIF release. Bak, Bid, Bcl-XS, and Bax are “death enhancers” that are capable of forming the permeability transition pore. Studies in rodents in which Bcl-2 or Bcl-XL is overexpressed show that these proteins are neuroprotective.

Other apoptotic pathways have also been implicated during ischemia. The extrinsic, or receptor-mediated, pathway may also be involved since some studies have detected the presence of tumor necrosis factor α (TNF-α) and Fas ligand (FasL) in ischemic brain. These factors bind to their respective receptors (TNFR1 and Fas), resulting in activation of caspase 8, which directly activates caspase 3 independent of cytochrome c release.

CONCLUSIONS

The molecular biology of ischemic injury is a rapidly growing field that may lead to the identification of novel stroke therapies. To date, no pharmacologic neuroprotectant has been found efficacious in humans. However, recent studies using mild hypothermia to prevent neurologic damage in patients suffering cardiac arrest are promising. Because hypothermia may target multiple cell death pathways, it may someday prove to be the ultimate neuroprotectant.

FURTHER READING


In 1996, the US Food and Drug Administration (FDA) approved the use of recombinant tissue-plasminogen activator (t-PA), a thrombolytic agent, for selected patients with ischemic stroke if treatment is begun within 3 hours of stroke onset. This marked the beginning of a new era of acute stroke therapy. While intravenous t-PA remains the only scientifically proven and FDA-approved pharmacologic or mechanical treatment for acute ischemic stroke, it is important to understand the scientific basis for its approval, its practical use and limitations, the experience with other intravenous thrombolytic agents, and the future of thrombolytic agents for acute stroke.

### INTRAVENOUS t-PA FOR ACUTE ISCHEMIC STROKE

#### The evidence base

The two critical studies that formed the basis for approval of t-PA were funded by the National Institute of Neurological Disorders and Stroke (NINDS) and reported as the NINDS t-PA Stroke Trial.1–7 Patients in these studies had to have t-PA administered within 3 hours of stroke onset, and nearly half of patients had t-PA started within 90 minutes of onset.

The dose of t-PA used in the NINDS studies was 0.9 mg/kg given intravenously over 1 hour, with 10% of the total dose given as a bolus. The maximum dose was 90 mg. This dose was determined by an NINDS-funded pilot dose-escalation study8 in the late 1980s in which four of the five symptomatic intracerebral hemorrhages occurred at a dose of 0.95 mg/kg or higher, one at dose of 0.89 mg/kg, and none at lower dose tiers (P < .02). No difference in favorable outcome was detected between lower and higher dose tiers in this small nonrandomized study.

In the subsequent randomized NINDS t-PA Stroke Trial, patients treated with t-PA were more likely to have an excellent functional outcome at 3 months as determined by one of four neurologic or functional rating scales (absolute difference of 11% to 13% vs placebo group).2 A subsequent report from the NINDS t-PA Stroke Trial showed that the benefit seen among patients treated with t-PA was maintained at 1 year.7 t-PA was also cost-effective overall since patients treated with t-PA were likely to be discharged earlier and to home, and were less likely to require nursing home care or extensive rehabilitation.6

The major risk of t-PA is bleeding into the damaged brain. Symptomatic intracerebral hemorrhage within 36 hours after stroke onset occurred in 6.4% of patients given t-PA in the NINDS t-PA Stroke Trial and in 0.6% of the placebo group (P < .001), but there was no significant difference in overall 90-day mortality between the t-PA (17%) and placebo groups (21%; P = .30).5

A subsequent report from the NINDS t-PA Stroke Trial indicated that the beneficial effect of t-PA is time-dependent, even within the first 3 hours of onset.9 t-PA appears to be effective for all ischemic stroke subtypes and patient subgroups, provided that patients meet all of the inclusion and exclusion criteria of the NINDS t-PA Stroke Trial.1

There have been three other major randomized trials of intravenous t-PA for acute ischemic stroke. Two of these trials evaluated the safety and efficacy of t-PA in stroke patients treated within 0 to 6 hours: the European Cooperative Acute Stroke Study (ECASS and ECASS II).10,11 The Atlantis Trials (Part A, time window of 0 to 6 hours; Part B, time window of 0 to 5 hours) focused primarily on patients treated within 3 to 5 hours of stroke onset.12

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Except for the fact that ECASS I used a slightly higher dose of t-PA (1.1 mg/kg), these studies were similar to the NINDS t-PA Stroke Trial in design and endpoints, and differed primarily in the time from stroke onset to start of t-PA administration.

None of these other t-PA studies was positive, as defined by a statistically significant difference between t-PA and placebo, with regard to the a priori primary clinical endpoint, although the direction of benefit was in favor of t-PA. Several predefined secondary analyses and post hoc analyses, including those using the defined primary endpoint from the NINDS t-PA Stroke Trial, did indicate a positive benefit for patients treated with t-PA in the two ECASS trials. The risk of symptomatic intracerebral hemorrhage in the three trials was similar to, but nonsignificantly higher than, that reported for the NINDS t-PA Stroke Trial.

A recent pooled analysis of the six larger randomized studies of intravenous t-PA (Lancet, in press) indicates that time to treatment is extremely critical, with the greatest likelihood of an excellent outcome when t-PA is given within the first 90 minutes to 2 hours after stroke onset. This analysis also indicates that t-PA given beyond 3 hours—and maybe up to 4 to 5 hours—may provide benefit. This hypothesis is currently being tested in the ECASS III and IST 2 studies.

Community experience
Community use of t-PA since 1996 has resulted in a similar percentage of successful outcomes and a similar rate of symptomatic intracerebral hemorrhage when the NINDS treatment protocol has been followed. Deviations from the NINDS treatment protocol have been associated with higher rates of symptomatic intracerebral hemorrhage. Currently only 1% to 2% of all ischemic stroke patients in the United States are estimated to be treated with intravenous t-PA within 3 hours of onset, although the recent experience of the first four Coverdell State Stroke Registries suggests an overall rate of about 3% to 4%. The rate may be slightly higher at selected tertiary-care centers. The major reason for failure to treat is that most patients arrive beyond the 3-hour window.

An excellent summary of the NINDS protocol for treatment with intravenous t-PA, including inclusion and exclusion criteria, management of blood pressure, and treatment of complications, is found in a recent book chapter by Marler and Lyden.

Response and genotype
One unique observation in the past several years is that the response to intravenous t-PA may depend on the genotype of the patient. In the NINDS t-PA Stroke Trial, persons with an Apo E2 phenotype were much more likely to have an excellent response to t-PA than were persons with an Apo E4 or Apo E3 genotype, even though these latter patient groups also had a beneficial response. This finding is currently being explored in in vivo clot models.

OTHER THROMBOLYTIC AGENTS

Streptokinase
Three randomized trials of intravenous streptokinase for acute ischemic stroke have been reported. All studies were stopped prematurely because of excess mortality and intracranial hemorrhage. The Australian Streptokinase Trial did find a trend toward benefit in patients treated within 3 hours of stroke onset. The reasons for streptokinase failure included a much later time to treatment in the streptokinase studies as compared with the NINDS t-PA Stroke Trial, as well the use of the full cardiac dose of streptokinase as compared with about two thirds of the cardiac dose of t-PA in the NINDS t-PA Stroke Trial.

Newer therapies and strategies
Pilot studies of newer thrombolytic agents and platelet-receptor antagonists are ongoing. Tenec-tiplase (TNK), a molecule derived from the t-PA molecule, is currently being tested for use within 3 hours of stroke onset in an NINDS-funded phase 1 pilot study, and results are encouraging. Reteplase has also been used in small series of patients with acute stroke but has yet to be evaluated in a controlled trial. Desmoteplase is currently under investigation in a study using MRI to select appropriate patients beyond 3 hours of stroke onset. Small series of patients treated with the combination of a GPIIb/IIIa receptor antagonist and t-PA or reteplase have been reported, and larger pilot studies are beginning, one of which (the CLEAR trial) is a subject for another presentation at this conference.

Finally, the combination of low-dose intravenous t-PA followed by intra-arterial t-PA and clot manip-
ulation (the EMS and IMS trials) is currently being tested in pilot studies.23

**SUMMARY**

Intravenous t-PA is effective if given to appropriate patients within 3 hours of stroke onset, and its effectiveness increases even within the first 3 hours when given as soon as possible. t-PA is reasonably safe if used in a carefully defined manner that ensures close attention to blood pressure, careful patient monitoring, no use of heparin and aspirin during first 24 hours, and appropriate patient selection.13 It is still unclear whether a lower dose of t-PA given with 3 hours could be as effective as but safer than the currently approved intravenous dose of 0.9 mg/kg over 1 hour.

The effectiveness and safety of intravenous t-PA when given beyond 3 hours after stroke onset has yet to be conclusively demonstrated. One attractive development is the potential use of imaging, such as diffusion/perfusion MRI to determine if salvageable brain remains and if t-PA should be given in patients who are beyond the 3-hour time window. The drawback to MRI is the additional time required before the start of recanalization therapy.

**REFERENCES**


In the 1980s, several reports of intra-arterial (IA) thrombolysis therapy in acute ischemic stroke were published.1–3 The thrombolytic agents used in these early case series were urokinase or streptokinase. Studies of IA thrombolysis for acute ischemic stroke were initially limited to uncontrolled protocols.4,5 There was great variability in technique, and efficacy and complication rates varied among the reported series. As a result, in 1996 an American Heart Association Special Writing Group published its recommendations for the use of thrombolytics in acute ischemic stroke. Based on the strength of the scientific evidence at that time, this group concluded that IA thrombolysis “should be considered investigational and only used in the clinical trial setting” and recommended “further testing of” IA thrombolysis.6

Subsequently, the results of the first randomized multicenter controlled trials of IA thrombolysis, the Prolyse in Acute Cerebral Thromboembolism trials (PROACT I7 and PROACT II8), were reported in 1998 and 1999, respectively. PROACT II remains the only randomized, controlled, multicenter trial to demonstrate the efficacy of IA thrombolysis in patients with acute ischemic stroke of less than 6 hours’ duration due to middle cerebral artery (MCA) occlusion. Trials comparing the IA and the intravenous (IV) modes of application are not available and are not very likely to be performed in the future.

IA THROMBOLYSIS: GENERAL TECHNIQUE

Diagnosis and access

In advance of any procedure, the basic and crucial CT criterion is to rule out hemorrhage. A complete four-vessel cerebral angiogram, from a transfemoral approach, is necessary to evaluate the site of vessel occlusion, extent of thrombus, number of territories involved, and collateral circulation. An MRA or CTA can first be done to identify the primary site of occlusion. A diagnostic catheter is guided into the high cervical segment of the vascular territory to be treated, followed by a 2.3-French coaxial microcatheter with a steerable microguidewire. Under direct fluoroscopic visualization, the microcatheter is gently navigated through the intracranial circulation until the tip is embedded within or through the central portion of the thrombus.

Many variations in catheter design and delivery technique have been described.9 Two types of microcatheters are used most often for local cerebral thrombolysis, depending on the extent of clot formation. For the majority of intra-arterial cases, a single end-hole microcatheter is used, while for longer segments of clot formation, multiple side-hole infusion microcatheters are used. Superselective angiography through the microcatheter is performed at regular intervals to assess for degree of clot lysis and to adjust the dosage and volume of the thrombolytic agent. A superselective angiogram is performed, and if there is partial clot dissolution, the catheter is advanced into the remaining thrombus, where additional thrombolysis is performed. Infusion of the thrombolytic agent distally into a vessel with no flow should be avoided. The goal is to achieve rapid recanalization with as little thrombolytic agent as possible to limit the extent of brain infarction and to reduce the risk of hemorrhage. However, common experience indicates that it can take up to 2 hours to achieve recanalization after the procedure begins, that thrombolytic agents alone (ie, without mechanical manipulation) rarely achieve recanalization in less than 30 minutes, and that recanalization is often incomplete. Among other factors, clot composition plays a key role in the rapidity and degree of recanalization achieved with IA thrombolysis. Advances in microcatheter technology have allowed superselective catheterization of even distal branches of occluded intracranial vessels.
Thrombolytic agents
Recombinant pro-urokinase (r-pro-UK), the thrombolytic agent used in PROACT II (see below), is currently not approved by the US Food and Drug Administration (FDA) and not commercially available. Although some thrombolytic agents have theoretical advantages over others, there is no proof that one is superior to another in terms of safety, recanalization, or clinical efficacy in acute ischemic stroke. Therefore, it is not clear if the results of PROACT II are applicable when agents other than r-pro-UK are used for IA thrombolysis.

Commercially available agents include urokinase (UK), recombinant tissue-plasminogen activator (rt-PA), reteplase (r-PA), and tenecteplase (TNKase). These thrombolytic agents differ in stability, half-life, and fibrin selectivity. UK is not fibrin-selective and thus can result in systemic hypofibrinogemia. rt-PA and r-pro-UK are fibrin-selective and are only active at the site of thrombosis. However, r-pro-UK requires heparin for maximal thrombolytic effect. Newer agents like r-PA have long half-lives, allowing bolus administration, or are more fibrin-selective, like TNKase.

Local fibrinolysis makes it possible to monitor not only the frequency of recanalization but also how fast it occurs. All current single thrombolytic agents often require 30 to 60 minutes for recanalization, even with direct IA application. Even 325,000 IU urokinase or 40 mg rt-PA takes 100 minutes to recanalize, based on our experience with 140 patients. A very promising concept involves using Lys-plasminogen with rt-PA during local IA infusion.

Other factors influencing thrombolysis outcomes
Hacke has described an ideal patient for thrombolysis: a young person with good collaterals who has an MCA occlusion distal to the lenticulostriates due to a fresh fibrin-rich thrombus that passed through a patent foramen ovale. The presence of collateral flow is one of the prime determinants of outcome. Good leptomeningeal collaterals may limit the extent of ischemic damage and prolong the therapeutic window. Good collateral flow is also associated with higher rates of reperfusion, presumably by allowing a greater amount of thrombolytic to reach the clot by means of redistribution. Clot composition is a neglected factor in recanalization success rates. Fresh thrombi, which are rich in fibrin and plasminogen, are easier to lyse than aged atherothrombi, which are more organized and have low fibrin and plasminogen contents and high amounts of platelets and cholesterol. Fresh cardiac emboli may therefore respond better to thrombolysis than atherothrombotic occlusion or calcific embolism.
Intracerebral hemorrhage after thrombolysis for stroke can occur at sites distant from the ischemic region. Cerebral amyloid angiopathy has been implicated as a causative factor for brain hemorrhages after thrombolysis for myocardial infarction.

The PROACT trials
PROACT I. Patient enrollment in the first placebo-controlled, double-blind, multicenter trial of I.A. thrombolysis in acute ischemic stroke, PROACT I, began in February 1994. The results were published in 1998. The thrombolytic agent used in this study was r-pro-UK, which is, as noted above, not yet commercially available. r-pro-UK is a recombinant single-chain zymogen of an endogenous fibrinolytic, UK or u-PA. Infusion of r-pro-UK does not result in a systemic dysfibrinogenemia with its associated higher risk of hemorrhagic side effects. Another clinically relevant characteristic of r-pro-UK is the facilitatory effect of coadministered heparin, which improves the fibrinolytic efficacy of r-pro-UK.

The study compared safety and recanalization efficacy between 6 mg I.A. r-pro-UK and I.A. saline placebo in 40 patients with acute ischemic stroke of less than 6 hours’ duration due to MCA occlusion. Only patients with Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 occlusion of the M1 or M2 MCA on diagnostic cerebral angiography were included. Additional major inclusion criteria were a minimum NIHSS score of 4 (except for isolated aphasia or hemianopsia) and a maximum score of 30. Major exclusion criteria were uncontrolled hypertension (>180/100 mm Hg), a history of hemorrhage, recent surgery, or trauma. Early CT changes were not an exclusion criterion. Mechanical disruption of the clot was not permitted since the trial’s goal was to demonstrate the efficacy and safety of r-pro-UK. Patients also received heparin in addition to r-pro-UK. The first 16 patients received “high-dose” heparin consisting of a bolus of 100 IU/kg followed by infusion of 1,000 IU/hr for 4 hours; anticoagulation was prohibited for the following 24 hours. Based on a recommendation from the external safety committee, the heparin regimen was changed after the first 16 patients to a 2,000-IU bolus followed by 500 IU/hr for 4 hours.

The recanalization rate was 57.7% in the r-pro-UK group and only 14.3% in the placebo group. In the “high-dose” heparin group, the recanalization rate was 81.8% in the r-pro-UK recipients but the symptomatic intracranial hemorrhage (ICH) rate was 27%. In contrast, in the “low-dose” heparin...
group the recanalization rate was 40% in the r-pro-UK recipients but the ICH rate decreased to 6%. Overall, symptomatic ICH occurred in 15.4% of treated patients and in 14.3% of placebo recipients. Although this was not a clinical efficacy trial, there appeared to be a 10% to 12% increase in excellent outcomes in the IA r-pro-UK group as compared with the control group.

PROACT II. The follow-up clinical efficacy trial, PROACT II, was launched in February 1996 and the results published in December 1999. This was a randomized, controlled, multicenter trial but differed from PROACT I in that it used an open-label design with blinded follow-up. Patient selection was essentially the same as in PROACT I, with the major exception being that patients were excluded if they had early signs of infarction in greater than one third of the MCA territory (the so-called ECASS criteria) on the initial CT scan. Additionally, a 9-mg dose of r-pro-UK was used instead of 6 mg and “low-dose” heparin was used in the treatment and control groups. A total of 180 patients were randomized to receive either 9 mg of IA r-pro-UK plus low-dose IV heparin or low-dose IV heparin alone. The patients in PROACT II had a very high baseline stroke severity (median NIHSS score of 17). The median time from symptom onset to initiation of IA thrombolysis was 5.3 hours.

The primary outcome measure was the proportion of patients who achieved a modified Rankin score of 2 or less at 90 days, which signifies slight or no neurologic disability. For the r-pro-UK group there was a 15% absolute benefit (P = .043). The benefit was most noticeable in patients with a baseline NIHSS score between 11 and 20. On average, 7 patients with MCA occlusion would require IA thrombolysis for 1 patient to benefit. Recanalization rates at 2 hours were 66% for the treatment group and 18% for the placebo group (P < .001). Symptomatic brain hemorrhage occurred in 10% of the r-pro-UK group and in 2% of the control group.

Considering the later time to treatment and greater baseline stroke severity in PROACT II, the symptomatic brain hemorrhage rate compared favorably with the rates in the IV rt-PA trials (6% in the NINDS t-PA Stroke Trial, 9% in ECASS II, and 7% in ATLANTIS). As in the NINDS trial, in PROACT II patients benefited overall from therapy despite the higher brain hemorrhage rate, and there was no excess mortality (24% in the r-pro-UK group vs 27% in the control group).

CAROTID TERRITORY IA THROMBOLYSIS: SPECIAL FEATURES

The majority of hemispheric vessel occlusions are due to embolism. In thrombolysis trials, the 30-day mortality rate in hemispheric stroke is between 15% and 20% and does not differ significantly between treatment and placebo. Thrombolytic treatment has had no impact on survival but rather improves the clinical outcome of patients with less than massive strokes. Most successful recanalizations of the carotid circulation involve the MCA. Recanalization of the internal carotid artery origin is seldom achieved even with direct IA approaches. Some interventionalists advocate passing the catheter through the obstructing thrombus to access the MCA. Occlusion of the carotid “T” eliminates the posterior communicating artery and ophtalmic artery collaterals, so that leptomeningeal collaterals and the anterior communicating artery often are not sufficient to save major parts of the hemisphere even for a short period of time. Recanalization of the carotid “T” is difficult and rarely leads to good clinical results; such patients are commonly excluded from clinical trials.

VERTEBROBASILAR IA THROMBOLYSIS: SPECIAL FEATURES

In the posterior circulation, two special conditions have to be kept in mind: the natural history of acute basilar occlusion is extremely poor, with mortality rates ranging from 83% to 91%, and atherothrombotic occlusions of the basilar artery are relatively more common than embolic occlusions. Hence, there is often need for angioplasty of an underlying basilar artery atherostenosis. Accordingly, IA thrombolysis is preferred in patients with acute basilar artery occlusion. In a compilation of reported cases of vertebrobasilar thrombolysis, mortality was 90% in patients not responding to recanalization compared with 31% in patients achieving at least partial reperfusion. Approximately 278 cases have been reported, with an overall basilar recanalization rate of 60%. Good outcomes are strongly associated with recanalization after thrombolytic therapy. The majority of patients with successful vertebrobasilar recanalization have only mild or moderate disability, compared with less than 14% of patients whose vessels remained occluded.

Distal basilar artery occlusions have a higher recanalization rate because they often consist of soft emboli, which are easier to lyse than atherosclerosis-
related thrombi. In addition, the high rate of reocclusion worsens the prognosis of mid- or lower basilar atherothrombosis. Recent excellent experience supports the use of angioplasty for stabilizing atherothrombotic recanalization. Short-segment occlusions are easier to lyse than longer-segment occlusions. Patients who are younger have higher recanalization rates, probably because of the increased incidence of embolic occlusions in this age group. The time window for thrombolysis was thought to be longer in the posterior circulation. Many series have included patients up to 72 hours after symptom onset. However, thrombolysis with such prolonged time windows makes sense only in patients with prolonged stuttering courses, such as vertebrobasilar patients with chronic atherothrombotic disease in whom collaterals have developed over time. Except in such cases with favorable hemodynamic conditions, treatment beyond the 6-hour window has a very poor prognosis, especially in the presence of coma or tetraparesis for several hours. The importance of signs of infarction on CT in the brainstem and other posterior circulation locations is controversial. The decision must be made individually regarding the lethal thread and the clinical status related to the CT findings. A clearly hypodense, destructed brainstem in a comatose, reflexless individual is for sure not an indication.

INVESTIGATIONAL ENDOVASCULAR THERAPIES FOR ACUTE STROKE

Combined IV and IA thrombolysis

It may be feasible to combine IV and IA thrombolysis to take advantage of the early infusion possible with IV administration and the greater recanalization efficacy of IA therapy. This approach was studied in the pilot Emergency Management of Stroke (EMS) Bridging Trial. Patients with stroke of less than 3 hours’ duration were given a loading dose (0.6 mg/kg) of IV rt-PA or placebo followed by angiography and IA thrombolysis if a vascular occlusion remained. Of all patients, 70% still had clot on angiography after IV therapy. There was improved MCA recanalization in patients who then received IA rt-PA, but there also was an increased risk of life-threatening bleeding complications. The results of the follow-up IV plus IA rt-PA trial (Interventional Management of Stroke [IMS]) were recently reported. Among 62 patients with a baseline NIHSS score greater than 10 enrolled in the IMS trial, 44 (71%) required both IV (0.6 mg/kg) and IA rt-PA. The symptomatic brain hemorrhage rate was 6.2% in patients receiving combination IV/IA thrombolysis, and 90-day outcomes appeared to be favorable compared with historical controls from the NINDS IV rt-PA trial. Dissected atherothrombotic plaques in the coronary artery and in the basilar artery often carry platelet-rich thrombi. The platelet glycoprotein (GP) IIb/IIIa receptor inhibitors abciximab and eptifibatide improve the speed and completeness of recanalization in acute coronary interventions and have also been used in patients undergoing cerebrovascular interventions. Coronary doses of IV abciximab appear to be relatively safe in patients with acute ischemic stroke. Because of underlying atherostenosis, GP IIb/IIIa inhibitors may play a significant role in basilar artery endovascular intervention. Many interventionalists initiate an abciximab bolus and infusion as soon as a basilar thrombosis is demonstrated on CTA or MRA. Whether GP IIb/IIIa inhibitors speed up recanalization with emboli in advance of or during local rt-PA fibrinolysis is also under study.

Mechanical procedures

The speed and completeness of recanalization are suboptimal with thrombolytic agents alone. Thus, new technologies for mechanical clot removal are in early feasibility and safety trials in both the United States and Europe. Reports have all been individual case series from single institutions. The techniques include treatment of acute ischemic stroke by direct mechanical balloon angioplasty of the thrombus, mechanical snaring of clot from the MCAs, and use of suction thrombectomy devices for establishing reperfusion, all of which require relatively coarse manipulation. Techniques employing a power-assisted endovascular Doppler probe (EKOS®) for clot destabilization or the EP AR® probe, which transforms laser energy into photoacoustic energy to vaporize the clot, allow a more gentle approach to the clot and reduce the recanalization time.

CURRENT STATUS AND FUTURE OF IA THROMBOLYSIS: PERSONAL PERSPECTIVES

Since a clinical trial comparing IV with IA or combination thrombolysis will be difficult to perform, and since IV rt-PA within 3 hours of stroke onset
remains the only FDA-approved acute stroke therapy; decisions on the best approach to reperfusion in an individual patient must take into account numerous factors discussed above. The advantages of local fibrinolysis include precise angiographic information, control of the progress of recanalization (including the option to use mechanical devices), lower systemic thrombolytic activity, and higher recanalization rates for large-vessel occlusions. The fear of serious procedural complications was not borne out in the PROACT I and II trials, in which cerebral angiography was associated with a 0.1% rate of permanent complications and a 0.02% death rate.

On the other hand, IA thrombolysis requires access to a team of physicians (an interventionalist and tertiary stroke team) capable of performing IA thrombolysis. Such expertise is not readily available in many developing countries or in many communities across Europe and the United States, as it is usually limited to large academic centers. Treatment delays are also inherent to IA thrombolysis. In PROACT II, the median time to drug infusion from stroke onset was 5.3 hours, and the average time from arrival at the hospital to the initiation of IA r-pro-UK was 3 hours. IA thrombolysis also involves costs and procedural risks not inherent to IV thrombolysis. As the total number of intra-arterially treated patients is small, not much is known about drug and dose-efficacy relations. Recently an IA Web registry was established to gather more information.

Relative merits and drawbacks of IV thrombolysis
IV thrombolysis has the important advantages of time, ease of administration, and widespread availability. However, currently less than 5% of acute stroke patients receive IV rt-PA, mainly because of the 3-hour treatment window. The difficulty in demonstrating a benefit from IV thrombolysis beyond 3 hours from stroke onset arises from a number of factors. The proportion of patients with major stroke who have salvageable brain decreases with time, while the brain hemorrhage rate with thrombolysis increases. A worse than expected outcome due to the inclusion of patients with early signs of infarction on CT contributed to the negative results of ECASS I. Conversely, a better than expected outcome made it difficult to demonstrate a benefit in ECASS II when such patients were excluded. Vascular imaging studies were not done in the IV thrombolysis trials, so that neither the sites of arterial occlusion nor the recanalization rates are known. Patients with ischemic stroke of less than 6 hours’ duration have a wide variety of occlusion sites, and 20% have no visible occlusion, despite similar neurologic presentations.

Rapid and complete recanalization is the key
The key issue is to achieve complete recanalization as quickly as possible. A good clinical outcome is significantly related to recanalization regardless of how it is achieved. The factors that determine individual susceptibility to ischemia are not completely understood, and there clearly is a great deal of variability in time to irreversible damage among individuals—ie, there are many therapeutic windows. Greater recanalization efficacy is taken as an explanation of why the time window for successful IA thrombolysis may be longer than for IV administration. Based on PROACT II, a 6-hour window appears to be a realistic goal for IA therapy in anterior circulation ischemia. However, in PROACT II only patients with MCA occlusions were treated, an occlusion type in which the probability of good collateralization is high, recanalization occurs frequently, and a chance of recanalization “in time” is most probable. Patient selection contributed highly to the degree of efficacy in PROACT, and this is now a central challenge in acute reperfusion therapy.

Progress linked to improved patient selection
It is increasingly obvious that selecting reperfusion therapy based only on time from stroke onset, a neurologic examination score, and a routine CT scan is inadequate. Since the evolution of new-generation MR devices, and partially also after the development of multislice spiral CT, a great variety of information can now be made available within minutes to describe the anatomic and pathophysiologic status of the brain tissue. This enables clinicians to make highly selective treatment decisions. With this in mind, the Kompetenznetzwerk Schlaganfall (B5) Study Group has investigated in a multicenter, prospective trial stroke patients with and without IV fibrinolytic treatment who were selected by MRI protocol that included diffusion-weighted and perfusion-weighted imaging (DWI and PWI), T2*-weighted imaging, time-of-flight MRA, and, if necessary, contrast-enhanced MRA. The trial used a 6-hour treatment window. Only patients exhibiting at least 20% DWI/PWI mismatch in a hemispheric infarct of not more than one third of the MCA ter-
tory were included. Calculating the number needed to treat for the major trials with a 6-hour window using a dichotomized modified Rankin score of 0–2/>3 shows that 12 patients were needed for ECASS II and 7 patients for PROACT II. The number needed to treat in the B5 Study Group cohort was 5 patients. This again shows that, as in PROACT II, more precise and pathophysiologic patient selection may translate into greater efficacy regardless of the thrombolytic method.

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**REFERENCES**


Acutely ischemic stroke is a leading cause of death and disability throughout the developed world. Although early vascular reperfusion has been shown to improve clinical outcomes, fewer than 5% of patients with acute ischemic stroke actually receive thrombolytic therapy. The challenge of thrombolytic therapy is rapidly shrinking recovery of brain tissue coupled with increasing vulnerability to reperfusion injury. The result, a narrow time window, has proved to be the stumbling block in wider dissemination of this treatment. Conceivably, coadministration of a "tissue protectant" could enhance the effectiveness of thrombolysis while expanding the time window and reducing the risks of reperfusion.

A promising candidate to serve this purpose is hypothermia. A wealth of animal experiments demonstrated that hypothermia, or simply fever prevention, diminishes ischemic damage with transient occlusion followed by reperfusion. In models of permanent occlusion, reduction of infarct size was less impressive. In transient models, hypothermia was most effective when administered during the period of vascular occlusion (intra-ischemic) or immediately after vascular reperfusion (postischemic). According to these models, hypothermia is efficacious in concert with reperfusion in only a narrow time window. Some investigations suggest that lengthy periods of hypothermia enhance the benefit of its early postischemic induction, even in permanent occlusion models. Consequently, in patients with acute stroke, therapeutic hypothermia will more likely confer benefit in conjunction with early vascular reperfusion and when applied over prolonged time periods.

The use of antipyretic agents alone has not been shown to effectively reduce core temperature after stroke, although post-stroke fever can be inhibited. Therapeutic mild to moderate hypothermia can be achieved by surface cooling (external cooling) or by using intravenous counter-current heat exchange (endovascular cooling). Other modalities, such as localized hypothermia, are being developed. Limitations of external cooling are almost invariably associated with imprecise timing and continuation of the hypothermic effect. With endovascular cooling, heat is directly removed from or added to the thermal core, thus bypassing the heat sink and insulating effects of peripheral tissues. Several early open and controlled studies have shown that endovascular cooling is safe and can effectively manage core temperatures in the mild to moderate hypothermic range.

This lecture will review key experimental and clinical studies to advance the understanding of mechanisms by which hypothermia may enhance stroke outcomes and how these insights may help to translate the benefits of hypothermia from bench to bedside.

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The past decade has seen impressive advances in the prevention and treatment of cerebrovascular disease. Nevertheless, stroke remains the leading cause of serious adult disability in the United States, as more than 4 million Americans are estimated to be stroke survivors. Physical therapy, occupational therapy, and speech therapy are the mainstay of rehabilitative efforts, but in many cases significant disabilities remain following stroke.

Several new therapies are under investigation to address the long-term disability of stroke survivors. Growth factors, amphetamines, cortical stimulation, and new approaches to physical therapy (eg, constraint-induced therapy) offer the possibility of improving neurologic deficits months or years after the recovery process has reached a plateau. Cell transplantation was pioneered for the treatment of Parkinson disease (PD) and has now been applied to other neurologic diseases, including stroke. However, treatment with transplanted cells is somewhat more complex for stroke than for PD. In PD, cellular therapy is aimed at replacing dopaminergic cells in the substantia nigra, whereas in stroke, multiple cell types and neurotransmitters are lost.

There is uncertainty about the mechanism by which cell transplantation might improve stroke deficits. Transplanted cells would ideally replace cells that are damaged by ischemia and take over the function of these cellular elements. However, it is also possible that transplanted cells secrete trophic factors that help to maintain marginally surviving cells or otherwise enhance the local environment sufficiently to improve function. Transplantation might also conceivably produce a host reaction that could include sprouting of new axons and synapse formation.

**POTENTIAL CELL SOURCES**

A number of sources of transplanted cells are available. Transplanted fetal stem cells survive and integrate into host brains in animal models of stroke. Functional improvement occurs as long as the cells remain immature. In human studies of PD, initial improvement in neurologic disability was mitigated by severe late dyskinesias. Whether similar problems might occur with stroke is unknown. Use of fetal stem cells is constrained by ethical concerns and limited availability.

Neuroprogenitor cells are found in the periventricular region of developing brains and in adults. After brain injury, including ischemia, these cells react by migrating to the area of injury and undergoing differentiation. When transplanted into brains of rats subjected to ischemia, these cells survive, differentiate, and proliferate. Because neuroprogenitor cells are derived from fetal brains, ethical issues similar to those with fetal stem cells limit availability.

Bone marrow stromal cells are capable of differentiating into multiple cell types, including neuronal cells. Transplantation of these cells into striatum of rats subjected to ischemia significantly improves function. Similar results have been achieved with intravenous infusion. Unfortunately, the yield of stromal cells from bone marrow is low and the safety of these cells is uncertain.

Multipotential cells have also been isolated from umbilical cord blood. This source of cells for transplantation is appealing because of ready availability and the lack of ethical issues. Functional improvement has been demonstrated in animal stroke models with implantation or intravenous injection similar to bone marrow stromal cells.

Immortalized cell lines offer a ready source of cells for transplantation without the ethical concerns that surround fetal tissues. One source of cells is the NTera 2/cl.D1 (NT2) human embryonic carcinoma-derived cell line. These cells proliferate in culture and differentiate into pure, postmitotic human neuronal cells (LBS-Neurons, Layton BioScience, Sunnyvale, Calif.) upon treatment with retinoic acid.
Thus, NT2 precursor cells appear to function as central nervous system (CNS) progenitor cells with the capacity to develop diverse mature neuronal phenotypes. When transplanted, these neuronal cells survive, extend processes, express neurotransmitters, form functional synapses, and integrate with the host. The final product is greater than 95% pure populations of human neuronal cells that appear virtually indistinguishable from terminally differentiated postmitotic neurons. The cells are capable of differentiation to express different neuronal markers characteristic of mature neurons, including all three neurofilament proteins (NFL, NFM, and NFH); microtubule-associated protein 2 (MAP2), the somal/dendritic protein; and tau, the axonal protein. Their neuronal phenotype makes them a promising candidate for replacement in CNS disorders, as a virtually unlimited supply of pure, postmitotic, terminally differentiated human neuronal cells.

**TRANSPLANTED LBS-NEURONS: EVIDENCE TO DATE**

Sanberg, Borlongan, and colleagues were the first to show that transplants of LBS-Neurons could reverse the deficits caused by stroke. Animals that received transplants of LBS-Neurons (and cyclosporine treatment) showed amelioration of ischemia-induced behavioral deficits throughout a 6-month observation period. They demonstrated recovery in the passive avoidance test, as well as recovery of motor function in the elevated body swing test. In comparison, control groups receiving transplants of rat fetal cerebellar cells, medium alone, or cyclosporine failed to show significant behavioral improvement. A second study that evaluated response relative to the number of cells transplanted confirmed the efficacy of transplanted LBS-Neurons in reversing the behavioral deficits resulting from transient ischemia in a middle cerebral artery occlusion rat model.

The first clinical study using LBS-Neurons included 12 patients with stroke primarily involving the basal ganglia and producing significant motor deficits. In the first 4 subjects, 2 million cells were implanted. The next 8 patients were randomized to receive 2 million or 6 million cells. The major objective of this study was to assess safety, but patients were also assessed for outcome using the European Stroke Scale (ESS) and the National Institutes of Health Stroke Scale. No complications occurred related to the implantation procedure. After more than 36 months of follow-up, there were no complications attributable to the implanted cells.

Though efficacy was not the major focus of this initial study, neurologic improvement occurred in some patients and a trend toward improved ESS scores was seen after 12 months. Changes were greater in the group receiving 6 million cells. The significance of such findings in this small uncontrolled trial is uncertain. FDG-PET studies were performed in all patients at baseline and at 6 and 12 months. Improvement in metabolism in the region of implantation was observed in 6 patients. Whether such changes represent metabolism in the grafted cells, increased function of host cells, or simply an inflammatory response to the implanted cells is unknown. In a few patients, the metabolism increases disappeared at 12 months, but in others the changes persisted. Two patients died of unrelated causes, and in 1 an autopsy was obtained. Surviving implanted LBS-Neurons were identified at the injection site within the area of infarction.

A phase 2 dose-response trial of patients with basal ganglia stroke and significant motor deficits was recently completed comparing implantation of 5 million and 10 million cells. An additional 4 control patients received no cell implants. There were no serious complications from the procedures.

Longer-term safety and efficacy results should enhance our understanding of cell implantation therapy for the treatment of stroke.

**BIBLIOGRAPHY**


A number of prospective randomized trials have examined the efficacy of carotid endarterectomy (CEA) in patients with carotid stenosis. This brief review surveys their findings, concluding with some observations that stem from this collective body of evidence.

TRIALS FOR ASYMPTOMATIC CAROTID STENOSIS

The CASANOVA (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin) study randomized patients with asymptomatic carotid stenosis (> 50% but < 90%) to either immediate CEA (n = 206) or no immediate surgery, including some patients who underwent delayed surgery after developing ischemic symptoms, progressive severe stenosis, bilateral stenosis, or contralateral stenosis (n = 204). At 3-year follow-up, with death or new stroke as primary end points, there was no difference in the primary outcome (ipsilateral stroke or death) between the immediate-surgery group and the other group of patients (10.7% vs 11.3%). However, nearly half the patients in the “no immediate surgery” group eventually did have an endarterectomy for one of the reasons stated above. This study’s unusual design lessens its statistical validity.

The VA Asymptomatic Stenosis Trial randomized patients with asymptomatic carotid stenosis (> 50%) to operative (n = 211) or nonoperative (n = 233) therapy. At a mean follow-up of 4 years, the combined incidence of ipsilateral neurologic ischemic events (transient ischemic attack [TIA] and stroke) was reduced in the surgical group (8%) compared with the medical group (20.6%) (P < .001). However, the sample size was not large enough to show a statistically significant difference in rates of stroke alone. For the outcome of ipsilateral stroke, the incidence was 4.7% (including perioperative strokes) in the surgical group compared with 9.4% in the medical group (P = .056). However, when perioperative mortality (1.9%) was included with the surgical stroke rate, the difference between the two groups was not statistically significant.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) substantiated the hypothesis that CEA may prevent stroke in certain patients with asymptomatic carotid stenosis. This trial randomized 1,662 patients with high-grade carotid stenosis (> 60% diameter reduction by ultrasonography and/or angiography) to medical management alone or to medical management plus CEA. Over 5 years (mean follow-up = 2.7 years), the primary outcome measure, ipsilateral stroke, was reported in 5.1% of the patients who received CEA compared with 11.0% of the nonsurgical patients, for a projected overall 53% relative risk reduction. Although 9% of patients were not treated according to their randomization status, the stroke risk reduction was comparable whether analysis was done by intention to treat or by actual treatment received. Stroke risk reduction was more prominent in men and was apparently independent of the degree of stenosis or contralateral carotid artery disease. A substantial portion of the surgical risk was attributable to angiography (1.2% stroke rate), and the initial risk for surgery plus angiography was offset by a constant risk of ipsilateral stroke at approximately 2.2% per year in the nonsurgical group. The surgical benefit was apparent by 10 months and was statistically significant at 3 years.

TRIALS FOR SYMPTOMATIC STENOSIS

The European Carotid Surgery Trial (ECST) randomized patients with asymptomatic carotid stenosis (> 50%) to operative (n = 211) or nonoperative (n = 233) therapy. At a mean follow-up of 4 years, the combined incidence of ipsilateral neurologic ischemic events (transient ischemic attack [TIA] and stroke) was reduced in the surgical group (8%) compared with the medical group (20.6%) (P < .001). However, the sample size was not large enough to show a statistically significant difference in rates of stroke alone. For the outcome of ipsilateral stroke, the incidence was 4.7% (including perioperative strokes) in the surgical group compared with 9.4% in the medical group (P = .056). However, when perioperative mortality (1.9%) was included with the surgical stroke rate, the difference between the two groups was not statistically significant.

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for patients in the mild and severe stenosis groups. Among the 374 patients with mild stenosis, there was no significant difference in ipsilateral stroke rates between the surgical and nonsurgical groups. There were more treatment failures in the surgery group, which was attributed to the 2.3% risk of death or disabling stroke during the first 30 days after surgery. Among patients with severe stenosis, however, surgery was shown to be beneficial in preventing stroke. There was a 7.5% risk of ipsilateral stroke or death within 30 days of surgery. At 3 years of follow-up, there was an additional 2.8% risk of stroke in the surgery group, for a total risk of 10.3%, compared with a 16.8% risk in the nonsurgery group (P < .0001). Importantly, the incidence of death or ipsilateral disabling stroke was reduced from 11% in the nonsurgery group to 6% in the surgery group. ECST used a different criterion for determining carotid stenosis than did the NASCET (see below), VASST (see below), or ACAS investigations. When reanalyzed using the NASCET criteria, patients in ECST with greater than 70% stenosis had a stroke risk and achieved benefit from surgery at rates comparable to those in NASCET or VASST.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)6 prematurely stopped randomizing patients with carotid stenosis greater than 70% because of the overwhelming stroke risk reduction observed in the surgical group. A total of 659 patients in this stenosis category were randomized to surgical (n = 331) or nonsurgical (n = 328) therapy. At a mean follow-up of 24 months, the primary outcome measure, ipsilateral stroke, was noted in 26% of nonsurgical patients vs 9% of patients who had undergone endarterectomy, for an absolute risk reduction of 17% (relative risk reduction of 71%). The benefit for surgical patients was highly significant (P < .001) in a variety of outcome measures, including stroke in any territory, major stroke, and major stroke or death from any cause. A perioperative morbidity/mortality of 5.8% was rapidly surpassed in the nonsurgical group, such that surgical benefit was apparent by 3 months. Moreover, the protective effect of surgery was durable over time, with few strokes noted in the endarterectomy group beyond the perioperative period. A secondary outcome, functional disability (assessed by a standardized disability scale), was significantly less severe in the surgery group over time (P < .001).7 Multivariate analysis demonstrated that surgical benefit was independent of a variety of demograph-

- **META-ANALYSIS OF SYMPTOMATIC STENOSIS TRIALS**

To determine the long-term risk of stroke following CEA, and to identify risk factors, Kaplan-Meier analysis was used to calculate ipsilateral carotid territory ischemic stroke risk starting on the 30th day after CEA in 1,728 patients who underwent surgery in the ECST investigation.8 The risks of disabling ipsilateral-
al ischemic stroke and any ipsilateral ischemic stroke were constant after CEA, reaching 4.4% (95% CI = 3.0% to 5.8%) and 9.7% (95% CI = 7.6% to 11.7%), respectively, by 10 years. Presentation with cerebral symptoms, diabetes, peripheral vascular disease, and elevated systolic blood pressure were associated with an increased risk of late stroke following CEA, but severity of preoperative stenosis, plaque morphology, and use of a patch graft were not.

A recent meta-analysis of pooled data from the ECST, NASCET, and VASST investigations was derived from the trials' original electronic data files, with outcome events redefined, if necessary, to achieve comparability. Data for 6,092 patients, with 35,000 patient-years of follow-up, were pooled. The risks of the main outcomes in both treatment groups did not differ among trials, and neither did the effects of surgery. Surgery increased the 5-year risk of ipsilateral ischemic stroke in patients with less than 30% stenosis (n = 1,746, absolute risk reduction of –2.2%, P = .05), had no effect in patients with 30% to 49% stenosis (n = 1,429, absolute risk reduction of 3.2%, P = .6), was of marginal benefit in those with 50% to 69% stenosis (n = 1,549, absolute risk reduction of 4.6%, P = .04), and was highly beneficial in those with 70% or greater stenosis without near-occlusion (n = 1,095, absolute risk reduction of 16.0%, P < .001). There was a trend toward benefit from surgery in patients with near-occlusion at 2 years' follow-up (n = 262, absolute risk reduction of 5.6%, P = .19), but no benefit at 5 years (absolute risk reduction of –1.7%, P = .9).

## SUMMARY AND OBSERVATIONS

Several notable features are common to these trials examining the efficacy of CEA for symptomatic stenosis. First, CEA provided profound protection against subsequent ipsilateral stroke in patients with high-grade symptomatic stenosis. A lesser but significant degree of protection was observed in asymptomatic high-grade or symptomatic intermediate-grade stenosis. The stroke risk reduction was realized early after surgery, persisted over extended periods of time, and was independent of other risk factors.

Second, stroke rates in the nonsurgical high-grade symptomatic patient cohort considerably exceeded those reported from prior prospective and retrospective studies. Symptomatic patients receiving aspirin in prior prospective multicenter trials had annual stroke rates ranging from 3% to 7%, compared with rates between 15% and 20% in nonsurgical patients (mostly receiving aspirin) from NASCET and VASST.

The efficacy of CEA depends in part on an acceptable level of perioperative morbidity and mortality. The risk of late ipsilateral ischemic stroke following CEA for symptomatic stenosis is only about 1% per year, and it remains low for at least 10 years after CEA. Several risk factors may be useful in identifying patients at particularly high risk for late postoperative stroke. Meta-analysis of the trials with the same measurements and definitions yielded highly consistent results. Surgery is of some benefit for patients with 50% to 69% symptomatic stenosis and is highly beneficial for those with 70% or greater symptomatic stenosis but without near-occlusion. Benefit in patients with carotid near-occlusion is marginal in the short term and uncertain in the long term. These are the standards against which alternative treatments should be judged.

## REFERENCES

Carotid endarterectomy (CEA) was first proposed as a treatment for preventing stroke by C. Miller Fisher in the 1950s, and CEA was first performed in 1954 by DeBakey in the United States and by Eastcott in England. Forty years were to pass, however, before there was any evidence that CEA was beneficial. The publication of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in 1991 provided the first definitive proof of the utility of endarterectomy in preventing stroke. Carotid artery stenting was first performed in 1994, and with the completion of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial in 2002, we had clear evidence that in selected patient groups protected carotid stenting was superior to CEA.

RATIONALE FOR SAPPHIRE’S HIGH-RISK FOCUS

The SAPPHIRE trial focused on patients at potentially increased surgical risk for several reasons. At the time of the trial’s design, clinical equipoise did not exist, particularly in the surgical and neurologic communities, for the randomization of low-surgical-risk patients to an interventional treatment. Although patients with the types of comorbid conditions included in the SAPPHIRE trial were frequently excluded from the previous major randomized trials of CEA, they do frequently require and undergo CEA. Indeed, they appear to represent the majority of patients undergoing CEA, and concerns have been raised about the generalizability of the CEA trial results in view of the degree of patient selection.

STUDY DESIGN AND ENROLLMENT CRITERIA

The SAPPHIRE trial was a randomized study comparing carotid stenting with the AngioGuard embolic protection device to CEA in patients at increased risk for carotid surgery. The trial was conducted at 29 US centers, all of which were carefully screened by the executive committee, and surgeons and interventionalists were required to submit experience and results. For surgeons the median annual number of endarterectomies was 30 (range, 15 to 100). The mean stroke, death, or MI complication rate was less than 3%. For interventionalists the median total number of carotid stent procedures performed was 64 (range, 20 to 700) and the mean stroke, death, or MI complication rate was 4%.

To be enrolled, patients had to have 50% or greater stenosis by ultrasonography if they were...
symptomatic or 80% or greater stenosis if they were asymptomatic, as well as meet one or more comorbidity criteria, listed in Table 1, that placed them at increased risk for surgery.

All patients were seen by a team made up of a neurologist, a surgeon, and an interventionalist. Randomization required consensus of the entire team. If the surgeon felt that he or she could not operate, and the interventionalist felt that intervention was possible, the patient was entered into a stent registry. Conversely, if the interventionalist did not feel that he or she could perform the intervention, and the surgeon felt that surgery was possible, the patient was entered into a surgical registry.

Patients were randomized on the basis of ultrasoundography, and the surgical patients did not undergo angiography.

The primary end points are a composite of death, any stroke, or MI 30 days after the procedure, as well as ipsilateral stroke or death 1 year after the procedure. There are multiple secondary end points, including restenosis rates, technical procedural success, quality of life, and economic outcomes.

## ENROLLMENT DATA AND PATIENT CHARACTERISTICS

A total of 723 patients were enrolled in the trial. The registry arm was completed in February 2002 with 409 patients entered in the stent registry and 7 patients entered in the surgical registry. The randomized arm was stopped in June 2002 with a total of 307 patients entered (156 randomized to stenting and 151 randomized to CEA).

In the randomized trial, the mean patient age was 72, and one third of patients were symptomatic. There was a high prevalence of coronary artery disease, previous bypass surgery, and previous endarterectomy. The patients entered into the stent registry had a higher incidence of radiation treatment, previous endarterectomy, high or low lesions, and presence of more than one high-risk criterion as compared with the patients entered into the randomized study.

Publication of clinical outcomes of the SAPPHIRE trial will be forthcoming.

## REFERENCES


### TABLE 1

<table>
<thead>
<tr>
<th>Comorbidity criteria for SAPPHIRE trial enrollment</th>
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<tbody>
<tr>
<td>Congestive heart failure (NYHA class III or IV)</td>
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<tr>
<td>Left ventricular ejection fraction &lt; 30%</td>
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<tr>
<td>Need for open heart surgery within 6 weeks</td>
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<tr>
<td>Recent myocardial infarction</td>
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<tr>
<td>Unstable angina</td>
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<tr>
<td>Severe pulmonary disease</td>
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<tr>
<td>Contralateral carotid occlusion</td>
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<tr>
<td>Contralateral laryngeal nerve palsy</td>
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<tr>
<td>Radiation therapy of the neck</td>
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<tr>
<td>Radical neck surgery</td>
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<tr>
<td>Previous endarterectomy with recurrent stenosis</td>
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<tr>
<td>High cervical ICA lesions or CCA lesions below the clavicle</td>
</tr>
<tr>
<td>Severe tandem lesions</td>
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<tr>
<td>Age &gt; 80 years</td>
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NYHA = New York Heart Association; ICA = internal carotid artery; CCA = common carotid artery
Noncardioembolic ischemic stroke accounts for at least 60% of all strokes due to atherothrombosis or thromboembolism involving the large cervicocephalic vessels, the medium intracranial vessels, or the small perforating vessels. In the intracranial vasculature, the proposed mechanisms of an acute vascular event include plaque rupture and thrombotic occlusion or thromboembolism due to platelet adhesion/activation/aggregation and subsequent cross-linking with fibrin. Theoretically, both antiplatelet and oral anticoagulant therapies should be effective in preventing these events.

However, most clinical trials assessing the efficacy of antithrombotic therapies have focused on the index event (such as transient ischemic attack [TIA], reversible ischemic neurologic deficit, minor or moderate stroke) or the involved vascular territory (carotid vs vertebral/basilar) as a starting point without much analysis beyond excluding those subtypes that require anticoagulation (atrial fibrillation, recent myocardial infarction [MI], prosthetic valve) or that require surgical therapy (severe symptomatic carotid stenosis). As a result, the most frequently cited clinical trials, including most of the aspirin trials, the Ticlopidine-Aspirin Stroke Study (TASS), the European Stroke Prevention Study (ESPS-2), and the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, do not allow for subset analyses devoted to patients with intracranial atherosclerosis. Without adequate identification of stroke subtypes or knowledge of the differences in stroke subtype mix among the studies, it is also impossible to make meaningful indirect efficacy comparisons among the various antithrombotic therapy trials. These factors are largely responsible for the ongoing controversy regarding optimal therapy for patients with cerebrovascular disease due to causes other than atrial fibrillation or carotid stenosis.

ASPIRIN AND OTHER ANTIPLATELETS

Aspirin remains the standard preventive therapy for most patients at risk for stroke. Its initial US Food and Drug Administration approval in 1980 specified its use in men with TIAs “due to fibrin platelet emboli” based on a trial that used 1,300 mg daily, although current recommendations favor 50 to 325 mg daily. Meta-analyses of trials in patients with cerebrovascular disease showed that aspirin at dosages of 75 to 325 mg/day reduced the combined end point of stroke, MI, or vascular death by 25%, but its major effect comes from its 22% reduction of nonfatal stroke, which is the most common recurrent event in this population. Subgroup analyses (based on fewer than 400 events) in 25 trials showed no significant differences in reduction of vascular events between doses of 75 to 150 mg (26%), 160 to 325 mg (28%), or 500 to 1,500 mg, and the lower doses currently in use are primarily favored for their lower rates of gastrointestinal side effects and hemorrhage.

In the Extracranial-Intracranial (EC/IC) Bypass Study, patients with carotid occlusion, intracranial carotid/siphon stenosis, or middle cerebral artery stenosis received best medical care with or without the addition of bypass surgery. The antiplatelet therapy chosen was aspirin 1,300 mg/day. Although patients randomized to surgery had more and earlier recurrent and fatal strokes (Table 1), patients in the medical arm also experienced a high rate of stroke (about 10% per patient-year).
ESPS-2. The combination of aspirin and dipyridamole has been studied in five clinical trials, but none specifically assessed patients for intracranial disease. The early trials did not reveal an additional benefit of combination therapy over high-dose aspirin alone (doses of 900 to 1,300 mg daily). ESPS-2 compared aspirin 25 mg twice daily, modified-release dipyridamole 200 mg twice daily, their combination, and placebo. Primary end points were stroke and stroke or death. Compared with placebo, the relative reduction in stroke risk was 18% with low-dose aspirin alone, 16% with dipyridamole alone, and 37% with the combination, suggesting an additive effect. The combination was 23% better than low-dose aspirin alone in preventing stroke, supporting a synergistic effect with combination antiplatelet therapy.

In TASS, ticlopidine 250 mg twice daily reduced the risk of recurrent stroke in patients with noncardioembolic TIA and minor stroke by a significant 19% compared with high-dose aspirin (650 mg twice daily). Although angiography was commonly performed in patients with carotid symptoms, only data regarding extracranial carotid stenosis were presented.

In the CAPRIE trial, clopidogrel 75 mg daily significantly reduced the relative risk of the combined end point of stroke, MI, or vascular death by 9% over aspirin 325 mg daily in 19,185 patients with a recent stroke or MI or with symptomatic peripheral vascular disease. There was no significant difference for the stroke cohort of more than 6,000 patients, although the analyses were not powered to specifically address subsets. Intracranial stenosis was not addressed in the CAPRIE trial and is also not addressed in the ongoing MATCH trial comparing clopidogrel 75 mg daily plus aspirin 325 mg daily with clopidogrel 75 mg daily alone.

WARFARIN VS ASPIRIN

Hemorrhagic risks and a lack of randomized trials limited the use of warfarin in stroke prevention until contemporary atrial fibrillation trials demonstrated an acceptable risk with modern therapeutic ranges and careful international normalized ratio (INR) monitoring. However, patients with cerebrovascular disease may have higher rates of anticoagulation-associated intracranial hemorrhage, as suggested by comparing the higher complication rates at INRs of 3.0 to 4.5 for patients with primary cerebrovascular disease in the SPIRIT trial.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) compared warfarin (INR initially targeted to 1.4 to 2.8 and later to 2 to 3) with aspirin 325 mg daily in patients with minor to moderate stroke who were followed for 2 years. The primary end point was recurrent stroke or death. Information was prospectively collected on stroke mechanism, and intracranial atherosclerosis was largely supported by magnetic resonance angiography and transcranial Doppler ultrasonography, which has limitations in sensitivity/specificity in the diagnosis of intracranial stenosis. Stroke subtype at entry included 56% lacunar stroke and 12% large-artery stenosis/occlusion, which included an unknown proportion of patients with intracranial stenosis. The 11% benefit in favor of aspirin was not statistically significant for the group or the subset with large-artery disease. Rates of major hemorrhage were low, at 1.92% per year with aspirin and 1.2% per year with warfarin, but patients with hypertension and a National Institutes of Health Stroke Scale score greater than 5 fared worse on warfarin. One fourth of patients had failed to respond to aspirin on entry. Although the overall 2-year recurrent stroke or death rate was significantly higher for these patients who had failed aspirin than for those who were naïve to aspirin (21.4% vs 13.8%), the fate of these aspirin nonresponders was not improved by switching to warfarin.

Retrospective, nonrandomized pilot data obtained by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group suggested that warfarin reduced the risk of stroke and vascular death (primarily nonfatal stroke) by 50% (95% confidence interval, 23% to 86%) compared to aspirin.
with aspirin despite a 1.8% per patient-year risk of major hemorrhage. Stroke risk varied with the location and severity of intracranial stenosis, with the greatest risk seen in those patients with severe intracranial vertebrobasilar stenosis (Table 2).

Prospective WASID findings
The major goal of WASID, a 5-year NINDS-supported prospective, randomized, double-blind, multicenter trial, was to compare warfarin (INR of 2 to 3) with aspirin (1,300 mg/day) for preventing stroke (ischemic and hemorrhagic) and vascular death in 403 patients with symptomatic, angiographically documented, 50% or greater stenosis of a major intracranial artery. (Sample size was based on stroke and vascular death rates of 33%/3 years in the aspirin group vs 22%/3 years in the warfarin group, an α of 0.05, a β of 0.80, a 24% withdrawal-of-therapy rate, and a 1% dropout rate). The study’s aims were:

- To determine whether warfarin or aspirin is more effective for patients with symptomatic intracranial arterial stenosis
- To identify patients whose rate of ischemic stroke in the territory of the stenotic intracranial artery on best medical therapy is sufficiently high (ie, >6% per year) to justify a subsequent trial comparing intracranial angioplasty with best medical therapy.

The trial was halted by its performance, safety, and monitoring board in August 2003 because of patient safety concerns. Data will be presented at the American Stroke Association’s International Stroke Conference in February 2004.

### SELECT BIBLIOGRAPHY


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### TABLE 2
Incidence of clinical outcomes in the WASID retrospective study

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n = 88)</th>
<th>Aspirin (n = 63)</th>
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<tbody>
<tr>
<td>Stroke (%) / yr</td>
<td>3.6</td>
<td>10.4</td>
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<tr>
<td>Fatal MI or sudden death (%) / yr</td>
<td>3.0</td>
<td>4.2</td>
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<tr>
<td>Major hemorrhage (%) / yr</td>
<td>1.8</td>
<td>0</td>
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<tr>
<td>Same-territory stroke, 50%–69% stenosis (%) / yr</td>
<td>1.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Same-territory stroke, 70%–99% stenosis (%) / yr</td>
<td>3.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Same-territory stroke, severe vertebrobasilar stenosis (%) / yr</td>
<td>8.2</td>
<td>15.1</td>
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A significant cause of ischemic stroke is intracranial atherosclerotic disease caused by either hypoperfusion or distal embolization. The incidence has been reported to be 6% to 10% in whites, 6% to 22% in blacks, 11% in Hispanics, and 11% to 22% in Asians. Prognosis and morbidity for patients with intracranial stenosis vary widely, with the morbidity rate ranging from 10% to 46% per year, independent of medical therapy. The surgical option of an extracranial-to-intracranial bypass procedure has not been shown to be of significant benefit over optimal medical therapy for these patients.

Over the past decade, a number of centers have been reporting their experience with intracranial angioplasty and stenting as a treatment option for patients in whom maximal medical therapy with antiplatelet and anticoagulant medications has failed. Although prospective randomized studies have not yet been performed, results from these centers have indicated that this procedure is technically feasible and that there are good preliminary data demonstrating efficacy.

**PROCEDURE AND TECHNIQUE FOR INTRACRANIAL ANGIOPLASTY/STENTING**

A baseline brain CT or MRI scan is initially performed to assess for evidence of cerebral ischemia, infarction, or both. Hemodynamic quantitative blood flow studies using CT xenon perfusion imaging, MR perfusion/diffusion imaging, nuclear medicine perfusion imaging, or positron emission tomography are also performed to assess the degree of perfusion to brain tissue. All patients undergo a four-vessel diagnostic cerebral arteriogram to determine the site and degree of stenosis, collateral circulation, and associated vascular pathology.

Patients then receive systemic anticoagulation with intravenous heparin (100 units/kg), and the lesion is carefully crossed under fluoroscopic guidance with a microguidewire (0.014 inches) and a balloon angioplasty catheter (2.0 to 4.0 mm in diameter) that matches the normal luminal diameter. The balloon is inflated for 5 to 10 seconds across the lesion until the plaque is sufficiently dilated. In most cases, a metallic stent is then placed across the lesion to further improve the luminal diameter and to reduce the incidence of vessel dissection with secondary restenosis.

Patients are then carefully monitored in the neurologic intensive care unit for 24 to 48 hours, with close attention paid to anticoagulation levels and blood pressure levels. They are then discharged on antiplatelet medications: clopidogrel 75 mg/day or ticlopidine 250 mg twice a day for 4 to 6 weeks, plus aspirin 325 mg/day indefinitely.

**RESULTS TO DATE**

In 1996, Higashida et al published their early experience in 33 patients treated with intracranial balloon angioplasty after failure of best medical therapy; they reported a 69.7% technical success rate with improved neurologic outcome, although there was a 30.3% rate of associated stroke and death. Clark et al reported a series of 17 patients in whom 22 vessels were treated with balloon angioplasty: the success rate was 72%, and the 30-day morbidity rate was 11.7%. Connors and Wojak reported a retrospective analysis of balloon angioplasty in 70 patients with intracranial atherosclerosis: the overall stroke rate was 4.2%, the mortality rate was...
2.9%, and there were no technical failures.

More recently, several centers have reported on the use of intracranial stents for these lesions. Among 10 patients with 12 intracranial atherosclerotic lesions, Mori et al. reported an 80% technical success rate in accessing the lesion with a stent; in those patients who received stents, there were no periprocedural complications and there was significant improvement of neurologic symptoms during the 8 to 14 months of follow-up. Gomez et al. reported a series of 12 patients who underwent elective stenting of the basilar artery after episodes of vertebrobasilar ischemia; medical therapy had failed in all of these patients. Stent placement was successful in all cases, with improvement in luminal diameter from a mean of 71.4% to a mean of 10.3%, without any procedural complications. Clinical follow-up at 0.5 to 16 months (mean, 5.9 months) demonstrated no new complications, clinical improvement in all patients, and residual symptoms in only 2 patients. The researchers concluded that intracranial stenting was feasible and posed minimal risk to the patient, but its long-term impact was still not known.

**DISCUSSION**

In patients suffering from medically refractory transient cerebral ischemia, stroke, repetitive strokes, or other focal neurologic deficits stemming from intracranial symptomatic atherosclerotic lesions, intracranial balloon angioplasty, stenting, or both may be a useful therapeutic procedure. The development of better balloon catheters and stent delivery systems has dramatically reduced the technical difficulties and failures previously associated with these intracranial techniques. Although best medical therapy has not yet been determined for these patients, extrapolation from the extracranial circulation for carotid atherosclerotic disease indicates that if a direct surgical or endovascular revascularization procedure can be performed with acceptable technical success rates (ie, low rates of periprocedural complications), it may be better than medical therapy in certain types of patients. Clearly, once medical therapy with antiplatelet and/or anticoagulant medications has failed in a patient, then either an endovascular procedure or a surgical bypass procedure may be indicated as a possible alternative.

Although long-term follow-up (> 2 to 5 years) is not yet complete for patients who have undergone intracranial balloon angioplasty and/or stenting, the short-term results appear to be encouraging terms of improving symptoms and decreasing the risk of major stroke.

As medical therapies and endovascular treatment techniques both continue to improve, hope remains that ever better treatment options will be available for patients with intracranial atherosclerotic lesions.

**REFERENCES**

Most of the interest in antithrombotics for stroke prevention has been for the prevention of later recurrence, over a period of, say, 2 years or more. Part of the reason for this has been the assumption that sufficient time would be needed for the event rate to show itself, since events in the first few hours or days, during hospitalization, might be difficult to study with any degree of success.

STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION

The results of primary prevention trials in the setting of atrial fibrillation make it widely assumed that not only those seeking prevention of a first stroke (primary prevention) but also those with atrial fibrillation who have already suffered a stroke require dose-adjusted oral anticoagulation (to a target international normalized ratio [INR] of 2.5 ± 0.5). Although warfarin has proved itself superior to a range of other therapies, including placebo, rates of recurrent stroke, even on warfarin, are higher than those of first stroke. The INR effects in secondary prevention trials show a similar-shaped curve to that for primary prevention trials, flattening between INRs of 1.5 to 2.0 and remaining relatively stable for higher values to 3.0.

Issues of safety have not been as well established. Acceptably low hemorrhage rates have been reported with INRs of 2.0 to 3.0 in patients with atrial fibrillation in some studies of prevention of first and recurrent stroke. Yet major hemorrhagic complications at an INR of 2.8 (treatment range of 2.2 to 3.5) forced discontinuation of a trial for prevention of recurrent stroke in patients with atrial fibrillation, although the lower-intensity range of 1.5 to 2.1 proved safe. These more recent experiences leave unsettled the actual safety of anticoagulants in the prevention of recurrent, as opposed to primary, ischemic stroke.

PREVENTION OF NONCARDIOGENIC STROKE: THE WARSS FINDINGS

As recently as 1989, a report from the World Health Organization expressed dissatisfaction with the lack of a proven medical therapy to prevent recurrent ischemic stroke. In the decade that followed, considerable effort was directed toward this problem, along several lines. Initially, concerns for safety with warfarin prompted work that was largely limited to antithrombotic agents of the platelet antiaggregant type.

Warfarin vs aspirin for noncardioembolic stroke
The Warfarin-Aspirin Recurrent Stroke Study (WARSS) took as its point of departure the question of whether the 30% risk reduction for primary stroke in the setting of atrial fibrillation could be approximated for noncardioembolic recurrent ischemic stroke. No precedent existed for such a finding except the supportive evidence that at least some instances of noncardioembolic stroke appeared, on clinical grounds, to suggest an embolic mechanism, even though none could be found, a category embraced by the general term “cryptogenic stroke.” A target of 30% risk reduction at least allowed for the calculation of sample size using the roughly 8% per year recurrence rate achieved in most trials with aspirin. WARSS was therefore never conceived as an equivalence trial. The patients in WARSS underwent a degree of laboratory workup reflecting current standards of care.
The overall rates of stroke and death (372 of 2,206 patients, 16.9%) at 2 years (recorded as 761 days, or 1 month beyond 2 years) in WARSS approximated those of the original hypotheses used to calculate sample size, and sufficed for prespecified analyses. By intent-to-treat analysis comparing the two treatment arms, there was no difference for the primary outcome of death or recurrent ischemic stroke (relative risk [RR] = 1.13 for warfarin; 95% CI, 0.92 to 1.38; \( P = .25 \)). Among patients treated with warfarin, 47 died and 149 suffered recurrent ischemic stroke, for a total of 196 primary events among 1,103 warfarin recipients (17.7%). Among patients treated with aspirin, 53 died and 123 suffered recurrent ischemic stroke, for a total of 176 primary events among 1,103 aspirin recipients (15.9%).

Because more than 30 patients (<1.5% of the total) ended their study participation for a variety of uncontrollable reasons (moving to another state, etc.), a special computation was made to undertake an efficacy analysis for the remaining 2,164 patients. The findings of the trial were not changed.

**Observations from WARSS**

Taken as a condensed summary, the overall findings from WARSS failed to confirm 30% superiority of warfarin over aspirin. They also failed to show a statistically significant difference between the two treatment arms. WARSS was not powered to be an equivalence trial, and the results should be understood to have failed to confirm statistically significant differential therapeutic effects for the two treatments. A difference might exist, but the study’s findings do not allow a statement of difference or of equivalence. That said, data seeking differences for any clinically identifiable subtypes of ischemic stroke are even more limited. The results leave unclear whether warfarin can be justified for any but obvious cardioembolic strokes, or whether each of the treatments appears justifiable for any of the stroke subtypes.

Two other general findings are worth comment as well. First, several clinicians expressed concern that the time required for warfarin to take effect might bias the trial toward early recurrent events in the warfarin arm, nullifying any beneficial effects later. To address this concern, a prespecified null hypothesis was explored for the slope of events for the first 30 days; there was no statistically significant difference between the two treatment groups for this period. A second concern related to safety and hemorrhage, as discussed in the following section.

**INR RANGE, COMPLICATIONS, AND PREVENTION OF RECURRENT STROKE: WARSS AND BEYOND**

Safety in WARSS at the 1.4 to 2.8 INR range was to prove adequate. To the surprise of many of the investigators, major hemorrhage rates proved comparable between the aspirin and warfarin groups. Major hemorrhage occurred in 68 patients, 38 of whom were randomized to warfarin (3.44% incidence) and 30 to aspirin (2.71% incidence). The difference was not statistically significant (RR for warfarin = 1.28; 95% CI, 0.80 to 2.07; \( P = .304 \)), and rates of major adverse events were below the prespecified threshold for ending the trial early. “Major hemorrhage” was defined as any intracranial or intraspinal hemorrhage, hemorrhage into the eye, or any hemorrhage in any other site leading to transfusion. Rates of minor hemorrhage in WARSS were significantly higher for warfarin than for aspirin, a finding replicated in other trials.

At issue in any trial comparing warfarin with aspirin is the choice of the target INR. For WARSS, the range selected approximated that in the atrial fibrillation trials, where efficacy and safety had been demonstrated at ranges from 1.5 to 3.0. The range of 1.4 to 2.8 was also selected in part on the basis of results from studies of levels of the prothrombin split product F1+2, indicating that suppression of thrombosis could be achieved by values of 1.4 and higher. The clinicians participating in the trial were prepared to accept this range as safe and presumably suitable for a test of efficacy. No clinical trial data had demonstrated safety of INRs above 2.5 at the time the trial was begun.

**Hemorrhage risk in SPIRIT/ESPRIT**

Complications with warfarin have been well documented in trials in populations with no prior stroke, as well as in the stroke population, which is mainly elderly and at higher risk for hemorrhage. Few studies have addressed the risk of serious hemorrhage in a setting of prior ischemic stroke. One such effort was the Stroke Prevention in Reversible Ischemia Trial (SPIRIT). This study, which began after WARSS had started enrolling patients and shared protocol details with WARSS, was an open-label comparison of warfarin with lower-dose aspirin following transient ischemic attack or stroke. Outcomes were reviewed by a panel blinded to therapy. No monitoring of INRs, institutional audits, or central laboratory performance of INRs...
were part of the research plan. This study, undertaken with a planned INR range of 3.0 to 4.5 (actual reported mean INR of 3.5), was brought to an end after the first interim analysis. The complications of therapy were due almost entirely to hemorrhage, and these events occurred mainly in the warfarin group. Among the 1,316 patients reported to have been enrolled at the first interim analysis, 81 of 651 patients in the anticoagulation group had events, compared with 36 of 665 patients in the aspirin group (hazard ratio = 2.3; 95% CI, 1.6 to 3.5). The bleeding incidence, calculated from this small sample, was estimated to have been increased by a factor of 1.43 (95% CI, 0.96 to 2.13) for each 0.5-unit increase in the achieved INR. No reports from SPIRIT have appeared documenting the stability of the INRs in the treated patients over time or documenting the percentages of patients above the upper or below the lower ranges of the planned INRs. For this reason, it cannot yet be inferred whether the rates of serious hemorrhage were related to large fluctuations, to time well above the targeted range, or to any other variable apart from the reported mean. The study has undergone revision and has restarted under a new name, ESPRIT.

Apart from this open-label study, other efforts in nonstroke settings with higher INR ranges than those used in WARSS have also had mixed results where warfarin was assessed in comparison with aspirin. In these latter trials, the cohort mainly has consisted of patients with cardiac disease, not stroke.

ISCHEMIC STROKE SUBTYPES AND DIFFERENTIAL EFFECTS OF THERAPY IN WARSS

Prior studies may have wisely shied away from attempts at characterizing the mechanism of ischemic stroke. Such efforts have a long history and a well-known degree of disagreement as to nomenclature and successful application of algorithms, having been described, refined, debated and contrasted with others, expanded, and, for at least some definitions, validated as clinically recognizable.

Accepting a minor degree of uncertainty in the exact application of diagnostic algorithms, the WARSS project classified recurrent ischemic strokes into three broad groups: lacunar, large-artery, and cryptogenic. Given the debates that continue on the mechanism of infarction each of these is thought to represent, it was notable that the number and percentage of events were found to be similar in each of the three major infarct subtypes:

- For lacunar stroke, primary events occurred in 107 of 612 patients (17.5%) on warfarin and in 95 of 625 patients (15.2%) on aspirin.
- For cryptogenic stroke, primary events occurred in 42 of 281 patients (14.9%) on warfarin and in 48 of 295 patients (16.3%) on aspirin.
- For large-artery stroke, primary events occurred in 27 of 144 patients (18.7%) on warfarin and in 18 of 115 patients (15.6%) on aspirin.

Were no further efforts made to analyze the basis for the diagnosis in such cases, there would be ample basis for concluding that prior trials loosely diagnosing "stroke" or "ischemic stroke" should suffice to settle the essential homogeneity of the therapeutic effects between an anticoagulant and a platelet antiaggregant. However, in the analysis plan constructed by the investigators and reviewed with the National Institutes of Health–supported performance, safety, and monitoring board, a number of detailed subset analyses had been planned and were undertaken. The results were presented at the Joint International Stroke Meeting in San Antonio, Tex. (Feb. 8, 2002), in a special symposium devoted to WARSS. The general results from parallel studies conducted within the WARSS cohort were presented, showing no effect on recurrent stroke and no differential response to warfarin or aspirin for any of the following groups:

- Patients showing an antiphospholipid profile considered sufficient for a diagnosis of the antiphospholipid syndrome
- Patients whose circulating values of the prothrombin split product F1.2 (formerly known as F1+2) were measured
- Patients with or without a cardiac patent foramen ovale.

Within the cryptogenic stroke group, which was the only subtype group showing the faintest hint of a warfarin effect (although not statistically significant), exploratory analyses found a 30% risk reduction ($P = .02$) for nonhypertensive patients whose infarcts affected the cerebral convexity or the convexity plus a deep ipsilateral infarct, or whose infarct was “large and deep” (beyond the size bounds usually considered examples of lacunar infarction). For many clinicians, the cryptogenic subtype is suspected to contain many occult examples of embolism, even if no obvious source is found. This 30% risk reduction could mean that such cases represent a...
link to the effects found at similar levels of risk reduction with warfarin. The data supporting this possibility come from a randomized, double-blind trial with prespecified subset analyses, and while these data may not satisfy the most vocal critics, they could provide a link with a warfarin effect in atrial fibrillation to occult embolism without atrial fibrillation. Further studies would be useful, but support for yet another warfarin trial may be limited.

Similar subset analyses provided no comfort for those whose practice has been to consider warfarin the stronger of the two agents for large-artery disease and lacunes. In these settings, warfarin use was associated with, if anything, a slightly higher rate of primary events. The lacune group (n = 1,237) was of sufficient size that the lack of difference between the two treatment arms, even a clear numerical difference favoring aspirin, is likely to blunt further similar direct comparisons. The large-artery stroke subgroup contained smaller numbers (n = 259) but also showed no treatment differences by intent-to-treat analysis. Subset analyses showed a far higher recurrence rate for the warfarin arm in primary brainstem infarction. One can only speculate how these data influence the ongoing trial comparing warfarin with aspirin, which seeks a 50% risk reduction favoring warfarin.

Pursued below the first level of analysis, the WARSS findings suggest that future trials should not be content to merely count “strokes” but would profit from a detailed data-collection mechanism as is now slowly emerging in more recent clinical trial designs, addressing issues of diagnosis subtype and estimates of severity. The field has gone beyond head counts to now demand information that bears on therapy directed at the cause of the clinical event. We should follow the lead of infectious disease specialists, who look to the nature of the organism and its sensitivities to various antimicrobials as the point of departure in treating a fever of infectious origin. Until stroke specialists insist on this same, we will still be using the vascular equivalent of broad-spectrum antibiotics.

**COMBINED WARFARIN AND ASPIRIN THERAPY**

Painful experience argues against the simple assumption that a decision between these two drug classes can be avoided by their simple combination for the prevention of recurrent ischemic stroke. No trial has directly assessed this point, but “stroke” as an outcome in several trials suggests that clinicians will be disappointed if they infer that the two agents can be managed safely if the INR is kept below 3.0.

A range of studies have pursued the possibility that a combination of aspirin and warfarin may achieve the best of both with a minimum of complications. Unfortunately, none of the efforts as yet appears to either show such benefits or achieve them without worrisome hemorrhagic complications. Two sets of studies exist, the first after myocardial infarction (MI) and the other in the setting of atrial fibrillation.

**Post-MI studies.** The original Coumadin Aspirin Reinfarction Study (WARIS) showed no superiority of fixed-dose warfarin (1 or 3 mg) plus 80 mg of aspirin over 160 mg of aspirin alone. The recently completed Warfarin-Aspirin Reinfarction Study (WARIS-II) achieved benefits with warfarin (INR of 2.0 to 2.5) plus aspirin (75 mg) vs aspirin (160 mg) alone, as well as with warfarin (INR of 2.8 to 4.2) vs aspirin (160 mg). However, the hope that hemorrhagic complications could be avoided with the combination if the INR were adjusted to the range of 2.0 to 2.5 was not realized: hemorrhagic complication rates were comparable to those for warfarin with high INR ranges. The CHAMP study fits between these two extremes, having compared warfarin (INR of 1.5 to 2.5) plus 81 mg of aspirin with 162 mg of aspirin alone (there is no expected difference between 160 mg and 162 mg if none has been found for wider differences in dose). As in other studies, no benefits accrued for the prevention of recurrent MI, and the combination group had a far higher rate of major bleeding (1.28 vs 0.72 events per 100 person-years; P < .001).

**Atrial fibrillation study.** A recent French study in the setting of atrial fibrillation has come to similarly disappointing conclusions. This 49-institution, placebo-controlled, double-blind trial randomized patients with atrial fibrillation aged 65 years or older who had had a prior “thromboembolic event” to either the oral anticoagulant fluindione plus placebo or fluindione plus aspirin. The targeted INR was 2.0 to 2.6. The primary end point was a composite of stroke (ischemic or hemorrhagic), MI, systemic arterial emboli, or vascular death. The 157 patients were followed for a mere 0.84 years, on average. The imbalance was great, with 10 nonfatal hemorrhagic complications in the combination group (13.1%) vs 1 in the anticoagulation-only group (1.2%) (P = .003).

The findings to date suffice to argue against safe-
ty, even given unsettled possible benefits from higher-dose combination therapies. The findings also argue that those inclined to use any combination therapy are, at best, unlikely to see enough patients in their practice to test any benefits and, at worst, unlikely to be aware of the risks from hemorrhagic complications amply documented in these studies. Assuming the findings are broadly representative for vascular disease in general, they may also dampen enthusiasm for combined warfarin and aspirin therapy in other vascular beds, cerebrovascular beds in particular.

**REFERENCES**

Recent recommendations from a joint scientific statement of the American Heart Association (AHA) and the American Academy of Neurology (AAN)1 address a number of key issues in the use of antiplatelet therapy for acute stroke. This review spotlights a number of these key recommendations and surveys the current evidence underlying them.

**ACUTE ASPIRIN ENDORSED FOR MOST PATIENTS**

The AHA/AAN joint statement recommends the following:

“Aspirin should be given within 24 to 48 hours of stroke onset in most patients (grade A recommendation).”1

Few trials of antiplatelet therapy have focused on stroke in the acute setting, but two of them2,3 had a similar trial design and together randomized more than 40,000 patients.

The International Stroke Trial2 (IST) involved 19,435 patients with acute stroke who were randomized within 48 hours of symptom onset to aspirin 300 mg/day, heparin, both, or neither for 14 days of therapy. Randomization was by a factorial design in which patients fell into 6 treatment groups: aspirin alone, aspirin and low-dose heparin (5,000 IU twice daily), aspirin and high-dose heparin (12,500 IU twice daily), low-dose heparin, high-dose heparin, or no study medication. The primary end points were death within 14 days and death or dependency at 6 months. Secondary end points included early (within 14 days) hemorrhagic stroke, recurrent ischemic stroke, major hemorrhage, and pulmonary embolism.

Compared with patients who did not receive aspirin, those who received aspirin had modestly but significantly lower rates of recurrent ischemic stroke (2.8% vs 3.9%) and of nonfatal stroke or death (11.3% vs 12.4%). At 6 months, the rate of death or dependency was also significantly lower for the aspirin-treated patients (61.2% vs 63.5%). Although patients who received heparin had significantly lower rates of recurrent ischemic stroke (2.9% vs 3.8%) and pulmonary embolism (0.5% vs 0.8%) compared with their counterparts who did not receive heparin, these benefits were offset by equally significant increases in the risk of hemorrhagic stroke (1.2% vs 0.4%) and major bleeding (1.3% vs 0.4%). As a result, the rate of death or dependency at 6 months was identical—62.9%—in both the patients who received heparin and those who did not. The subgroup that received aspirin and low-dose heparin looked like it might have fared better than the aspirin-only subgroup in the short term, with less early mortality (8% vs 9.3%) and less early recurrent stroke and intracranial hemorrhage (2.8% vs 3.7%), but the analysis of 6,000 patients was not large enough to be conclusive.2

The Chinese Acute Stroke Trial (CAST)3 randomized 21,106 patients with acute stroke within 48 hours of symptom onset to aspirin 160 mg/day or placebo for up to 28 days of therapy. Compared with placebo, aspirin reduced mortality (3.3% vs 3.9%) and the rate of nonfatal stroke or death (5.3% vs 5.9%). The rate of recurrent ischemic stroke was reduced by about 15% with aspirin use, although there was a small increase in the risk of hemorrhagic stroke.

Although the patients enrolled in IST and CAST differed, these studies taken together demonstrate a modest effect of early aspirin use in a wide range of patients with acute stroke. Although entry was per-
mitted within 48 hours of symptom onset, 14% of patients (5,600) were randomized within the first 6 hours, with treatment initiated immediately after randomization. The risk of early recurrent stroke was low (2% risk of ischemic stroke, 1% risk of hemorrhagic stroke, and 1% risk of stroke of unknown type), and recurrent strokes occurred primarily within the first week. Early aspirin administration reduced the risk of early recurrent ischemic stroke to 1.6% compared with 2.3% with control therapy, which corresponds to an absolute risk reduction of 7 per 1,000 and a relative risk reduction of 30%. At the same time, early aspirin use carried a slightly increased risk of hemorrhagic transformation or hemorrhagic stroke (1.0% vs 0.8%, for an absolute risk increase of 2 per 1,000). The effect of aspirin on reducing death or dependency at 6 months was somewhat better (45.6% vs 46.9%, for an absolute risk reduction of 12 per 1,000). Aspirin was associated with a definite excess in other major hemorrhages, particularly when heparin was used (0.7% for aspirin vs 0.5% for control, for an excess of 2 per 1,000; and 1.8% for aspirin plus heparin vs 0.9% for heparin alone, for an excess of 9 per 1,000).

In a meta-analysis, these results were not substantially affected by age, gender, level of consciousness, blood pressure, stroke subtype, CT findings, atrial fibrillation, or concomitant heparin use. In addition, for the 9,000 patients (22%) randomized without a prior CT scan and the 773 (2%) inadvertently randomized after a hemorrhagic stroke, there was no excess of adverse outcomes (hemorrhagic stroke or further stroke or death).  

**NO ADJUNCTIVE OR SUBSTITUTE ROLE FOR ACUTE ASPIRIN**

The AHA/AAN joint statement advises as follows:

"The administration of aspirin as an adjunctive therapy, within 24 hours of the use of thrombolytic agents, is not recommended (grade A)."

The Multicenter Acute Stroke Trial–Italy (MAST-I) was terminated prematurely after interim results showed, among other findings, an excess of intracranial hemorrhage and death in patients who received combination therapy with aspirin and streptokinase. The NINDS IV t-PA protocol permitted the treatment of patients taking aspirin so long as other exclusion criteria were met, but it prohibited the use of adjunctive antiplatelet or antithrombotic therapy within 24 hours of therapy. Indirect data from the cardiology literature indicate that the risk of systemic and intracranial bleeding is increased with the aggressiveness of combination therapies, particularly in the elderly.

The AHA/AAN joint statement also states:

"Aspirin should not be used as a substitute for other acute interventions, especially intravenous administration of rt-PA, for the treatment of acute ischemic stroke (grade A)."

Aspirin therapy is simple and readily available, but because its effect is modest, more effective therapies should take precedence.

**JURY STILL OUT ON ACUTE USE OF OTHER ANTIPLATELETS**

On the acute use of other antiplatelet agents, the AHA/AAN joint statement advises as follows:

"No recommendation can be made about the urgent administration of other antiplatelet aggregating agents (grade C)."

Most of the clinical trials assessing antiplatelet agents in stroke have focused on the long-term prevention of recurrent stroke in patients at risk for stroke. Although aspirin is the standard preventive therapy, the optimum dosage for the prevention of vascular events remains controversial despite 20 years of study. As an inhibitor of thromboxane A2 generation, aspirin has a modest effect. In patients with prior transient ischemic attack (TIA) or stroke, its major effect is the 23% reduction of recurrent nonfatal stroke. Thus, establishing superior preventive efficacy has been the goal for other antiplatelet agents targeting platelet surface glycoproteins, ADP receptors, or platelet-dependent thrombin generation, alone or in combination with aspirin.

Although hemorrhagic transformation of acute ischemic stroke can occur in the absence of any therapy, the risk is enhanced with the aggressiveness of such therapies, setting the risk-to-benefit ratio on a razor's edge. Although data on other antiplatelet therapies are extensive in the treatment of acute cardiovascular conditions, data on these therapies in the setting of acute stroke are limited.

For unstable angina or acute non–Q-wave myocardial infarction, the combination of clopidogrel 75 mg/day and aspirin 75 to 325 mg/day was superior to aspirin alone without an increase in stroke risk (1.2% vs 1.4%). A study with a similar design is now under way to compare clopidogrel 75
mg/day plus aspirin 75 mg/day with clopidogrel 75 mg/day alone in 7,600 high-risk patients with recent TIA or ischemic stroke. Results of this trial, known as MATCH (Management of Atherosclerosis with Clopidogrel in High-risk Patients), are expected by May 2004. Although it is not designed as an acute stroke trial, roughly one quarter of the initial 3,800 patients were entered within the first week of symptom onset, so some information on the safety of early combination antiplatelet therapy in acute ischemic stroke might be available.

**GPIIb/IIIa receptor antagonists**

There are currently some data exploring the safety of glycoprotein IIb/IIIa receptor antagonists in the setting of acute ischemic stroke, with small case series of tirofiban therapy in progressive stroke and of eptifibatide combined with intra-arterial t-PA in acute ischemic stroke. A small pilot dose-escalation study of abciximab was performed to assess its safety in acute ischemic stroke of less than 24 hours' duration, paving the way for a larger safety trial using the standard dose used in cardiac interventions.

The Abciximab in Emergent Stroke Treatment Trial (AbESTT) assessed the safety of abciximab (0.25-mg/kg bolus followed by 0.125-mg/kg/min infusion for 12 hours) in a randomized, double-blind, placebo-controlled trial involving 394 patients with acute ischemic stroke randomized within 6 hours of symptom onset. The primary safety end point, symptomatic intracranial hemorrhage through discharge or day 5, occurred more often with abciximab than with placebo (3.6% vs 1%), but asymptomatic intracranial hemorrhage on surveillance neuroimaging was more common in placebo recipients (16.6%, vs 12.3% in abciximab recipients). Although the trial was not powered for efficacy, analysis of functional outcomes at 3 months showed that significantly more abciximab recipients than placebo recipients achieved a modified Rankin score of 0 or 1 (53.9% vs 34.6%; \( P = .013 \)).

On the basis of these data, the pivotal trial, AbESTT 2, will enroll patients with acute ischemic stroke of less than 5 hours' duration.

**REFERENCES**

Abstracts/Poster Presentations

ABSTRACT 1
HYponatremia-Related Focal Cerebral Edema, A Mimic of Worsening Cerebral Edema Due to Intracerebral Hemorrhage

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Background. In the natural course of intracranial hematoma resolution, mass effect and edema peak at 4 to 5 days, after which there is gradual resolution and resorption of blood products over several weeks. We report the case of a patient with intracranial hemorrhage whose mass effect became worse 21 days after onset. Subsequent contrast-enhanced CT did not confirm initial suspicion of an underlying structural lesion. The persistent focal edema was related to diuretic-induced hyponatremia.

Case report. A 73-year-old right-handed woman presented with headache, dysarthria, and left-sided weakness. She was hypertensive on admission. She was not taking antithrombotic medication, and there was no history of preceding trauma. Examination revealed an NIH Stroke Scale score of 13. Brain CT showed a right frontoparietal hematoma. Following an initial improvement, her neurologic condition deteriorated 21 days after admission.

Discussion. Hyponatremia causes cerebral edema by transfer of water into brain cells across an osmolar gradient. Neurologic symptoms are more likely if this occurs acutely. While the edema usually is generalized, it may be focal in the setting of an underlying acute structural lesion. The pathogenesis, diagnosis, and management of hyponatremia in the neurologic intensive care unit is reviewed.

Conclusion. Hyponatremia, especially in the elderly, is prevalent in the neurologic intensive care unit and is a predictor of mortality and morbidity. Acute hyponatremia may cause focal cerebral edema that may alter the natural course of the underlying disease process and complicate the diagnosis. Care must be taken to prevent hyponatremia in at-risk groups, and to manage existing hyponatremia promptly.

ABSTRACT 2
Suboccipital Craniectomy for Acute Cerebellar Ischemic Stroke


Introduction. Suboccipital craniectomy may benefit patients with large cerebellar stroke. Patient selection and timing of surgery remain controversial. We sought to determine if surgery could improve clinical outcomes after stroke.

Methods. We performed a chart review of patients admitted with acute cerebellar infarction from May 1998 to July 2002 who underwent suboccipital craniectomy. Four patients were identified. Their presentation, CT findings, time to surgery, postoperative condition, and disposition were evaluated.

Results. Patient ages were 25, 50, 68, and 70 years. All patients had large cerebellar stroke with obstructive hydrocephalus. One patient had clinical signs of brainstem compression with nonreactive pupils; the other three had intact brainstem reflexes. Neurologic deterioration occurred in all four patients within 2 days. The mean time to surgery after stroke was 2.5 ± 1.7 days. All patients underwent posterior fossa craniectomy with duroplasty and ventriculostomy. Indications for surgery were clinical deterioration with CT signs of brainstem compression. Three of the four patients had substantial improvement on their neurologic exam following surgery (initial NIH Stroke Scale [NIHSS] score of 13 ± 8 vs postoperative NIHSS score of 4 ± 3; P = .13). The fourth patient (aged 70 years) initially presented comatose with unreactive pupils and remained unchanged postoperatively, after which the family withdrew support. Of the remaining three patients, two were discharged home and one to an acute rehabilitation facility.

Conclusion. Patients with neurologic deterioration after acute cerebellar stroke and findings of brainstem compression may benefit from suboccipital craniectomy. Patients with early signs of brainstem compromise may have poorer outcomes. Specific criteria are needed for the selection of patients who might benefit from this procedure.

ABSTRACT 3
The Feasibility and Safety of Mild Brain Hypothermia Obtained by Local Surface Cooling in Acute Stroke

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Background. Hypothermia is known to protect the brain from ischemic injury. However, systemic surface cooling is associated with various adverse effects that can heavily burden stroke patients, most of whom are elderly. The purpose of this study is to test the feasibility, safety, and effectiveness of local surface cooling as a tool for acute stroke therapy.

Methods. Nine patients with acute embolic stroke and
NIH Stroke Scale scores exceeding 10 (mean age, 65 years) were subjected to local surface cooling 3 to 12 hours after stroke onset. A helmet-type apparatus was attached to the head and neck of patients, and cooling was continued for 3 to 7 days without anesthesia. Temperatures were measured at the axilla, bladder, tympanic membrane, and internal jugular bulb.

Results. Surface cooling was performed successfully in all patients. During the surface cooling, the axillary and bladder temperatures remained unchanged while the tympanic and jugular bulb temperatures were reduced by 1.8 and 0.8 °C, respectively, as compared with the axillary temperature. None of the patients experienced serious adverse effects, although serum CPK levels rose in all patients as a result of mild shivering, and skin erosion and infections occurred in 2 and 3 patients, respectively.

Conclusion. Mild brain hypothermia can be achieved feasibly and safely by local surface cooling. While the neuroprotective effect of local cooling may be less powerful than that of systemic cooling, local cooling may be clinically more useful because of its safety and feasibility.

**ABSTRACT 4**

**THE DIVERTER, A NOVEL PERMANENT ARTERIAL DIVERSION DEVICE**

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Purpose. A novel permanent filtering device (the Diverter™, MindGuard Ltd.), indicated for the prevention of embolic stroke in high-risk patients with proximal sources of embolism, was tested for safety and performance. Self-expandable Diverter endovascular prostheses are intended for bilateral implantation in the two carotid bifurcations from the external carotid artery (ECA) to the common carotid artery, by means of a standard percutaneous endovascular procedure. The part of the Diverter facing the internal carotid artery (ICA) orifice is designed to prevent embolic material from entering the ICA, diverting it to the ECA.

Methods. Sixteen Diverter devices were percutaneously implanted in the swine iliofemoral bifurcation. Harvesting was performed at 3, 10, and 17 weeks after implantation. The patency of the Diverter-guarded orifice was calculated by morphometrical software. For an additional 10 implanted Diversers, animals were injected with bromodeoxyuridine (BrdU; 40 mg/kg). Immunohistolabeling was performed and the tissue proliferation rate at the filtering part was assessed.

Results. No discernable stenosis was noted. Microscopy and morphometry showed 99.0%±1.0%, 91.8%±10.6%, and 93.3%±8.8% filtering area patency at 3, 10, and 17 weeks, respectively. The percentage of BrdU-stained cells, which corresponds to proliferation rate, was 18.7±7.3%, 12.8%±4.6%, and 0.7%±0.6% after 1, 3, and 24 weeks, respectively. Proliferation thus reaches steady state within 6 months.

Conclusion. Permanent embolic filtration with the Diverter device is feasible and safe in the animal model.
and ocular signs in 1 patient. Behavioral and cognitive changes were seen in 40% of the patients, with aggression and confabulation in 2 patients (10%), speech and language disturbances in 4 patients (20%), and memory disturbance in 2 patients (10%).

Conclusion. Among thalamic stroke patients, 80% showed motor signs and 40% showed behavioral and cognitive changes. Behavioral and cognitive changes were not seen alone.

**ABSTRACT 7**

REVERSAL OF LOCKED-IN SYNDROME WITH ANTICOAGULATION, INDUCED HYPERTENSION, AND INTRAVENOUS t-PA

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Background. Spontaneous cervical artery dissection accounts for 10% to 25% of ischemic strokes in young and middle-aged patients. Anticoagulation with intravenous heparin is the currently recommended treatment for acute dissection, although the validity of this therapy has never been proven in randomized clinical trials. Acute management of posterior circulation ischemia, including anticoagulation, induction of hypertension, Trendelenburg positioning, and intravenous and intra-arterial thrombolysis, is a frequently debated area and still requires standardization.

Case report. We describe the case of a 39-year-old man who developed recurrent pontine ischemia due to right vertebral artery dissection producing a locked-in state that resolved with the combination of anticoagulation, Trendelenburg positioning, induced hypertension, and intravenous t-PA. None of the treatment modalities applied to our patient have been demonstrated to be safe and effective in the setting of arterial dissection. In fact, administration of intravenous t-PA outside the 3-hour window and in addition to anticoagulation with intravenous heparin and induction of hypertension (systolic blood pressure > 185 mm Hg) was contraindicated. In this scenario, the benefits outweighed the tremendous risk of hemorrhage: the patient recovered almost completely with a residual minimal left abducens palsy 2 weeks after symptom onset.

Conclusion. Good outcome can be achieved with the use of intravenous thrombolysis in combination with anticoagulation, induced hypertension, and Trendelenburg positioning in severe posterior circulation ischemia due to vertebral dissection.

**ABSTRACT 8**

DANTROLENE REDUCES THE THRESHOLD AND GAIN FOR SHIVERING

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Background. How dantrolene alters thermoregulatory control remains unknown. We aimed to determine whether dantrolene alters the thresholds for sweating, vasoconstriction, and shivering, or the gain of shivering.

Methods. Study 1—Nine volunteers (mean age, 25 ± 4 years; mean height, 172 ± 9 cm; mean weight, 66 ± 11 kg) were randomly assigned to control or dantrolene. On dantrolene day, they received 5 mg/kg/hr dantrolene for 30 minutes and 0.05 mg/kg/hr for 5 hours. Skin and core temperatures were increased with forced-air and circulating-water blankets to provoke sweating and were subsequently reduced to elicit vasoconstriction and shivering. Study 2—Seven healthy male volunteers (mean age, 27 ± 7 years; mean height, 178 ± 10 cm; mean weight, 72 ± 10 kg) were given cold (3 °C) Ringer’s solution intravenously on randomly assigned control or dantrolene days. On dantrolene day, they received 5 mg/kg/hr dantrolene for 30 minutes and 0.05 mg/kg/hr for 5 hours. Cooling was started 1 hour after dantrolene. A sustained increase in oxygen consumption identified the shivering threshold. The slope of a regression between core temperature and oxygen consumption identified shivering gain. Results are presented as mean ± SD; P < .05 is the threshold for statistical significance.

Results. Confounding factors were comparable between the study days. Dantrolene did not alter the sweating or vasoconstriction thresholds, but it reduced the shivering threshold by 0.3 ± 0.3 °C and increased the vasoconstriction-to-shivering range to 1.2 ± 0.2 °C. In study 2, dantrolene reduced the shivering threshold by 0.4 ± 0.3 °C and the gain of shivering by 130 ± 154 mL/min °C.

Conclusion. Although dantrolene reduced the threshold and gain of shivering, reductions were small and unlikely to explain the reported efficacy of this drug for treatment of potentially lethal nonspecific hyperthermia.

**ABSTRACT 9**

PREDICTING OUTCOME AFTER SUBARACHNOID HEMORRHAGE: COMPARISON OF DIFFERENT GRADING SYSTEMS

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Introduction. Predicting outcome after aneurysmal subarachnoid hemorrhage (SAH) is often difficult. Common grading systems include the Hunt-Hess Scale, Fisher grade, and Glasgow Coma Scale. Recently, a new 5-point scale was developed that includes patient age, aneurysm size, Hunt-Hess score, Fisher grade, and size and location of aneurysm (Ogilvy score). We previously demonstrated that the NIH Stroke Scale (NIHSS) score, originally developed for ischemic stroke, is also predictive of outcome after intracerebral hemorrhage. The NIHSS score has not been studied in SAH. In a retrospective study of 76 SAH patients, we tried to determine which grading system best predicted outcome.

Methods. A retrospective analysis of 76 patients with aneurysmal SAH admitted to the neurologic intensive care unit between January 2000 and July 2002 was conducted documenting demographic data, aneurysm size, and admis-
sion Hunt-Hess score, Fisher grade, Glasgow Coma Scale score, Ogilvy score, and NIHSS score. Outcomes data included Glasgow Outcome Score (GOS), modified Rankin scale score, and Functional Independence Score on discharge (dichotomized as good or poor outcome). Spearman correlation coefficient and logistic regression were used to assess relationships.

Results. The average patient age was 55.3 ± 14.2 years. On admission, the mean Hunt-Hess score was 2.6 ± 1.3, the mean Fisher grade was 2.8 ± 1.1, the mean Glasgow Coma Scale score was 11.8 ± 4.1, and the mean Ogilvy score was 1.8 ± 1.2. The mean NIHSS score was 7.4 ± 10.0. Overall, the mortality rate was 18%. A good outcome occurred in 42 patients (55.2%). Using the Spearman correlation coefficient, the following correlations were found with discharge GOS (from best to worst correlation):

- NIHSS score, –0.531 (95% CI, –0.73 to –0.34; P < .001)
- Hunt-Hess score, –0.523 (95% CI, –0.72 to –0.33; P < .001)
- Ogilvy score, –0.431 (95% CI, –0.64 to –0.10; P < .001)
- Fisher grade, –0.319 (95% CI, –0.54 to –0.10; P < .001).

In a subgroup of 42 patients with cerebral vasospasm, the following correlations were found:

- NIHSS score, –0.383 (95% CI, –0.68 to –0.09; P = .012)
- Ogilvy score, –0.336 (95% CI, –0.64 to –0.03; P = .03)
- Fisher grade, –0.320 (95% CI, –0.64 to –0.03; P = .039)
- Hunt-Hess score, –0.306 (95% CI, –0.61 to –0.02; P = .039).

Conclusion. The admission NIHSS score is predictive of outcome following SAH and is at least as good as, if not better than, other more commonly used grading systems. The Ogilvy score is also predictive of outcome but statistically is not significantly better than the Hunt-Hess score or Fisher grade alone. Larger studies are needed to determine the scale that best predicts outcome.

ABSTRACT 10
INTEGRATIVE MONITORING METHODS IN NEUROCRITICAL CARE
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Introduction. Neurocritical care is a relatively new field of medicine focusing on the management of critically ill patients with neurologic disease. One of the main functions of the neurologic intensive care unit (NICU) is to provide close monitoring of neurologic status. Most NICUs are equipped with a large range of sophisticated monitoring equipment that generates enormous volumes of information, mainly about cardiopulmonary status. Surprisingly, the central nervous system is largely neglected, even in patients with severe neurologic injuries in whom sedation and mechanical ventilation make clinical examination difficult. This leaves the neurointensivist with much cardiopulmonary data that is nearly impossible to interpret and analyze online, and with insufficient neurologic data. Despite advances in computer technology, an ideal bedside neuromonitoring system that collects, organizes, analyzes, and trends both cardiopulmonary and neurologic data is not available.

Design. At The Cleveland Clinic Foundation, we have developed a new monitoring system for the NICU that integrates cardiopulmonary monitoring modalities (blood pressure, heart rate, respiratory rate, oxygen saturation) and neuromonitoring modalities (intracranial pressure, cerebral perfusion pressure, brain tissue oxygenation, continuous EEG, and evoked potentials) into one bedside monitor. These parameters are transferred through an interface from the standard bedside Marquette monitors to a central workstation where the system extracts salient features from the raw waveforms, analyzes them, and displays them on the screen. Annotations that may affect the integrity of test results (for example, patient movement, suctioning, increasing or dosage of sedatives) can also be entered, and the system can be tailored to meet a particular patient’s needs. The system can be programmed to page the clinician when a potential problem is detected and to transmit the data over a hospital network.

Conclusion. The data acquisition and analysis offered by this system can provide a meaningful overall assessment of a patient’s condition and may give an early indication of potentially harmful secondary insults before irreversible brain damage occurs. We believe this approach of integrating multiple physiologic parameters into one user-friendly system that collects, organizes, analyzes, and trends data will revolutionize the delivery of neurocritical care.