Management of Intracranial Hypertension

Leonardo Rangel-Castillo, MD\textsuperscript{a},
Shankar Gopinath, MD\textsuperscript{b},
Claudia S. Robertson, MD\textsuperscript{b,*}

\textsuperscript{a}Department of Neurosurgery, University of Texas Medical Branch, Galveston, TX, USA
\textsuperscript{b}Department of Neurosurgery, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

Intracranial hypertension is a common neurologic complication in critically ill patients; it is the common pathway in the presentation of many neurologic and nonneurologic disorders. The underlying pathophysiology of increased intracranial pressure (ICP) is the subject of intense basic and clinical research, which has led to advances in understanding the physiology related to ICP. Few specific treatment options for intracranial hypertension have been subjected to randomized trials, however, and most management recommendations are based on clinical experience.

Intracranial pressure

Normal values

In normal individuals with closed cranial fontanelles, the central nervous system contents, including the brain, spinal cord, blood, and cerebrospinal fluid (CSF), are encased in a noncompliant skull and vertebral canal, constituting a nearly incompressible system. The system has a small amount of capacitance provided by the intervertebral spaces. In the average adult, the skull encloses a total volume of 1475 mL, including 1300 mL of brain, 65 mL of CSF, and 110 mL of blood [1]. The Monroe-Kellie hypothesis states that the sum of the intracranial volumes of blood, brain, CSF, and

This article was supported by National Institutes of Health grant P01-NS38660.
This is an updated version of an article that originally appeared in \textit{Critical Care Clinics}, volume 22, issue 4.
* Corresponding author.
\textit{E-mail address: claudiar@bcm.tmc.edu} (C.S. Robertson).
other components is constant, and that an increase in any one of these must be offset by an equal decrease in another, or else pressure increases. An increase in pressure caused by an expanding intracranial volume is distributed evenly throughout the intracranial cavity [2,3].

The normal range for ICP varies with age. Values for pediatric patients are not as well established. Normal values are less than 10 to 15 mm Hg for adults and older children, 3 to 7 mm Hg for young children, and 1.5 to 6 mm Hg for term infants. ICP can be subatmospheric in newborns [4]. For the purpose of this article, normal adult ICP is defined as 5 to 15 mm Hg (7.5–20 cm H 2O). ICP values of 20 to 30 mm Hg represent mild intracranial hypertension; however, when a temporal mass lesion is present, herniation can occur with ICP values of less than 20 mm Hg [5]. In most circumstances, ICP values of greater than 20 to 25 mm Hg require treatment. Sustained ICP values of greater than 40 mm Hg indicate severe, life-threatening intracranial hypertension.

Cerebral dynamics overview

Cerebral perfusion pressure (CPP) depends on mean systemic arterial pressure (MAP) and ICP, as defined by the following relationship:

\[
CPP = \frac{MAP}{C_0} - ICP
\]

As a result, CPP can be reduced by an increase in ICP, a decrease in blood pressure, or a combination of both factors. Through the normal regulatory process called pressure autoregulation, the brain is able to maintain a normal cerebral blood flow (CBF) with a CPP ranging from 50 to 150 mm Hg. At CPP values of less than 50 mm Hg, the brain may not be able to compensate adequately, and CBF falls passively with CPP. After injury, the ability of the brain to pressure autoregulate may be absent or impaired and, even with a normal CPP, CBF can passively follow changes in CPP.

When CPP is within the normal autoregulatory range (50–150 mm Hg), this ability of the brain to pressure autoregulate also affects the response of ICP to a change in CPP [6–8]. When pressure autoregulation is intact, decreasing CPP results in vasodilation of cerebral vessels, which allows CBF to remain unchanged. This vasodilation can result in an increase in ICP, which further perpetuates the decrease in CPP. This response has been called the vasodilatory cascade. Likewise, an increase in CPP results in vasoconstriction of cerebral vessels and may reduce ICP. When pressure autoregulation is impaired or absent, ICP decreases and increases with changes in CPP.

Intracranial hypertension

Causes of intracranial hypertension

The different causes of intracranial hypertension (Box 1) can occur individually or in various combinations. In primary causes of increased ICP, its
Intracranial hypertension secondary to traumatic brain injury

Special features should be considered in patients who have traumatic brain injury (TBI), in which lesions may be heterogeneous, and several factors often contribute to increase the ICP [12]:

- Traumatically induced masses: epidural or subdural hematomas, hemorrhagic contusions, foreign body, and depressed skull fractures
- Cerebral edemas [13]
- Hyperemia owing to vasomotor paralysis or loss of autoregulation [14]
Hypoventilation that leads to hypercarbia with subsequent cerebral vasodilation

Hydrocephalus resulting from obstruction of the CSF pathways or its absorption

Increased intrathoracic or intra-abdominal pressure as a result of mechanical ventilation, posturing, agitation, or Valsalva’s maneuvers

After evacuation of traumatic mass lesions, the most important cause of increased ICP was thought to be vascular engorgement [14]. Recent studies have suggested that cerebral edema is the primary cause in most cases [15].

A secondary increase in the ICP is often observed 3 to 10 days after the trauma, principally as a result of a delayed hematoma formation, such as epidural hematomas, acute subdural hematomas, and traumatic hemorrhagic contusions with surrounding edema, sometimes requiring evacuation [16]. Other potential causes of delayed increases in ICP are cerebral vasospasm [17], hypoventilation, and hyponatremia.

**Neurologic intensive care monitoring**

Intracranial hypertension is an important cause of secondary injury in patients who have acute neurologic and neurosurgical disorders and typically mandates specific monitoring. Patients who have suspected intracranial hypertension, especially secondary to TBI, should have monitoring of ICP; monitoring of cerebral oxygen extraction, as with jugular bulb oximetry or brain tissue PO2, may also be indicated. Brain-injured patients should also have close monitoring of systemic parameters, including ventilation, oxygenation, electrocardiogram, heart rate, blood pressure, temperature, blood glucose, and fluid intake and output. Patients should be monitored routinely with pulse oximetry and capnography to avoid unrecognized hypoxemia and hypoventilation or hyperventilation. A central venous catheter is commonly needed to help evaluate volume status, and a Foley catheter is used for accurate urine output.

**Intracranial pressure monitoring**

Clinical symptoms of increased ICP, such as headache, nausea, and vomiting, are impossible to elicit in comatose patients. Papilledema is a reliable sign of intracranial hypertension, but is uncommon after head injury, even in patients who have documented elevated ICP. In a study of patients who had head trauma, 54% of patients had increased ICP, but only 3.5% had papilledema on fundoscopic examination [18]. Other signs, such as pupillary dilation and decerebrate posturing, can occur in the absence of intracranial hypertension. CT scan signs of brain swelling, such as midline shift and compressed basal cisterns, are predictive of increased ICP, but intracranial hypertension can occur without these findings [19].
Types of monitors

The ventriculostomy catheter is the preferred device for monitoring ICP and the standard against which all newer monitors are compared [20]. An intraventricular catheter is connected to an external pressure transducer by way of fluid-filled tubing. The advantages of the ventriculostomy are its low cost, the option to use it for therapeutic CSF drainage, and its ability to recalibrate to minimize errors owing to measurement drift. The disadvantages are difficulties with insertion into compressed or displaced ventricles, inaccuracies of the pressure measurements because of obstruction of the fluid column, and the need to maintain the transducer at a fixed reference point relative to the patient’s head. The system should be checked for proper functioning at least every 2 to 4 hours, and with any change in the ICP, neurologic examination, or CSF output. This check should include assessing for the presence of an adequate waveform, which should have respiratory variations and transmitted pulse pressure.

When the ventricle cannot be cannulated, alternatives can be used. Different non–fluid-coupled devices are available for ICP monitoring and have replaced the subarachnoid bolt. The microsensor transducer and the fiber optic transducer are the most widely available. These transducer-tipped catheters can be inserted into the subdural space or directly into the brain tissue [21]. The main advantages of these monitors is the ease of insertion, especially in patients who have compressed ventricles; however, none of the transducer-tipped catheters can be reset to zero after they are inserted into the skull, and they exhibit measurement drift over time [22]. Subdural and epidural monitors for ICP measurements are less accurate, when compared with ventriculostomy or parenchymal monitors.

For surgical patients, the ICP monitor may be inserted at the end of the surgical procedure. ICP monitoring is continued for as long as treatment of intracranial hypertension is required, typically 3 to 5 days. A secondary increase in ICP may be observed 3 to 10 days after trauma in 30% of patients who have intracranial hypertension [16] secondary to development of delayed intracerebral hematoma, cerebral vasospasm, or systemic factors such as hypoxia and hypotension.

Types of intracranial pressure waveforms

The variations seen in the normal tracing of ICP originate from small pulsations transmitted from the systemic blood pressure to the intracranial cavity. These blood pressure pulsations are superimposed on slower oscillation caused by the respiratory cycle. In mechanically ventilated patients, the pressure in the superior vena cava increases during inspiration, which reduces venous outflow from the cranium, causing an elevation in ICP.
Pathologic waveforms

As the ICP increases, cerebral compliance decreases, arterial pulses become more pronounced, and venous components disappear. Pathologic waveforms include Lundberg A, B, and C types. Lundberg A waves, or plateau waves, are ICP elevations to more than 50 mm Hg lasting 5 to 20 minutes. These waves are accompanied by a simultaneous increase in MAP, but it is not clearly understood if the change in MAP is a cause or effect. Lundberg B waves, or pressure pulses, have an amplitude of 50 mm Hg and occur every 30 seconds to 2 minutes. Lundberg C waves have an amplitude of 20 mm Hg and a frequency of 4 to 8 per minute; they are seen in the normal ICP waveform, but high-amplitude C waves may be superimposed on plateau waves [23].

Indications for intracranial pressure monitoring

Monitoring of ICP is an invasive technique and has some associated risks. For a favorable risk-to-benefit ratio, ICP monitoring is indicated only in patients who have significant risk for intracranial hypertension (Box 2) [12]. Patients who have TBI and are particularly at risk for developing an elevated ICP include those with Glasgow Coma Scale of 8 or less after cardiopulmonary resuscitation and those who have an abnormal admission head CT scan. Such abnormalities might include low-density or high-density lesions, including contusions; epidural, subdural, or intraparenchymal hematomas; compression of basal cisterns; and edema [24]. Patients who are able to follow commands have a low risk for developing intracranial hypertension, and serial neurologic examinations can be followed.

Although CT scan findings are not accurate in determining the actual ICP, the risk for developing intracranial hypertension can be predicted. Sixty percent of patients who have a closed head injury and an abnormal CT scan have intracranial hypertension. Only 13% of patients who have

<table>
<thead>
<tr>
<th>Box 2. Indications for intracranial pressure monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glasgow Coma Scale score: 3–8 (after resuscitation)</strong></td>
</tr>
<tr>
<td>1. Abnormal admission head CT scan</td>
</tr>
<tr>
<td>a. Hematoma</td>
</tr>
<tr>
<td>b. Contusion</td>
</tr>
<tr>
<td>c. Edema</td>
</tr>
<tr>
<td>d. Herniation</td>
</tr>
<tr>
<td>e. Compressed basal cistern</td>
</tr>
<tr>
<td>2. Normal admission head CT scan plus two or more of the following</td>
</tr>
<tr>
<td>a. Age older than 40</td>
</tr>
<tr>
<td>b. Motor posturing</td>
</tr>
<tr>
<td>c. Systolic blood pressure less than 90 mm Hg</td>
</tr>
</tbody>
</table>
a normal CT scan have elevated ICP, except for patients who have certain risk factors, including age more than 40 years old, systolic blood pressure less than 90 mm Hg, and decerebrate or decorticate posturing on motor examination. Patients who have a normal CT scan have a 60% risk for intracranial hypertension if they have two risk factors and 4% if they have only one risk factor. Patients who have a Glasgow Coma Scale score greater than 8 might also be considered for ICP monitoring if they require treatment that would not allow serial neurologic examinations, such as prolonged anesthesia for surgery of multiple injuries or prolonged pharmacologic paralysis for ventilatory management, or if they require a treatment that might increase ICP, such as positive end-expiratory pressure (PEEP). Other, less common, indications include patients who have multiple systemic injuries with an altered level of consciousness and subsequent to removal of an intracranial mass (eg, hematoma, tumor) [12]. ICP monitoring must also be considered in nontraumatic conditions in which an intracranial mass lesion is present (eg, cerebral infarction, spontaneous intracerebral hemorrhage) and has a likelihood of expansion leading to intracranial hypertension and clinical deterioration. Monitoring lasts until ICP has been normal for 24 to 48 hours without ICP therapy.

Complications of intracranial pressure monitoring

The most common complication of ventriculostomy catheter placement is infection, with an incidence of 5% to 14%; colonization of the device is more common than clinical infection [25]. A study found no significant reduction in infection rate in patients undergoing prophylactic change of monitors before day 5, compared with those whose catheters were in place for 5 days or more [26]. Factors that are not associated with infection are insertion of the catheter in the neurologic ICU, previous catheter insertion, drainage of CSF, and use of steroids. In a group of patients who had prolonged ventricular drainage of 10 days or more, a nonlinear increase in daily infection rate was observed over the initial 4 days but remained constant, despite prolonged catheter use [27]. Use of antibiotic-coated ventriculostomy catheters has been shown to reduce the risk for infection from 9.4% to 1.3% [28]. Other complications of ventriculostomy catheters are hemorrhage (with an overall incidence of 1.4%), malfunction, obstruction, and malposition.

Intracranial pressure treatment measures: brief summary of goals of therapy

The goals of ICP treatment may be summarized as follows:

1. Maintain ICP at less than 20 to 25 mm Hg.
2. Maintain CPP at greater than 60 mm Hg by maintaining adequate MAP.
3. Avoid factors that aggravate or precipitate elevated ICP.
An overall approach to the management of intracranial hypertension is presented in Fig. 1.

**General care to minimize intracranial hypertension**

Prevention or treatment of factors that may aggravate or precipitate intracranial hypertension is a cornerstone of neurologic critical care. Specific factors that may aggravate intracranial hypertension include obstruction of venous return (head position, agitation), respiratory problems (airway obstruction, hypoxia, hypercapnia), fever, severe hypertension, hyponatremia, anemia, and seizures.

**Optimizing cerebral venous outflow**

To minimize venous outflow resistance and promote displacement of CSF from the intracranial compartment to the spinal compartment,
elevating the head of the bed and keeping the head in a neutral position are standards in neurosurgical care. Some investigators have advocated keeping the patient’s head flat to maximize CPP [7]. Other studies have shown a reduction in ICP without a reduction in either CPP or CBF in most patients with elevation of the head to 30° [29]. Still other investigators have observed that elevation of the head to 30° reduced ICP and increased CPP, but did not change brain tissue oxygenation [30]. The reduction in ICP afforded by 15° to 30° of head elevation is probably advantageous and safe for most patients. When head elevation is used, the pressure transducers for blood pressure and ICP must be zeroed at the same level (at the level of the foramen of Monro) to assess CPP accurately.

Increased intra-abdominal pressure, as can occur with abdominal compartment syndrome, can also exacerbate ICP, presumably by obstructing cerebral venous outflow. Several case reports have observed immediate reductions in ICP with decompressive laparotomy in such circumstances. A retrospective report indicated that, even when abdominal compartment syndrome is not present, abdominal fascial release can effectively reduce ICP that is refractory to medical treatment [31].

Respiratory failure

Respiratory dysfunction is common in patients who have intracranial hypertension, especially when the cause is head trauma. Hypoxia and hypercapnia can increase ICP dramatically, and mechanical ventilation can alter cerebral hemodynamics. Optimal respiratory management is crucial for control of ICP.

Thirty-six percent of comatose head injury patients present with hypoxia and respiratory dysfunction requiring mechanical ventilation on admission. Pneumonia and pulmonary insufficiency occur in 42% and 28%, respectively, as complications during hospitalization. In 227 spontaneously breathing patients who had neurologic disorders, mostly intracranial hypertension, North and Jennett [32] found that 60% had breathing abnormalities, including periodic respirations, tachypnea, and irregular breathing. Periodic breathing was not correlated, however, with any particular anatomic site of the neurologic injury. Periodic episodes of hypoventilation can precipitate increased ICP [33]. Controlled ventilation to maintain a normal PaCO₂ can eliminate this cause of intracranial hypertension.

Mechanical ventilation can also have adverse effects on ICP. PEEP, which may be needed to improve oxygenation, can increase ICP by impeding venous return and increasing cerebral venous pressure and ICP, and by decreasing blood pressure, leading to a reflex increase of cerebral blood volume. For PEEP to increase cerebral venous pressure to levels that would increase ICP, the cerebral venous pressure must at least equal the ICP. The higher the ICP, the higher the PEEP must be to have such a direct hydraulic effect on ICP. The consequences of PEEP on ICP also depend on
lung compliance, and minimal consequences for ICP are usually observed when lung compliance is low, as in patients who have acute lung injury [34].

**Sedation and analgesia**

Agitation and pain may significantly increase blood pressure and ICP. Adequate sedation and analgesia are an important adjunctive treatment. No sedative regimen has clear advantages in this patient population. In general, benzodiazepines cause a coupled reduction in cerebral metabolic rate of oxygen (CMRO₂) and CBF, with no effect on ICP, whereas the narcotics have no effect on CMRO₂ or CBF, but have been reported to increase ICP in some patients [35]. One consideration in the choice of sedative should be to minimize effects on blood pressure because most available agents can decrease blood pressure. Hypovolemia predisposes to hypotensive side effects and should be treated before administering sedative agents. Selection of shorter-acting agents may have the advantage of allowing a brief interruption of sedation to evaluate neurologic status.

**Fever**

Fever increases metabolic rate by 10% to 13% per °C and is a potent vasodilator. Fever-induced dilation of cerebral vessels can increase CBF and may increase ICP. Fever during the postinjury period worsens neurologic injury in experimental models of TBI [36]. In an observational study in patients who had TBI, Jones and colleagues [37] found a significant relationship between fever and a poor neurologic outcome. Although a patient is at risk for intracranial hypertension, fever should be controlled with antipyretics and cooling blankets. Infectious causes must be sought and treated with appropriate antibiotics when present.

**Hypertension**

Elevated blood pressure is seen commonly in patients who have intracranial hypertension, especially secondary to head injury, and is characterized by a systolic blood pressure increase greater than diastolic increase. It is associated with sympathetic hyperactivity [38]. It is unwise to reduce systemic blood pressure in patients who have hypertension associated with untreated intracranial mass lesions because cerebral perfusion is being maintained by the higher blood pressure. In the absence of an intracranial mass lesion, the decision to treat systemic hypertension is more controversial and may need to be individualized for each patient.

When pressure autoregulation is impaired, which is common after TBI, systemic hypertension may increase CBF and ICP. In addition, elevated blood pressure may exacerbate cerebral edema and increase the risk for postoperative intracranial hemorrhage.
Systemic hypertension may resolve with sedation. If the decision is made to treat systemic hypertension, the choice of antihypertensive agent is important. Vasodilating drugs, such as nitroprusside, nitroglycerin, and nifedipine, can be expected to increase ICP and may reflexively increase plasma catecholamines, which may be deleterious to the marginally perfused injured brain. Sympathomimetic-blocking antihypertensive drugs, such as β-blocking drugs (labetalol, esmolol) or central acting α-receptor agonists (clonidine), are preferred because they reduce blood pressure without affecting the ICP. Agents with a short half-life have an advantage when the blood pressure is labile.

*Treatment of anemia*

Anecdotal cases have been reported of patients who have severe anemia presenting with symptoms of increased ICP and signs of papilledema, which resolve with treatment of the anemia [39]. The mechanism is thought to be related to the marked increase in CBF that is required to maintain cerebral oxygen delivery when anemia is severe. Although anemia has not been clearly shown to exacerbate ICP after TBI, a common practice is to maintain hemoglobin concentration at a minimum of 10 g/dL. In view of a large randomized trial of critically ill patients that showed better outcome with a more restrictive transfusion threshold of 7 g/dL [40], the issue of optimal hemoglobin concentration in patients who have TBI needs further study.

*Prevention of seizures*

The risk for seizures after trauma is related to the severity of the brain injury; seizures occur in 15% to 20% of patients who have severe head injury. Seizures can increase cerebral metabolic rate and ICP, but no clear relationship exists between the occurrence of early seizures and a worse neurologic outcome [41]. In patients who have severe TBI, 50% of seizures may be subclinical and can be detected only with continuous electroencephalographic monitoring [42]. Significant risk factors for later seizures are brain contusion, subdural hematoma, depressed skull fracture, penetrating head wound, loss of consciousness or amnesia for more than 1 day, and age 65 years or older.

In a randomized clinical trial, phenytoin reduced the incidence of seizures during the first week after trauma, but not thereafter [43]. Based on this study, seizure prophylaxis for patients who have severe brain injury is recommended for the first 7 days after injury. Treatment with anticonvulsants beyond 7 days should be reserved for patients who develop late seizures [44].

*Measures for refractory intracranial hypertension*

For patients who have sustained ICP elevations of greater than 20 to 25 mm Hg, additional measures are needed to control the ICP. Emergent
surgical management should be considered whenever intracranial hypertension occurs suddenly or is refractory to medical management.

**Medical interventions**

*Heavy sedation and paralysis*

Routine paralysis of patients who have neurosurgical disorders is not indicated; however, intracranial hypertension caused by agitation, posturing, or coughing can be prevented by sedation and nondepolarizing muscle relaxants that do not alter cerebrovascular resistance [45]. A commonly used regimen is morphine and lorazepam for analgesia/sedation and cisatracurium or vecuronium as a muscle relaxant, with the dose titrated by twitch response to stimulation. A disadvantage of this therapy is that the neurologic examination cannot be monitored closely; however, the sedatives and muscle relaxants can be interrupted once a day, usually before morning rounds, to allow neurologic assessments.

Major complications of neuromuscular blockade are myopathy, polyneuropathy, and prolonged neuromuscular blockade. Myopathy is associated with the use of neuromuscular blocking agents, particularly in combination with corticosteroids [46]. Polyneuropathy has been observed in patients who have sepsis and multiple organ failure. Prolonged neuromuscular blockade is seen in patients who have multiple organ failure, especially with kidney and liver dysfunction. Recommendations to minimize these complications include limiting the use and dose of neuromuscular blocking agents, train-of-four monitoring, measuring creatine phosphokinase daily, and stopping the drug daily to evaluate motor response [47].

*Hyperosmolar therapy*

Mannitol is the most commonly used hyperosmolar agent for the treatment of intracranial hypertension. More recently, hypertonic saline also has been used in this circumstance. A few studies have compared the relative effectiveness of these two hyperosmotic agents, but more work is needed.

Intravenous bolus administration of mannitol lowers the ICP in 1 to 5 minutes, with a peak effect at 20 to 60 minutes. The effect of mannitol on ICP lasts 1.5 to 6 hours, depending on the clinical condition [48]. Mannitol usually is given as a bolus of 0.25 g/kg to 1 g/kg body weight; when urgent reduction of ICP is needed, an initial dose of 1 g/kg body weight should be given. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided. Two prospective clinical trials, one in patients who had subdural hematoma and the other in patients who had herniated from diffuse brain swelling, have suggested that a higher dose of mannitol (1.4 g/kg) may give significantly better results in these extremely critical...
situations than lower doses of mannitol [49,50]. When long-term reduction of ICP is needed, 0.25 to 0.5 g/kg can be repeated every 2 to 6 hours. Attention should be paid to replacing fluid that is lost because of mannitol-induced diuresis, or intravascular volume depletion will result.

Mannitol has rheologic and osmotic effects. Infusion of mannitol is immediately followed by an expansion of plasma volume and a reduction in hematocrit and blood viscosity, which may increase CBF and, on balance, increase oxygen delivery to the brain. These rheologic effects of mannitol depend on the status of pressure autoregulation [51]. In patients who have intact pressure autoregulation, infusion of mannitol induces cerebral vasoconstriction, which maintains CBF constant, and the decrease in ICP is large. In patients who have no pressure autoregulation, infusion of mannitol increases CBF, and the decrease in ICP is less pronounced. Mannitol also may improve microcirculatory rheology [50] and has free radical scavenging effects.

The osmotic effect of mannitol increases serum tonicity, which draws edema fluid from cerebral parenchyma. This process takes 15 to 30 minutes, until gradients are established. Serum osmolarity seems to be optimal when increased to 300 to 320 mOsm and should be kept at less than 320 mOsm to avoid the side effects of therapy, such as hypovolemia, hyperosmolarity, and renal failure. Mannitol opens the blood–brain barrier, and mannitol that has crossed the blood–brain barrier may draw fluid into the central nervous system, which can aggravate vasogenic edema. For this reason, when it is time to stop mannitol, it should be tapered to prevent a rebound in cerebral edema and ICP. The adverse effects of mannitol are most likely when mannitol is present in the circulation for extended periods, such as in slow or continuous infusions or with repeated administration of higher than necessary doses.

Hypertonic saline, given in concentrations ranging from 3% to 23.4%, also creates an osmotic force to draw water from the interstitial space of the brain parenchyma into the intravascular compartment in the presence of an intact blood–brain barrier, reducing intracranial volume and ICP. In some studies, hypertonic saline has been more effective than mannitol in reducing ICP [52,53]. Hypertonic saline has a clear advantage over mannitol in hypovolemic and hypotensive patients. Mannitol is contraindicated in hypovolemic patients because of the diuretic effects, whereas hypertonic saline augments intravascular volume and may increase blood pressure, in addition to decreasing ICP. Hypertonic saline was not associated with improved neurologic outcomes, however, when given as a prehospital bolus to hypotensive patients who had severe TBI [54]. Adverse effects of hypertonic saline administration include hematologic and electrolyte abnormalities (such as bleeding secondary to decreased platelet aggregation and prolonged coagulation times), hypokalemia, and hyperchloremic acidosis [55]. Hyponatremia should be excluded before administering hypertonic saline, to reduce the risk for central pontine myelinolysis [56].
Hyperventilation

Hyperventilation decreases PaCO₂, which can induce constriction of cerebral arteries by alkalinizing the CSF. The resulting reduction in cerebral blood volume decreases ICP. Hyperventilation has limited use in the management of intracranial hypertension, however, because this effect on ICP is time limited, and because hyperventilation may produce a decrease in CBF sufficient to induce ischemia.

The vasoconstrictive effect on cerebral arterioles lasts only 11 to 20 hours because the pH of the CSF rapidly equilibrates to the new PaCO₂ level. As the CSF pH equilibrates, the cerebral arterioles redilate, possibly to a larger caliber than at baseline, and the initial reduction in cerebral blood volume comes at the cost of a possible rebound phase of increased ICP [57,58]. For this reason, the most effective use of hyperventilation is acutely, to allow time for other, more definitive treatments to be put into action. When hypocarbia is induced and maintained for several hours, it should be reversed slowly, over several days, to minimize this rebound hyperemia [59].

Hyperventilation decreases CBF, but whether this reduction in flow is sufficient to induce ischemia in the injured brain is controversial. One prospective study showed that acutely reducing PaCO₂ from an average of 36 mm Hg to 29 mm Hg reduced global CBF and significantly increased the volume of brain that was markedly hypoperfused despite improvements in ICP and CPP [60]. Diringer and coworkers [61] showed similar changes in CBF with moderate hyperventilation, but did not observe any changes in regional CMRO₂, even when CBF was reduced to less than 10 mL/100 g/min in injured brain tissue, suggesting that energy failure associated with cerebral ischemia was not occurring.

Although hyperventilation-induced ischemia has not been clearly shown, routine chronic hyperventilation (to PaCO₂ of 20–25 mm Hg) had a detrimental effect on outcome in one randomized clinical trial [59]. The investigators of this study recommended using hyperventilation only in patients who have intracranial hypertension, rather than as a routine in all head-injured patients. This view is reinforced in TBI guidelines.

Barbiturate coma

Barbiturate coma should only be considered for patients who have refractory intracranial hypertension because of the serious complications associated with high-dose barbiturates, and because the neurologic examination becomes unavailable for several days [62]. Pentobarbital is given in a loading dose of 10 mg/kg body weight followed by 5 mg/kg body weight each hour for three doses. The maintenance dose is 1 to 2 mg/kg/h, titrated to a serum level of 30 to 50 µg/mL or until the electroencephalogram shows a burst suppression pattern. Although routine use of barbiturates in unselected patients has not been consistently effective in reducing morbidity or mortality after severe head injury [63,64], a randomized multicenter trial showed
that instituting barbiturate coma in patients who had refractory intracranial hypertension resulted in a twofold greater chance of controlling the ICP [65].

The mechanism of ICP reduction by barbiturates is unclear but it likely reflects a coupled reduction in CBF and CMRO₂, with an immediate effect on ICP. Studies by Messeter and colleagues [66,67] have suggested that the reduction in ICP with barbiturates is closely tied to the retention of carbon dioxide reactivity by the brain. Complications occurring during treatment with barbiturate coma include hypotension in 58% of patients, hypokalemia in 82%, respiratory complications in 76%, infections in 55%, hepatic dysfunction in 87%, and renal dysfunction in 47% [68]. Hypotension caused by pentobarbital should be treated first with volume replacement and then with vasopressors, if necessary. Experimental studies suggest that for the treatment of hypotension associated with barbiturate coma, volume resuscitation may be better than dopamine [69] because dopamine infusion increased cerebral metabolic requirements and partially offset the beneficial effects of barbiturates on CMRO₂.

Hypothermia

Although a multicenter randomized clinical trial of moderate hypothermia in severe TBI did not show a beneficial effect on neurologic outcome, fewer patients randomized to moderate hypothermia had intracranial hypertension [70]. A pilot randomized clinical trial of hypothermia in children who had TBI produced similar findings (ie, no improvement in neurologic outcome, but a reduction in ICP during the hypothermia treatment) [71]. Although routine induction of hypothermia is not indicated at present, hypothermia may be an effective adjunctive treatment of increased ICP refractory to other medical management.

Steroids

Steroids are commonly used for primary and metastatic brain tumors to decrease vasogenic cerebral edema. Focal neurologic signs and decreased mental status owing to surrounding edema typically begin to improve within hours [72]. Increased ICP, when present, decreases over the following 2 to 5 days, in some cases to normal. The most commonly used regimen is intravenous dexamethasone, 4 mg every 6 hours. For other neurosurgical disorders, such as TBI or spontaneous intracerebral hemorrhage, steroids have not been shown to have a benefit [73,74] and in some studies have had a detrimental effect [75,76].

The CRASH trial [75] is a recently completed, large (>10,000 patients enrolled), placebo-controlled randomized clinical trial of methylprednisolone for 48 hours in patients who have TBI. Administration of methylprednisolone resulted in a significant increase in the risk for death, from 22.3% to 25.7% (relative risk 1.15, 95% CI 1.07–1.24). This trial confirmed
previous studies and guidelines that routine administration of steroids is not indicated for patients who have TBI.

**Surgical interventions**

*Resection of mass lesions*

Intracranial masses producing elevated ICP should be removed when possible. Acute epidural and subdural hematomas are a hyperacute surgical emergency, especially epidural hematoma because the bleeding is under arterial pressure. Brain abscess must be drained, and pneumocephalus must be evacuated if it is under sufficient tension to increase ICP. Surgical management of spontaneous intracerebral bleeding is controversial [77].

*Cerebrospinal fluid drainage*

CSF drainage lowers ICP immediately by reducing intracranial volume, and more long term by allowing edema fluid to drain into the ventricular system. Drainage of even a small volume of CSF can lower ICP significantly, especially when intracranial compliance is reduced by injury. This modality can be an important adjunctive therapy for lowering ICP. However, if the brain is diffusely swollen, the ventricles may collapse, and this modality then has limited usefulness.

*Decompressive craniectomy*

The surgical removal of part of the calvaria to create a window in the cranial vault is the most radical intervention for intracranial hypertension, negating the Monro-Kellie doctrine of fixed intracranial volume and allowing for herniation of swollen brain through the bone window to relieve pressure. Decompressive craniectomy has been used to treat uncontrolled intracranial hypertension of various origins, including cerebral infarction [78], trauma, subarachnoid hemorrhage, and spontaneous hemorrhage. Patient selection, timing of operation, type of surgery, and severity of clinical and radiologic brain injury are all factors that determine the outcome of this procedure.

Sahuquillo and Arikan [79] reviewed the evidence in the literature of studies evaluating the effectiveness of decompressive craniectomy after TBI. They found only one small randomized clinical trial in 27 children who had TBI [80]. This trial found a reduced risk ratio for death of 0.54 (95% CI 0.17–1.72), and a risk ratio of 0.54 for death, vegetative status, or severe disability 6 to 12 months after injury (95% CI 0.29–1.07). All the available studies in adults are either case series or cohorts with historical controls. These reports suggest that decompressive craniectomy effectively reduces ICP in most (85%) patients who have intracranial hypertension refractory to conventional medical treatment [81,82]. Brain oxygenation measured by tissue Po2, and blood flow estimated by middle cerebral artery flow
velocity, are also usually improved after decompressive craniectomy [83,84]. Reported complications include hydrocephalus, hemorrhagic swelling ipsilateral to the craniectomy site, and subdural hygroma [81]. A case report of paradoxical herniation has also been reported after a lumbar puncture in a patient who had a decompressive craniectomy [85].

Results from randomized trials to confirm or refute the effectiveness of decompressive craniectomy in adults are limited. Reports suggest, however, that decompressive craniectomy may be a useful option when maximal medical treatment has failed to control ICP. Randomized controlled trials in TBI are ongoing (Rescue ICP [86] and DECRAN). In a pooled analysis of randomized trials in patients who had malignant MCA infarction, decompressive surgery undertaken within 48 hours of stroke was associated with reduced mortality and an increased proportion of patients who had a favorable functional outcome [87].

Summary

Effective treatment of intracranial hypertension involves meticulous avoidance of factors that precipitate or aggravate increased ICP. When ICP becomes elevated, it is important to rule out new mass lesions that should be surgically evacuated. Medical management of increased ICP should include sedation, drainage of CSF, and osmotherapy with either mannitol or hypertonic saline. For intracranial hypertension refractory to initial medical management, barbiturate coma, hypothermia, or decompressive craniectomy should be considered. Steroids are not indicated and may be harmful in the treatment of intracranial hypertension resulting from TBI.

References


Monitoring Intracranial Pressure in Traumatic Brain Injury

Martin Smith, MBBS, FRCA

Increased intracranial pressure (ICP) is an important cause of secondary brain injury, and ICP monitoring has become an established component of brain monitoring after traumatic brain injury. ICP cannot be reliably estimated from any specific clinical feature or computed tomography finding and must actually be measured. Different methods of monitoring ICP have been described but intraventricular catheters and microtransducer systems are most widely used in clinical practice. ICP is a complex variable that links ICP and cerebral perfusion pressure and provides additional information from identification and analysis of pathologic ICP wave forms. ICP monitoring can also be augmented by measurement of indices describing cerebrovascular pressure reactivity and pressure-volume compensatory reserve. There is considerable variability in the use of ICP monitoring and treatment modalities among head injury centers. However, there is a large body of clinical evidence supporting the use of ICP monitoring to detect intracranial mass lesions early, guide therapeutic interventions, and assess prognosis, and it is recommended by consensus guidelines for head injury management. There remains a need for a prospective, randomized, controlled trial to identify the value of ICP monitoring and management after head injury.

The primary aim of the intensive care management of traumatic brain injury (TBI) is to prevent and treat secondary ischemic injury using a multifaceted neuroprotective strategy to maintain cerebral perfusion to meet the brain’s metabolic demands for oxygen and glucose. Because the brain is encased by the nonexpandable skull, an increase in intracranial pressure (ICP) may impede cerebral blood flow (CBF) and lead to cerebral ischemia. Increased ICP is an important cause of secondary brain injury, and its degree and duration is associated with outcome after TBI.1,2 ICP monitoring is the most widely used intracranial monitor because prevention and control of increased ICP and maintenance of cerebral perfusion pressure (CPP) are fundamental therapeutic goals after TBI.

This review will summarize the technical aspects of ICP monitoring and its role in the clinical management of TBI. Research applications will be discussed and controversies highlighted.

From the National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, London, UK.

Accepted for publication September 17, 2007.

Address correspondence and reprint requests to Dr. Martin Smith, MBBS, FRCA, Consultant in Neuroanaesthesia and Neurocritical Care, Honorary Reader in Anaesthesia and Critical Care, The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, Queen Square, London, WC1N 3BG. Address e-mail to martin.smith@uclh.nhs.uk.

Copyright © 2007 International Anesthesia Research Society

DOI: 10.1213/01.ane.0000297296.52006.8e

PATHOPHYSIOLOGY

The principles of ICP were outlined by Professors Munroe and Kellie in the 1820s. In essence, they noted that, in adults, the brain is enclosed in a rigid case of bone and that the volume of its contents must remain constant if ICP is to remain constant. The intracranial compartment consists of brain approximately 83%, cerebrospinal fluid (CSF) approximately 11%, and blood approximately 6%. Under normal conditions there are two main components of ICP, CSF and vasogenic.3 The former is derived from the circulation of CSF and is responsible for baseline ICP. It may be deranged in pathologic states, causing an increase in ICP, because of resistance to CSF flow between intracerebral compartments secondary to brain swelling or expansion of intracranial mass lesions, or because CSF outflow is obstructed. The vasogenic component of ICP is associated with continuous, small fluctuations of cerebral blood volume (CBV). Vasogenic increases in ICP may be caused by hypercapnea, increase in cerebral metabolism, and cerebral hyperemia.

An increase in the volume of one of the components of the intracranial cavity (e.g., brain) requires a compensatory reduction in another (e.g., CSF) to maintain a constant pressure. Brain tissue is essentially incompressible, so any increase in ICP due to brain swelling initially results in extrusion of CSF and (mainly venous) blood from the intracranial cavity, a phenomenon known as “spatial compensation.”3 CSF plays the largest role in spatial compensation because it can be expelled from the intracranial cavity into the “reservoir” of the spinal theca.
Intracranial pressure (ICP) volume curve. The curve has three parts: a flat part representing good compensatory reserve (A–B), an exponential part representing reduced compensatory reserve (B–C) and a final flat part representing terminal derangement of cerebrovascular responses at high ICP (C–D).

The relationship between ICP and intracranial volume is described by the pressure-volume curve that comprises of three parts (Fig. 1). The first part of the curve is flat because compensatory reserves are adequate and ICP remains low despite increases in intracerebral volume (A–B in Fig. 1). When these compensatory mechanisms become exhausted, the pressure-volume curve turns rapidly upwards in an exponential fashion. Intracranial compliance is now critically reduced and a small increase in intracerebral volume causes a substantial increase in ICP (B–C in Fig. 1). At high levels of ICP, the curve plateaus as the capacity of cerebral arterioles to dilate in response to a reduction in CPP becomes exhausted. The high brain tissue pressure results in collapse of these dysfunctional vessels as cerebrovascular responses become terminally disrupted (C–D in Fig. 1).

After TBI, increased ICP can be related to intracranial mass lesions, contusional injuries, vascular engorgement, and brain edema. Recent clinical studies have shown that brain edema, and not increased CBV as a result of vascular engorgement, is the major culprit responsible for brain swelling after TBI. Vascular genic brain edema, emanating from the blood vessels subsequent to blood–brain barrier compromise, has classically been considered the prevalent edema after TBI but recent magnetic resonance imaging studies have indicated that, in patients with significant brain swelling, cytotoxic or cellular edema, occurring secondary to sustained intracellular water collection, predominates. Cytoxic edema is of decisive pathophysiologic importance, as it develops early and persists while blood–brain barrier integrity is gradually restored. These findings have implications for the treatment of TBI and suggest that cytotoxic and vasogenic brain edema are two entities that can be targeted simultaneously or independently, according to their temporal prevalence.

When cerebral autoregulation is absent, an increase in arterial blood pressure (ABP) causes an increase in CBV and hence in ICP. An increase in CBV and ICP may also occur in response to changes in other systemic variables, such as arterial PaCO₂, temperature and intrathoracic or intraabdominal pressures, or because of intracranial events such as seizures. Intracranial hypertension may also occur because of acute or chronic disturbances of CSF drainage (hydrocephalus) and other, often diffuse, pathological processes, such as cerebral edema secondary to hepatic failure.

**NORMAL AND PATHOLOGIC ICP**

Normal ICP varies with age, body position, and clinical condition. The normal ICP is 7–15 mm Hg in a supine adult, 3–7 mm Hg in children, and 1.5–6 mm Hg in term infants. The definition of intracranial hypertension depends on the specific pathology and age, although ICP >15 mm Hg is generally considered to be abnormal. However, treatment is instituted at different levels depending on the pathology. For example, ICP >15 mm Hg warrants treatment in a patient with hydrocephalus, whereas after TBI, treatment is indicated when ICP exceeds 20 mm Hg. Thresholds vary in children and it has been recommended that treatment should be initiated during TBI management when ICP exceeds 15 mm Hg in infants, 18 mm Hg in children <8-yr-of-age and 20 mm Hg in older children and teenagers.

ICP is not evenly distributed in pathologic states because CSF does not circulate freely and intracranial CSF volume may be low because of brain swelling. The assumption of one, uniform, ICP is therefore questionable and intraparenchymal pressure may not be indicative of “real” ICP, i.e., ventricular CSF pressure. In the injured brain, there may be intraparenchymal pressure gradients between the supra and infra-tentorial compartments and bilateral monitoring has revealed differential pressures across the midline in the presence of hematomas and also in the absence of space-occupying lesions.

Increased ICP causes a critical reduction in CPP and CBF and may lead to secondary ischemic cerebral injury. A number of studies have shown that high ICP is strongly associated with poor outcome, particularly if the period of intracranial hypertension is prolonged. Increased ICP can also cause actual shift of brain substance resulting in structural damage to the brain and to herniation through the tentorial hiatus or foramen magnum. The latter results in pressure on the brainstem causing bradycardia and hypertension (the classic Cushing reflex) and, if untreated, respiratory depression and death.
Intracranial Pressure Monitoring

ICP cannot be reliably estimated from any specific clinical feature or computed tomography (CT) finding and must actually be measured. Different methods of monitoring ICP have been described (Table 1) but two methods are commonly used in clinical practice: intraventricular catheters and intraparenchymal catheter-tip, microtransducer systems. Subarachnoid and epidural devices have much lower accuracy\(^{18,19}\) and are now rarely used. Measurement of lumbar CSF pressure does not provide a reliable estimate of ICP and may be dangerous in the presence of increased intracranial hypertension.\(^{20}\)

The “gold standard” technique for ICP monitoring is a catheter inserted into the lateral ventricle, usually via a small right frontal burr hole. This can be connected to a standard pressure transducer via a fluid-filled catheter. The reference point for the transducer is the foramen of Munroe, although, in practical terms, the external auditory meatus is often used. Some ventricular catheters have a pressure transducer within their lumen and the ICP wave form is generally of better quality than traditional fluid-filled catheters connected to an external transducer. Ventricular catheters measure global ICP and have the additional advantages of allowing periodic external calibration, therapeutic drainage of CSF, and administration of drugs (e.g., antibiotics).\(^{20,21}\) However, placement of the catheter may be difficult if there is ventricular effacement or displacement due to brain swelling or intracranial mass lesions. The use of intraventricular catheters is complicated by infection in up to 11% of cases.\(^{22,23}\) This is a serious complication resulting in significant morbidity and mortality. The risk of infection increases after 5 days\(^{23}\) and this has been presumed to be related to retrograde colonization of the catheter. However, recent data suggest that CSF infection is also likely to be acquired during introduction of the catheter in a significant number of cases.\(^{24}\) Intraventricular catheters may become blocked, especially in the presence of subarachnoid blood or increased CSF protein. If the drainage holes at the tip of the ventricular catheter become partially blocked, resistance to CSF flow increases at the tip of the drain and a pressure gradient develops across the catheter. Catheters with an integral pressure transducer may then grossly underestimate ICP.\(^{25}\) Although the patency of catheters can often be restored by gentle flushing, repeated attempts significantly increase the risk of infection.\(^{23}\) Regular microbiological analysis of CSF samples to permit early diagnosis of ventriculitis is recommended by some, whereas others believe that routine sampling may actually predispose to higher infection rates because of the repeated opening of the closed drainage system. The use of antibiotic-impregnated catheters is associated with a lower infection rate,\(^{26}\) although catheters coated with hydrogel to impede bacterial adherence are not associated with reduced infection rates.\(^{27}\)

Microwasculer-tipped ICP monitors can be sited in the brain parenchyma or subdural space, either through a skull bolt, a small burr hole or during a neurosurgical procedure. They are almost as accurate as ventricular catheters. Fiberoptic, strain gauge or pneumatic technologies are used to transduce pressure in modern microtransducer devices. The Camino ICP monitor (Integra Neuroscience, Plainsboro, NJ) uses a fiberoptic cable to direct light toward a miniature displaceable mirror at the catheter tip.\(^{28}\) Changes in ICP distort the mirror and the change in reflected light intensity is converted to a measured change in pressure. The Codman microsensor (Johnson and Johnson, Raynham, MA) incorporates two semiconductor strain gauges mounted on a thin diaphragm in titanium housing at the catheter tip. The diaphragm distorts in proportion to the applied pressure and a Wheatstone bridge transduces changes in pressure to changes in resistance that are subsequently displayed as ICP.\(^{29}\) The Neurovent-P ICP monitor (Raumedic AG, Munchberg, Germany) is also based on an electronic chip strain gauge coated by a thin silicon membrane mounted at the distal tip of the catheter. The incorporation of the Wheatstone bridge into the chip enhances the drift characteristics by reducing temperature sensitivity and the effects of nonpressure-related external strains.\(^{30}\) Neurovent catheters incorporating three monitoring variables (ICP, brain tissue oxygen partial pressure, and temperature) are now

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraventricular catheter</td>
<td>Gold standard</td>
<td>Insertion may be difficult</td>
</tr>
<tr>
<td></td>
<td>Measures global pressure</td>
<td>Most invasive method</td>
</tr>
<tr>
<td></td>
<td>Allows therapeutic drainage of cerebrospinal fluid</td>
<td>Risk of hematoma</td>
</tr>
<tr>
<td></td>
<td>In vivo calibration possible</td>
<td>Risk of ventriculitis</td>
</tr>
<tr>
<td>Microtransducer sensor</td>
<td>Robust technology</td>
<td>Small zero drift over time</td>
</tr>
<tr>
<td></td>
<td>Intraparenchymal/subdural placement</td>
<td>No in vivo calibration</td>
</tr>
<tr>
<td></td>
<td>Low procedure complication rate</td>
<td>Measures local pressure</td>
</tr>
<tr>
<td>Epidural catheter</td>
<td>Easy to insert</td>
<td>Limited accuracy</td>
</tr>
<tr>
<td></td>
<td>No penetration of dura</td>
<td>Rarely used</td>
</tr>
<tr>
<td>Lumbar CSF pressure</td>
<td>Extracranial procedure</td>
<td>Does not reflect ICP</td>
</tr>
</tbody>
</table>

Table 1. Comparison of Intracranial Pressure (ICP) Monitoring Devices
available, although clinical data with this device are limited.31 None of these devices allows in vivo pressure calibration and, after a preinsertion calibration during which they are zeroed relative to atmospheric pressure, their output is subject to the zero drift of the sensor. However, microtransducer systems perform well during in vitro testing, with drift as low as 0.6 ± 0.9 mm Hg after 5 days continuous use.32 Microtransducer systems are reliable and easy to use in the clinical setting, with recordings that are stable over time with minor zero drift.33 They have minimal infection and other complication rates34 but measured pressure may not be representative of true CSF pressure because of the intraparenchymal pressure gradients that may exist after TBI.35 More recently, a device incorporating pneumatic technology has been introduced. The Spiegelberg ICP monitor (Spiegelberg GmbH, Hamburg, Germany) uses a small air pouch balloon at the end of a catheter to sense changes in pressure.36 It can be used in parenchymal and intraventricular sites and zeroes automatically in vivo.

There is a desire to develop less invasive methods of measuring ICP and methods using tympanic membrane displacement37 and ultrasound “time of flight” techniques38 have been described. Tympanic membrane displacement is a poor surrogate for invasive ICP measurements, but serial intra-patient measurements may be useful to determine temporal changes in ICP. More recently, transcranial Doppler ultrasonography has been used to provide a noninvasive estimate of ICP that may be clinically applicable,39 and CPP with an accuracy of ±10–15 mm Hg.40

Continuous digital recording of ICP is the most accurate method of data acquisition and display. ICP changes with time and averaging over at least 30 min should be used to calculate mean ICP and inform treatment decisions.9 Clinical records, particularly intensive care unit charts, often use single end-hour ICP recordings made by nurses and these correlate well with continuous recordings obtained during monitoring of brain injury.41 In a study of 115 patients with hydrocephalus, there was also a strong correlation between digital recordings of ICP and end-hour measurements, with a mean difference of 0.3 ± 1.26 mm Hg between the 2 methods.42 Computerized data collection allows display, interpretation and analysis of continuous ICP monitoring data as well as integration with other intracranial monitoring systems.43

### GENERAL INDICATIONS FOR ICP MONITORING

Despite the widespread application of ICP monitoring, there are no data from randomized controlled trials that can clarify its role in acute coma.44 With the exception of monitoring after severe TBI, the indications for ICP monitoring are not well established and vary from center to center (Table 2). Case-mix adjusted mortality in comatose patients with intracranial hemorrhage is lower in those who receive ICP monitoring compared with those who do not45 and increased ICP is associated with poor prognosis after subarachnoid hemorrhage.46 There is little evidence to support ICP monitoring in other neurological conditions, such as acute stroke, when there is no benefit over clinical monitoring alone.47 ICP monitoring after anoxic injury after cardiac arrest has little value in targeting treatment, although it may be useful in hepatic encephalopathy.

### ICP MONITORING AFTER TBI

In 1982, Narayan et al.48 demonstrated in a prospective study of 133 patients that outcome prediction after TBI was increased when ICP monitoring was added to standard clinical observations. Subsequently, analysis of the National Traumatic Coma Data Bank showed that the proportion of hourly ICP recordings more than 20 mm Hg was the next most significant predictor of poor outcome after the usual clinical descriptors of age, admission motor score, and abnormal pupil responses.1,2

Despite the absence of Class 1 evidence demonstrating the benefit of ICP monitoring on outcome after TBI, there is a large body of clinical evidence supporting its use to guide therapeutic interventions, detect intracranial mass lesions early, and assess prognosis. ICP monitoring is recommended by consensus guidelines for head injury management10,49 and is accepted as a relatively low-risk, high-yield and value for money intervention.

The Brain Trauma Foundation recommends ICP monitoring in all patients with a severe TBI (Glasgow Coma Score 3–8) and either an abnormal CT scan or a normal scan and the presence of two or more of the following three risk factors at admission: age >40 yr; unilateral or bilateral motor posturing; a systolic BP <90 mm Hg.49 There is around 60% chance of increased ICP in these patients.

Much information is available from ICP monitoring in addition to the measurement and display of absolute ICP. CPP is easily calculated as the difference between mean ABP (MAP) and ICP (CPP = MAP - ICP) and is a measure of the pressure gradient across the cerebral vascular bed. Pathologic ICP wave forms can be identified and analyzed. ICP monitoring can also be augmented by measurement of indices describing cerebrovascular

<table>
<thead>
<tr>
<th>Table 2. Indications for Intracranial Pressure Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe head injury</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Cerebral edema</td>
</tr>
<tr>
<td>Central nervous system infections</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
</tr>
</tbody>
</table>
pressure reactivity (CVR) and pressure-volume compensatory reserve.\(^9,50\)

ICP changes in a limited number of patterns after TBI\(^5\):

1. Low (<20 mm Hg) and stable ICP: This pattern is seen after uncomplicated head injury or during the early hours after severe TBI, before brain swelling evolves.
2. High (>20 mm Hg) and stable ICP: This is the most common pattern seen after severe TBI.
3. ICP waves: These reflect reduced intracranial compliance and are discussed in detail below.
4. ICP changes related to changes in ABP: These occur in the presence of abolished cerebral autoregulatory responses when ICP changes directly with ABP.
5. Refractory intracranial hypertension: In the absence of aggressive treatment strategies this may progress to herniation and death.

**ICP WAVE FORM**

In 1965, Nils Lundberg et al. characterized ICP slow waves.\(^{51}\) “A” waves or “plateau” waves are steep increases in ICP from baseline to peaks of 50–80 mm Hg that persist for 5–20 min. These waves are always pathologic and may be associated with early signs of brain herniation, such as bradycardia and hypertension. They occur in patients with intact autoregulation and reduced intracranial compliance and represent reflex, phasic vasodilation in response to reduced cerebral perfusion.\(^{52,53}\) The development of plateau waves leads to a vicious cycle, with reductions in CPP predisposing to the development of more plateau waves, further reductions in CPP and irreversible cerebral ischemia. “B” waves are rhythmic oscillations occurring at 0.5–2 waves/min with peak ICP increasing to around 20–30 mm Hg above baseline. They are related to changes in vascular tone, probably due to vasomotor instability when CPP is at the lower limit of pressure autoregulation. “C” waves are oscillations occurring with a frequency of 4–8/min and are of much smaller amplitude than B waves, peaking at 20 mm Hg. They occur synchronously with ABP, reflect changes in systemic vasomotor tone, and are of no pathologic significance.

Analysis of the ICP wave form in the time domain reveals three fundamental components: pulse wave form, respiratory wave form, and slow waves. The pulse wave form has several harmonic components, the fundamental of which has a frequency equal to the heart rate. The amplitude of this component (AMP) is used for the evaluation of various ICP-derived indices (see below). The respiratory wave form is related to the frequency of the respiratory cycle and occurs at 8–20 waves/min. Slow waves are generally less precisely defined than those described by Lundberg et al. and encompass all waves within the frequency limits of 0.05–0.0055 Hz (20 s to 3 min).

Several studies have shown that low power of slow waves may predict poor outcome after TBI.\(^{54}\) There is also a strong correlation between slow waves and fluctuations in the electroencephalogram,\(^{55}\) supporting the presence of a primary neuromasculature in the brainstem responsible for fluctuations in CBF and generation of slow waves. Maintenance of ICP slow waves after TBI might therefore represent preservation of this pacemaker activity and of brainstem function.

**CVR**

The ICP response to slow spontaneous changes in ABP depends on the pressure-reactivity of cerebral vessels. This is a key component of pressure autoregulation and disturbed pressure reactivity implies disturbed pressure autoregulation. A pressure reactivity index (PRx) can be derived from continuous monitoring and analysis of slow waves in ABP and ICP.\(^5,56\) PRx is the linear correlation coefficient between ABP and ICP and its value ranges from −1 to +1. When the cerebrovascular bed is normally reactive, an increase in ABP leads to cerebral vasoconstriction within 5–15 s and a secondary reduction in CBV and ICP. Opposite effects occur when ABP is reduced. When CVR is impaired, changes in ABP are passively transmitted to CBV and ICP. PRx is determined by calculating the correlation coefficient of consecutive time-averaged data points of ICP and ABP recorded over a 4-min period.\(^56\) A negative value for PRx, when ABP is inversely correlated with ICP, indicates a normal CVR, and a positive value a nonreactive cerebral circulation. PRx correlates with standard measures of cerebral autoregulation based on transcranial Doppler ultrasonography\(^{56}\) and abnormal values are predictive of poor outcome after TBI.\(^{20}\) PRx can be monitored continuously and has been used to define individual CPP targets after TBI.\(^{57}\)

**PRESSURE VOLUME COMPENSATORY RESERVE**

The relation between ICP and changes in intracerebral volume can be used to define an index of compensatory reserve (RAP). RAP is the relationship (R) between the AMP (A) and the mean ICP over 1–3 min (P).\(^{58}\) Values of this index also range from −1 to +1. In the first, flat, part of the ICP-volume curve there is lack of synchronization between AMP and ICP, representing good compensatory reserve. Here the RAP is zero and the ICP wave form amplitude is low. On the steep part of the curve, when compensatory reserves begin to fail, AMP varies directly with ICP and RAP is +1. ICP wave form amplitude now begins to increase as mean ICP increases, at first slowly and then more rapidly as compensatory reserves are exhausted. Finally, on the terminal part of the curve, RAP is <0. Now there is terminal derangement of the cerebral vasculature and a decrease in pulse pressure transmission from the arterial bed to the intracranial compartment resulting in low or absent ICP wave form.
amplitude. RAP can therefore be used to indicate a patient’s position on the pressure-volume curve and may be used to predict the response to treatment and the risk of clinical deterioration or herniation.\(^\text{50}\) RAP <0.5 in association with ICP >20 mm Hg is predictive of poor outcome after TBI.\(^\text{58}\)

More recently, the Spiegelberg brain compliance monitor has been used to provide similar information. This method relies on the measurement of the ICP response to a known small increase in volume by inflating and deflating the air pouch at the end of the Spiegelberg ICP catheter. Although the device is still a research tool, it offers the possibility of early warning of critical decompensation and risk of herniation\(^\text{59}\) but its correlation with outcome has not been demonstrated.

**CONTROVERSIES OF ICP MONITORING AFTER TBI**

Increased ICP correlates with higher risk of mortality and morbidity, but not all patients with intracranial hypertension have poor outcome.\(^\text{60}\) This is perhaps unsurprising because monitoring of ICP and CPP does not tell the whole story. It is impossible to know in an individual patient whether the targeted ICP or CPP is sufficient to allow the brain’s metabolic demands to be met at a particular moment. A recent study has demonstrated that brain resuscitation based on control of ICP and CPP alone does not prevent cerebral hypoxia in some patients after TBI.\(^\text{61}\) Measurement of ICP and CPP in association with monitors of the adequacy of cerebral perfusion, such as measurement of cerebral oxygenation (e.g., jugular venous oximetry, brain tissue oxygen partial pressure) and metabolic status (e.g., cerebral microdialysis), provide a more complete picture of the injured brain and its response to treatment. There is preliminary evidence to suggest that therapy directed to maintain brain tissue oxygenation as well as ICP/CPP is associated with reduced mortality after severe TBI.\(^\text{62}\) Multimodality intracranial monitoring is now widely used during neurointensive care to provide early warning of impending brain ischemia and guide targeted therapy to optimize cerebral perfusion and oxygenation.\(^\text{63}\)

Despite its limitations, ICP monitoring remains central to the monitoring and management of severe TBI. Conventional approaches to management have concentrated on a reduction in ICP to prevent secondary cerebral ischemia. Treatment is usually initiated if ICP increases >20 mm Hg,\(^\text{10}\) although it is likely that the duration of intracranial hypertension and its response to treatment are also important prognostic indicators.\(^\text{64}\) Over the last decade, there has been a shift of emphasis from primary control of ICP to a multifaceted approach of maintenance of CPP and brain protection. High ICP and low CPP may result in cerebral ischemia and are strongly associated with fatal outcome.\(^\text{16}\) Induced hypertension using fluid resuscitation and vasopressors has been advocated to maintain CPP,\(^\text{65}\) but therapies to maintain high CPP are controversial. In one study, there was a fivefold increase in the occurrence of acute lung injury in a group of TBI patients managed with a CPP threshold of 70 mm Hg vs 50 mm Hg,\(^\text{66}\) suggesting that high CPP targets may only be achieved at the expense of significant complications. These might outweigh the potential benefits of this treatment strategy. Furthermore, if cerebral autoregulatory capacity is lost, an increase in CPP may result in hyperemia, increase in vasogenic edema and a secondary increase in ICP.\(^\text{67,68}\)

It has recently been shown that excessive CPP is associated with a lower likelihood of favorable outcome after TBI.\(^\text{16}\) Debate remains about the optimal level of CPP,\(^\text{69}\) but the Brain Trauma Foundation has recently recommended that the CPP target after severe TBI should lie within the range of 50–70 mm Hg and that aggressive attempts to maintain CPP >70 mm Hg should be avoided because of the risk of acute lung injury.\(^\text{70}\) It is also now apparent that a CPP threshold (an “ideal” CPP) exists on an individual basis for patients with TBI.\(^\text{71}\) Patient and time-dependent differences in adequate and inadequate CPP are considerable and optimal CPP should be defined for each patient individually and frequently. Multimodality monitoring may assist the clinician in detecting optimal CPP and in balancing the risks and benefits of ICP and CPP-directed strategies.

There has never been a randomized, controlled trial demonstrating outcome benefit in patients in whom treatment is guided by ICP monitoring. As a consequence, there is considerable variability in the use of monitoring and treatment modalities among institutions.\(^\text{72,73}\) In a study from the United States, ICP monitors were placed in only 58% of patients who fulfilled established criteria for monitoring, and therapies to reduce increased ICP were routinely applied in those patients with no monitoring.\(^\text{72}\) In a European survey,\(^\text{73}\) ICP monitoring was performed in only 37% of appropriate patients and, although ICP monitoring was almost universal in a Canadian study of severe TBI, only 20% of neurosurgeons believed that outcome was affected by ICP monitoring.\(^\text{74}\)

The differences in the approach to ICP monitoring and management after TBI are likely to reflect the conflicting evidence available to clinicians. In one study, an “aggressive” management protocol, including the placement of ICP monitors, was associated with decreased risk of mortality (hazard ratio, 0.43; 95% confidence interval, 0.27–0.66) and shorter length of hospital stay, although there was no difference in functional status in survivors at discharge.\(^\text{72}\) Another study demonstrated that adherence to a protocol for TBI management based on the Brain Trauma Foundation guidelines is associated with a nonsignificant reduction in mortality and a significant improvement in functional outcome in survivors.\(^\text{75}\) Invasive monitoring of systemic and cerebral variables to guide
treatment decisions results in increased resource usage, but the significant improvement in outcome justifies the increased cost of the treatment episode. However, one study has challenged some of these established findings. CREMER et al. conducted an observational study to investigate the effect of ICP/CPP targeted therapy on outcome and therapy intensity in 333 patients with severe TBI. This study compared patients managed in two centers. Admission to each center was determined only by the geographical location in which the original trauma occurred, and patient characteristics were well balanced between the two centers. In center A, ICP was not monitored but supportive intensive care was provided to maintain MAP >90 mm Hg. Other therapeutic interventions were directed by clinical observations and CT findings. In center B, ICP was monitored and treatment provided to maintain ICP <20 mm Hg and CPP >70 mm Hg. In-hospital mortality was similar in both centers (34% vs 33%, P = 0.87) and the odds ratio for a more favorable outcome after ICP/CPP-targeted therapy was 0.95 (95% confidence interval, 0.62–1.44). Intensity of treatment, measured by use of sedatives, vasopressors, mannitol and barbiturates, was higher in center A. The conflicting data on monitoring and management of ICP have reignited the debate about the need for a prospective, randomized, controlled trial of ICP monitoring and ICP/CPP-targeted treatment. Evidence suggesting that targeting brain tissue oxygenation in addition to ICP/CPP might bring additional outcome benefits suggests that any such trial should be extended to include other aspects of multimodal monitoring. The time is perhaps right for interested groups to reconsider the possibility of conducting an outcome trial to compare ICP/CPP-targeted treatment versus diagnosis and targeted therapy based on multimodality monitoring versus supportive intensive care without monitoring after TBI. However, the practicality and ethical acceptability of such a trial will, no doubt, be the subject of continued debate.

**SUMMARY**

ICP is a complex variable. It provides information about ICP and CPP, cerebral compensatory mechanisms and mechanisms contributing to CBF regulation. Continuous measurement of ICP and analysis of ICP wave forms offers insights into pathophysiology and prognosis. ICP monitoring has become an established component of brain monitoring after TBI and is used to guide treatment. Despite the introduction of new monitoring technologies measuring a multitude of intracranial variables, ICP remains robust, only moderately invasive and widely applicable after TBI.

**REFERENCES**


© International Anesthesia Research Society. Unauthorized Use Prohibited.
60. Resnck DK, Marion DW, Carlier P. Outcome analysis of patients with severe head injuries and prolonged intracranial hypertension. J Trauma 1997;42:1108–11
69. Ling GS, Neal CJ. Maintaining cerebral perfusion pressure is a worthy clinical goal. Neurocrit Care 2005;2:75–81
71. Vespa P. What is the optimal threshold for cerebral perfusion pressure following traumatic brain injury? Neurosurg Focus 2003;15:E4
In patients with traumatic brain injury (TBI), an uncontrolled increase in intracranial pressure (ICP) heralds a poor prognosis and can lead to considerable morbidity and mortality. The causes of increased ICP after TBI are numerous and not necessarily associated with the nature of the original injury. Possible causes include cerebral edema, hyperemia, mass lesion, cerebral vasodilation, systemic hypertension, hydrocephalus, venous sinus thrombosis or other obstruction, posttraumatic seizure activity, increased intrathoracic or intra-abdominal pressure, hyperthermia or febrile states, and lightening from coma with inadequate sedation. This review discusses the use, benefits, and complications of common surgical interventions for managing this devastating condition, with emphasis on decompressive craniectomy (DC) for control of ICP and its associated long-term outcomes.

PubMed and Cochrane Library searches yielded 194 articles that reported studies involving either adults or children, using DC of any type, and assessing the effect of DC on both ICP and outcomes. In patients with TBI, the onset of increased ICP should be anticipated, although symptoms may be vague and nonspecific (e.g., confusion, headache, and drowsiness). A decrease in the Glasgow Coma Scale score is 1 indicator. An unenhanced computed tomography (CT) head scan can show clinically nonobvious abnormalities that may lead to development of increased ICP as well as those amenable to surgery. The scan will also show evidence of cerebral mass effect, and an abnormal scan increases the risk of subsequent intracranial hypertension. In patients with a normal CT scan, subsequent development of increased ICP was associated with age older than 40 years, systolic blood pressure less than 90 mm Hg, and evidence of decerebrate or decorticate posturing.

Patients with extraparenchymal mass lesions should have surgical evacuation because the lesion will contribute to the development of increased ICP and secondary brain injury. These lesions include acute extradural hematoma, acute subdural hematoma, intraparenchymal lesion, frontal/temporal contusion, and posterior fossa lesion. The practice in most centers is to initiate treatment when ICP is greater than 20 to 25 mm Hg; the Brain Trauma Foundation guidelines suggest treatment when ICP is 20 mm Hg or greater. Studies on the effect of increased ICP on cerebral perfusion pressure (CPP) have given conflicting results, and the relative importance of treating ICP and CPP after TBI is still debated. However, ICP cannot be managed independently of CPP, and current protocols have targets for both ICP and CPP. The British Trauma Foundation recommends that ICP be maintained at less than 20 mm Hg and CPP at 50 to 70 mm Hg.

Although medical management is the first-line treatment, surgical interventions include ventricular catheterization and DC procedures. Intracranial pressure can be monitored with intraparenchymal systems or ventricular catheterization; readings from the 2 systems generally have comparable accuracy. If an external ventricular drain (EVD) is used, ICP monitoring and cerebrospinal fluid (CSF) drainage can be done simultaneously. This allows CSF drainage to be a second-line therapy for controlling increased ICP refractory to initial measures. The extent of drainage can be guided by the effect on ICP. The EVD can be removed when ICP has been normal for 48 to 72 hours after withdrawal of ICP therapy. Prospective studies have found that CSF drainage from ventriculostomy can be effective in lowering ICP to less than pathological levels. Using an EVD for ICP control has also been associated with favorable outcomes at follow-up after hospital discharge. Although the procedure is invasive, an EVD is a reasonable second-tier option; many centers use early ventricular catheterization to allow concurrent CSF drainage and ICP monitoring. Complications of the surgical procedure include infection, hemorrhage, and malfunction of the EVD itself.

Considerable variability can be found among centers in their indications for and use of DC for managing severe refractory increased ICP after TBI when medical management has failed. Outcome measures for assessing the clinical value of DC include ICP control, mortality, and functional outcome. An important aspect is functional outcome because some studies have found that survivors may remain in a vegetative state or are unable to be independent. The trend seems to be toward a reduction in mortality with DC, although care of TBI before hospital admission and medical management in the intensive care unit may contribute to the decreased mortality rates. Studies published since 2006 indicate that DC can lead to a notable decrease in ICP, although not always to less than 20 mm Hg, but the effect does not necessarily lead to improved long-term clinical outcomes. One randomized controlled trial (RCT) supported the use of DC in pediatric patients. Patient selection is an important aspect also, and factors to be considered include preoperative Glasgow Coma Scale score, size of pupils on admission, and age. However, no specific evidence points to patient groups in which DC would be the most beneficial, and no tests definitively determine which patients are suitable for DC.

The surgical technique must consider the location, hemisphere, size of decompression, and dural technique. The CT scan can provide the location and hemisphere; contusions, extradural or subdural hemorrhage, or unilateral swelling or midline shift would indicate need for unilateral decompression. Bifrontal decompression would be necessary for diffuse cerebral edema with no apparent midline shift on the CT scan. The timing of DC has variable results also. Favorable outcomes have been associated with surgery at less than 24 hours, or with early decompression at less than 16 hours, or not associated with timing at all. One study comparing DC versus hinge craniectomy found that the hinge procedure, in which the bone flap is not completely removed, was as effective as the traditional DC in.
controlling ICP without an increased risk of reoperation. Complications of DC that must be considered in relation to the benefits include subdural hygroma (16%-50%), progression of hemorrhage/contusion (5%-58%), intracranial infection (2%-6%), contralateral extradural or subdural hemorrhage (6%-28%), hydrocephalus (2%-29%), herniation through the skull defect (26% in 1 case study), syndrome of the trhephined, and paradoxical herniation. Complications of subsequent cranioplasty include bone flap resorption/sinking after cranioplasty (1.6%-12%), infection (11%), and status epilepticus (1.6%).

Two current RCTs are under way because TBI has severe physical, psychological, social, and economic consequences; no class I evidence from RCTs for use of DC to control increased ICP in patients with TBI is available as yet, and complication rates can be determined from such studies. The 2 studies, RESCUEicp study and DECREA trial, are multicenter prospective RCTs, with the former comparing neurological outcome with DC versus maximal medical management of increased ICP in TBI and the latter evaluating the effect of early (within 72 hours of injury) DC on neurological function in patients with TBI. Both studies are still recruiting patients, and the results will have critical implications for determining the role of DC for control of increased ICP and indications for its use. From these outcomes, guidelines can be developed to more definitively advise the medical community on the use and timing of DC for patients with increased ICP after TBI.

COMMENT

The focus of management of patients after TBI is to minimize secondary brain injury by avoiding hypoxia, maintaining adequate CPP, and controlling ICP. In this comprehensive review, Dr Li and her colleagues from the Academic Neurosurgery Unit at the University of Cambridge and Addenbrooke's Hospital summarize the current state of the evidence with regard to surgical intervention after TBI, including timely evacuation of mass lesions, EVD insertion, and DC.

A key component in the management of TBI is to recognize which patients are at risk of developing raised ICP after injury, so that adequate monitoring and management protocols can be put in place. Awake patients can be assessed for clinical signs of raised ICP, including headache, confusion, and drowsiness. However, these signs cannot be assessed in patients with reduced level of consciousness. The Brain Trauma Foundation published guidelines that include indications for ICP monitoring after TBI. Patients who meet these indications are not always monitored, and literature reviews suggest that monitored patients, possibly with more severe head trauma, have worse survival.

The Cambridge group previously reported an improvement in outcome when patients at risk of developing raised ICP are managed in a specialized center using protocol-driven management regimens.

Surgical intervention in TBI may involve evacuation of a mass lesion or surgical techniques to control ICP (ie, EVD or DC). It is broadly accepted that extraparenchymal lesions causing notable mass effect should be evacuated. More controversial is the role for surgical intervention in the management of intraparenchymal lesions. A multicenter RCT attempting to clarify this problem has been initiated.

What is the current conventional wisdom concerning CPP and ICP limits? Current Brain Trauma Foundation recommendations advocate maintaining ICP at less than 20 mm Hg and CPP at 50 to 70 mm Hg. Management protocols generally consist of a number of "tiers," with medical therapy supplied in an escalating manner if ICP and CPP targets are not reached. Surgical approaches can be considered when ICP continues to be inadequately controlled. Ventricular catheterization as a means of measuring ICP has the advantage that it allows ICP monitoring as well as drainage of CSF to relieve elevated ICP. Evidence supports the intervention as a relatively safe and effective means of reducing ICP, although measured ICP values must be interpreted with caution, because they may differ substantially from intraparenchymal ICP.

The role of DC, despite first description more than a century ago, either early in the management of patients at risk of raised ICP or as a rescue therapy for refractory cerebral edema, remains controversial. The authors present the existing evidence from the only RCT published on this technique to date, as well as other recently published evidence. Although the trend in the literature is toward a reduction in mortality and ICP after DC, favorable long-term outcome may not occur in the majority of patients. The evidence is inconsistent and at times contradictory. There are also many confounding factors making the interpretation of the evidence in the published studies difficult and highlighting the need for robust evidence from RCTs.

The results of 2 ongoing RCTs are eagerly awaited, as they should provide some clarity with regard to the role and timing of DC. The Cambridge-led RESCUEicp study will examine the effect of DC versus maximal medical therapy for refractory intracranial hypertension on outcome and quality of life up to 2 years after injury. The Australian DECREA trial will evaluate the effect of early DC (within 72 hours of injury) on outcome in patients with severe brain injury.

In focusing on the surgical approach to management of TBI, the authors have not mentioned some recent medical advances in neurotrauma critical care. There is growing evidence favoring the use of hypertonic saline as a resuscitation fluid and as osmolar therapy for ICP control. In addition, β-blockers have shown promising neuroprotective effects in animal models of TBI and retrospective trauma registry reviews, although prospective studies are lacking. The precise role of therapeutic hypothermia has yet to be defined. Advances in monitoring technology continue, including the broadening clinical application of microdialysis catheters to monitor intraparenchymal tissue oxygenation. Although progress has certainly been made in prevention and treatment of TBI, what defines optimal management remains controversial. Ongoing research initiatives should ensure further progress in this field.

Comment by Mortimer Kelleher, MB, FCARCSI and Anthony J. Cunningham, MD, FRCPC

REFERENCES


Perioperative Hypothermia (33°C) Does Not Increase the Occurrence of Cardiovascular Events in Patients Undergoing Cerebral Aneurysm Surgery: Findings From the Intraoperative Hypothermia for Aneurysm Surgery Trial

Hoang P. Nguyen, * Jonathan G. Zaroff, † Emine O. Bayman, ‡ Adrian W. Gelb, † Michael M. Todd, † and Bradley J. Hindman, ‡ on behalf of the IHAST-MIDS and IHAST Investigators

(Anesthesiology; 113:327–342, 2010)

*Department of Medicine, Kaiser San Francisco Medical Center; and †Kaiser Northern California Division of Research, San Francisco, CA; ‡Department of Anesthesia, Carver College of Medicine, and ¶Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA; and †Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA.

Copyright © 2011 by Lippincott Williams & Wilkins

DOI: 10.1097/01.SA.00003494256.11197.64

The use of mild systemic hypothermia in treating neurological insults carries known risks along with potential benefits. The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a multicenter, prospective, randomized, partially blinded trial to determine whether mild intraoperative systemic hypothermia could improve neurological outcome in patients with intracranial aneurysms compared with intraoperative normothermia. The IHAST prospectively followed events in other systems, including the cardiovascular system. This study was designed to determine whether intraoperative hypothermia is associated with a greater incidence of cardiovascular events. Because perioperative hypothermia can increase cardiac injury and dysfunction associated with subarachnoid hemorrhage (SAH), a subset of IHAST patients underwent preoperative and postoperative assessments of myocardial injury and left ventricular (LV) function.

The patients were having surgery for cerebral aneurysm and were randomized to intraoperative hypothermia (n = 499, 33.5°C ± 0.8°C) or normothermia (n = 501, 36.7°C ± 0.5°C). Cardiovascular events, including hypotension, arrhythmias, vasopressor use, myocardial infarction, and others, were prospectively followed up for 3 months and compared in the 2 groups of patients. A subset (Myocardial Injury and Dysfunction Sub-study [MIDS]) of 33 patients from the hypothermia group and 29 from the normothermia cohort also had preoperative and postoperative (within 24 hours) measurement of cardiac troponin I and transthoracic echocardiography to determine the association between perioperative hypothermia and troponin release, LV dysfunction, or regional wall motion abnormalities.

Overall, patients in the 2 groups were similar in age, sex, pre-SAH cardiovascular history, preoperative neurological condition, severity of SAH, and characteristics of the cerebral aneurysm. The 2 groups did not differ in temperature on arrival to the operating room. Rewarming of hypothermic patients began after final clip placement, but core temperatures increased by only ~1°C by the end of surgery. Thus, 60% of the hypothermic patients remained intubated at arrival to the post-anesthesia care unit compared with 24% of the patients in the normothermia group. At 2 hours postoperatively, 25% of hypothermic patients were still intubated compared with 13% in the normothermia group. At 24 hours postoperatively, ~10% of patients in each group were still intubated. During the perioperative period, the most common cardiovascular events were administration of vasopressor to 25% of patients and unintended hypertension in 7% of patients. Arrhythmias and unintended hypotension occurred in less than 5% of patients. Postoperatively, vasopressor administration, congestive heart failure or pulmonary edema, and unintended hypertension were reported in 22%, 9%, and 9% of patients, respectively. Nonventricular arrhythmias, unintended hypotension, and myocardial infarction and ventricular arrhythmias were infrequent occurrences. The 2 groups did not differ in the occurrence of any single cardiovascular event or in composite cardiovascular events, nor did the groups differ in postoperative versus preoperative LV regional wall motion or ejection fraction. Sixty-one patients died between randomization and 3-month follow-up, although the mortality rate was 6% in both groups. Causes of death were neurological in 46 patients (75%), respiratory in 6 (10%), pulmonary embolus in 4 (7%), sepsis in 4 (7%), and cardiovascular in a single patient (<2%). Eight hypothermic patients and 6 normothermic patients had 30 postoperative cardiovascular intermittent events rated as fatal by investigators. However, none was a direct or primary cause of death. The preoperative and intraoperative characteristics of the 62 MIDS patients did not differ from the rest of the IHAST population of 938 patients except that the use of a perioperative vasopressor was reported in 60% of MIDS patients compared with 23% of non-MIDS patients. The development of cardiovascular events did not differ between the MIDS and IHAST patients, nor did the aneurysm characteristics in MIDS patients or occurrence of cardiovascular events in the hypothermia or normothermia groups. Hypothermic MIDS patients showed no net change in cardiac troponin levels in preoperative and postoperative samples, whereas normothermic patients had a small postoperative increase of 0.01 μg/L. These results indicate that, in patients in the IHAST and IHAST-MIDS studies, perioperative hypothermia is not associated with an increased frequency of cardiovascular events in patients undergoing surgery for good-grade cerebral aneurysms.

COMMENT

Mild therapeutic hypothermia (33°C) has been reported to improve neurological outcome and reduce mortality in patients after anoxic-ischemic brain injury, cardiac arrest, and traumatic brain injury. However, potential neurological benefits of using mild hypothermia may come at a prohibitive cost. Perioperative hypothermia has been reported to be associated with an increased incidence of cardiovascular complications.1-3 Cardiovascular injury and dysfunction are also known to be associated with SAH. These cardiac abnormalities appear to be mediated through increased sympathetic activity.6,7 Could perioperative hypothermia aggravate SAH-associated cardiac dysfunction?
The IHAST study was a 1000-patient, multicenter, prospective, randomized, partially blinded investigation carried out between 2000 and 2003, whose primary aim was to determine whether mild intraoperative systemic hypothermia would improve neurological outcome in patients with intracranial aneurysms compared with normothermia. As part of trial safety design, a subset of patients, the MIDS, underwent preoperative and postoperative cardiac enzymes and echocardiographic assessment of myocardial function.

The investigators reported no difference between hypothermic and normothermic patients in postoperative versus preoperative LV ejection fraction or regional wall motion. A small postoperative increase in cardiac troponin (median increase of 0.01 μg/L) was recorded in normothermic patients. The remarkable study finding was that there was no difference in cardiovascular events between the normothermic and hypothermic IHAST groups. Mild hypothermia did not increase the incidence of arrhythmias or adverse cardiovascular events.

Notable study design limitations include post hoc analyses, partial blinding, small MIDS sample size, smaller number of centers in MIDS subgroup, and low incidence of preoperative SAH-related cardiac dysfunction in the MIDS population, resulting in underpowering of the MIDS study. Although all patients had continuous arterial blood pressure monitoring, the anesthetic technique was not standardized, and the method of achieving the desired blood pressure (fluids and/or vasoactive medication) was decided by the treating anesthesiologist.

How relevant are the study findings? Endovascular treatment has largely superseded craniotomy and surgical clipping of aneurysms, and hypothermia is not standard practice with this technique. Nonetheless, this is the largest study of intraoperative hypothermia conducted to date, and the findings are in marked contrast with earlier studies that reported an increased incidence of cardiovascular complications. A number of factors may have been associated with increased cardiovascular complications in the hypothermia patients, including a higher incidence of coronary artery disease, longer duration surgery, and greater blood loss. Maintaining sedation postoperatively while rewarminmg in the hypothermic patients in the current study may have attenuated some of the adrenergically mediated cardiovascular effects of hypothermia.

Comment by Jane Bruton, MB, FCArCS and Anthony J. Cunningham, MD, FRCPC

REFERENCES


The Acute Management of Intracerebral Hemorrhage: A Clinical Review

Justine Elliott and Martin Smith

Department of Neuroanaesthesia and Neurocritical Care, The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Service, NHS Trust, London, United Kingdom. Copyright © 2011 by Lippincott Williams & Wilkins. DOI: 10.1097/01.ANA.0000394257.88325.06

Intracerebral hemorrhage (ICH) is a devastating disease that has high rates of mortality and morbidity. Chronic arterial hypertension and oral anticoagulation are major risk factors for ICH. After the initial hemorrhage, hematoma expansion and perihematoma edema lead to secondary damage and a worse outcome. A rapid onset of focal neurological deficit with clinical signs of increased intracranial pressure strongly suggests a diagnosis of ICH, although cranial imaging is needed to differentiate it from ischemic stroke. Intracerebral hemorrhage is a medical emergency, and initial management should concentrate on urgent stabilization of cardiorespiratory variables and treatment of intracranial complications. More than 90% of patients present with acute hypertension, and evidence exists that acute arterial blood pressure reduction is safe and associated with a slowing of hematoma growth and a lessened risk of early neurologic deterioration. However, early optimism that the outcome can be improved by early administration of recombinant factor VIIa (rFVIIa) has not been proved in a large phase 3 study. Intracerebral hemorrhage is the most feared complication of warfarin anticoagulation, and the need to stop intracranial bleeding outweighs all other considerations. Treatment options for reversing warfarin include vitamin K, fresh frozen plasma, prothrombin complex concentrates, and rFVIIa. Evidence is lacking to guide the specific management of antiplatelet therapy–related ICH. With the exception of placement of a ventricular drain in patients with hydrocephalus and evacuation of a large posterior fossa hematoma, the timing and nature of other neurosurgical interventions are controversial as well. Substantial evidence exists that management of patients with ICH in a specialist neurointensive care unit, where treatment is focused on monitoring and managing cardiorespiratory variables and intracranial pressure, is associated with an improvement in outcomes. Attention must be paid to fluid and glycemic management, minimizing the risk of ventilator-acquired pneumonia, fever control, provision of enteral nutrition, and thromboembolic
prophylaxis. Awareness is increasing that aggressive management in the acute phase can result in improved outcomes after ICH.

COMMENT

Intracranial hemorrhage, defined as a spontaneous extravasation of blood into the brain parenchyma and critically associated with chronic arterial hypertension and oral anticoagulant therapy, can be followed by up to 50% mortality at 30 days and the potential for poor functional outcome in survivors. This review considers that the majority of intracranial hemorrhages are not primary spontaneous, but rather secondary events as a result of arterial hypertension. Hypertension, especially in the older population, is the most important modifiable risk factor. Unfortunately, 50% of hypertension-related ICH occurs in the deeper basal ganglia and thalamic structures. Warfarin-related ICH can be associated with an 8- to 19-fold increased ICH risk, suggesting that any means that circumvent the need for anticoagulation in atrial fibrillation should be explored, wherever feasible. These options might include, for example, pharmacological or electrical cardioversion, pulmonary vein isolation, left atrial appendage occlusion, or the Maze procedure.

The review highlights the dynamic nature of ICH progression from initial hemorrhage to hematoma expansion to perihematoma edema. Initial clinical features, such as change in consciousness, headache, and vomiting can be subtle. Hence, a high index of suspicion should be reserved for those at risk. Early brain computed tomography scan is the cornerstone of diagnosis and identification of complications such as hydrocephalus, enabling the proven benefit of early placement of a ventricular drain. The volume of blood and Glasgow Coma Score are the most powerful predictors of 30-day mortality.

Management is resource-intensive, and good infrastructure for transfer to a specialized center should be considered. Patient outcome is optimal in a tertiary neurocritical care referral center. Here, general and neuroprotective supportive measures should be instituted in a protocol-driven fashion. If the clinical condition permits, appropriately timed angiography allows detection of anatomical abnormalities such as angiographically occult arteriovenous malformations. This is particularly important in young patients with no obvious risk factors. Good blood pressure control has been reported to halt hematoma expansion and improve outcome, in contrast with ischemic stroke, because of a lack of an ischemic penumbra. Blood pressure reduction, in contrast, has not proven safe in severely affected patients with a large hematoma and increased intracranial pressure.

The review features detailed discussion of the relative risks and benefits of hemostatic interventions, including vitamin K, fresh frozen plasma, prothrombin complex concentrate, and rFVIIa. The benefit of rFVIIa is offset by high cost and increased thromboembolic complications. Early computed tomography angiography may help identify patients who would benefit most. Prompt administration of vitamin K and clotting factors, regardless of the original indication for anticoagulation, is paramount. Surgical intervention, including minimally invasive clot evacuation, may be of benefit in patients with superficial clots and milder deficits. Large cerebellar hemorrhages with brainstem compression or obstructive hydrocephalus should be evacuated emergently. Aggressive management in the acute phase of ICH may improve patient outcome by ensuring a less fatalistic perception and more timely and concerted effort in preventing secondary brain injury.

REFERENCES


Stenting Versus Endarterectomy for Treatment of Carotid-Artery Stenosis


*Mayo Clinic, Jacksonville, FL; †University of Medicine and Dentistry of New Jersey, Newark, NJ; ‡University of Alabama at Birmingham, Birmingham, AL; §Lenox Hill Hospital, New York, NY; and ¶Oregon Health and Science University, Portland, OR; §Central Baptist Hospital, Lexington, KY; ¶Centres Hospitaliers et Universitaires de l’Enfant-Jesus, Quebec, Canada; ‡‡University of Calgary, Calgary, Alberta, Canada; ‡§Boston University School of Medicine, Boston, MA; ‡¶University of Oregon Health Sciences University, Portland, OR; ‡§§University of California, Los Angeles, CA; ‡§§§University of Buffalo, State University of New York, Buffalo, NY; ¶¶¶Harvard Clinical Research Institute, Harvard Medical School, Boston, MA; ¶¶¶¶Saint Luke’s Mid America Heart Institute, Kansas City, MO; ###Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; ####MetroHealth Medical Center, Cleveland, OH; ####‡‡‡Neuroscience Institute, Las Vegas, NV; †††University of Toronto, Toronto, Ontario, Canada; §§§University of Medicine and Dentistry of New York, New York, NY; and ||||University of Maryland Medical Center, Baltimore, MD.

Copyright © 2011 by Lippincott Williams & Wilkins

DOI: 10.1097/01.SA.0000394258.88325.ef

Carotid artery stenting (CAS) and carotid endarterectomy (CEA) are options to treat symptomatic and asymptomatic patients with carotid artery atherosclerosis/stenosis. The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) is a randomized, controlled trial designed to compare the outcomes of CAS with those of CEA in a blinded end-point adjudication. Patients were enrolled from 108 centers in the United States and 9 in Canada. Eligibility criteria for symptomatic patients were stenosis of 50% or greater on angiography, 70% or greater
on ultrasonography, or 70% or greater on computed tomography angiography or magnetic resonance angiography if stenosis on ultrasonography was 50% to 69%. For asymptomatic patients, criteria were stenosis of 60% or greater on angiography, 70% or greater on ultrasonography, or 80% or greater on computed tomography or magnetic resonance angiography if the stenosis on ultrasonography was 50% to 69%. Carotid artery stenting and CEA were performed according to published guidelines. Patients undergoing CAS received the RX Acculink stent (Abbott Vascular Solutions, Redwood City, CA) and, if possible, the RX Accucut embolic protection device (Abbott Vascular Solutions). Before CAS, patients were given aspirin (325 mg twice a day) and clopidogrel (75 mg twice daily). Doses for patients undergoing stenting within 48 hours of randomization were 650 mg aspirin and 450 mg clopidogrel 4 hours or more before the procedure. Postoperatively, patients received aspirin for 30 days and either clopidogrel or ticlopidine for 4 weeks. Patients in the CEA group received 325 mg aspirin daily and then continued with that dose for 1 year or longer. Alternatives were ticlopidine 250 mg twice daily, clopidogrel 75 mg daily, aspirin 81 mg daily, or aspirin and extended-release dipyridamole twice a day. All patients received medical therapy consistent with standards of care, including treatment for hypertension and hyperlipidemia. Neurological evaluation was done at baseline and 18 to 54 hours and then 1 month and every 6 months after the procedure. Assessment tools included the National Institutes of Health Stroke Scale, the modified Rankin scale, and the Transient Ischemic Attack Stroke Questionnaire. The primary composite end point was stroke, myocardial infarction, or death from any cause during the procedural period or any ipsilateral stroke within 4 years after randomization.

The final patient cohorts, from 2522 patients randomly assigned, included 1262 and 1240 in the CAS and CEA groups, respectively. The 2 groups were similar in baseline characteristics, although dyslipidemia occurred in 85.8% of patients in the CEA group compared with 82.9% in the CAS group. Both groups had high rates of vascular risk factors, and more than 80% of patients had severe stenosis. Median time from randomization to the procedure was 6 days for CAS and 7 for CEA. In the CAS group, 96.1% of patients had embolic protection; in the CEA group, 90.0% of patients had the procedure done under general anesthesia. Median duration of follow-up was 2.5 years, during which the level or prevalence of selected risk factors remained similar between the 2 groups, except for smoking. The estimated 4-year rates of the primary end point between CAS and CEA were 7.2% and 6.8%, respectively, not a statistically significant difference. Seven patients in the CAS group and 6 in the CEA group had fatal strokes; 1 myocardial infarction was fatal and occurred in a CEA patient. Rates for the primary end point during the periprocedural period were 5.2% and 4.5% for the CAS and CEA patients, respectively. However, individual end points differed between the CAS and CEA groups, with death occurring in 0.7% and 0.3%, stroke in 4.1% and 2.3%, and myocardial infarction in 1.1% and 2.3%, respectively. After the procedural period, the incidence of ipsilateral stroke was 2.0% for CAS and 2.4% for CEA. No modification of the treatment effect was found for the patients’ symptomatic status or sex. Treatment efficacy had an interaction with age, with a crossover at about age 70 years. Carotid artery stenting had greater efficacy at younger ages and CEA at older ages. During the periprocedural period, rates of the primary end point were 6.7% and 5.4% for the CAS and CEA groups, respectively, and 3.5% and 3.6% among asymptomatic patients. Rates of cranial nerve palsies were 0.3% and 4.7% in the CAS and CEA groups, respectively. The 4-year rates of stroke or death were 6.4% and 4.7% in the CAS and CEA groups, respectively, with respective rates of 8.0% and 6.4% among symptomatic patients and 4.5% and 2.7% among asymptomatic patients. Major and minor stroke had an effect on physical health at 1 year, with minor stroke also having a notable effect on mental health at 1 year.

The results indicate that CAS and CEA had similar rates of the primary composite outcome of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke in patients with symptomatic or asymptomatic carotid stenosis. The low absolute risk of recurrent stroke indicates that both CAS and CEA are clinically durable and likely reflect the advances in medical therapy.

**COMMENT**

Carotid endarterectomy and, more recently, CAS have become established procedures to prevent ischemic strokes in symptomatic and asymptomatic patients with carotid artery atherosclerosis. Comparative studies of the 2 procedures have reported conflicting outcome data.\(^1\)\(^2\) The CREST North American investigators conducted a well-designed, large (2522 patient), multicenter randomized trial comparing carotid CAS and CEA for the treatment of carotid artery stenosis. Important clinical end points including death, stroke, and myocardial infarction were considered with an adequate 4-year duration and complete follow-up.

The risk of composite primary outcome of stroke, myocardial infarction, and death in patients with both symptomatic and asymptomatic carotid stenosis was similar in the 2 procedure groups. However, the incidence of perioperative stroke was lower in the CEA group, whereas the incidence of periprocedural myocardial infarction was lower in the stenting group. Age may be a consideration regarding choice of procedure because younger patients had a better outcome with stenting and older patients with CEA, possibly related to increased vascular tortuosity and calcification in older patients.

The 6.0% rate of stroke or death in symptomatic patients undergoing CAS in this CREST study was reported. This may be a reflection of patient heterogeneity rather than the superiority of 1 intervention over the other. The rates of stroke and death during the 4 years were 2.7% and 4.5%, respectively, in the asymptomatic patients. Important caveats in interpreting the study findings include the optimal aspirin and clopidogrel medical therapy, the 96.1% use of embolic protection in the CAS group, and the 90.0% use of general anesthesia. Follow-up studies might include a reevaluation of current best medical therapy and interventional therapy and consideration of difference in procedural cost and length of hospital stay.

*Comment by Li Tan, MB, FCARCSI and Anthony J. Cunningham, MD, FRCP*
Abstract: We provide a summary of the 2010 literature pertinent to the care of neurosurgical patients and those requiring neurocritical care. In addition, we address topics in the basic neurosciences as they relate to neuroanesthesiology. This review incorporates studies not only from both neuroanesthesiology and general anesthesiology-focused journals, but also from neurology, neurosurgery, critical care, and internal medicine journals and includes articles published after January 1, 2010, through those available on-line by November 31, 2010. We will review the broad categories of general neuroanesthesiology, with particular emphasis on cerebral physiology and pharmacology, intracranial hemorrhage, carotid artery disease, spine surgery, traumatic brain injury, neuroprotection, and neurotoxicity. When selecting articles for inclusion in this review, we gave priority to those publications that had: (1) new or novel information, (2) clinical utility, (3) a study design possessing appropriate statistical power, and/or (4) meaningful, unambiguous conclusions.

Key Words: craniotomy, spine surgery, carotid endarterectomy, traumatic brain injury, intracranial hemorrhage, subarachnoid hemorrhage, neuroprotection

(J Neurosurg Anesthesiol 2011;23:67–99)

GENERAL NEUROANESTHESIOLOGY

Accreditation

Currently, there is a trend among anesthesiology subspecialties to seek accreditation by the Accreditation Council for Graduate Medical Education (ACGME), for standardization of fellowship training programs. As recently as one decade ago, the only anesthesiology subspecialties that offered ACGME certification were pain medicine and critical care. During the ensuing years, the ACGME instituted accreditation for adult cardiothoracic and pediatric anesthesiology. Regional anesthesiology, a non-ACGME accredited subspecialty, has established national guidelines for fellowship training.¹ In this context, accreditation and standardization of neuroanesthesiology fellowship training programs have once again come under discussion.²⁻⁵ Mashour et al⁶ performed a survey of members of the Society of Neuroscience in Anesthesiology and Critical Care residing in the United States (n = 339) to assess attitudes and opinions with regard to the need for accreditation of Neurosurgical Anesthesiology and guidelines for neuroanesthesiology fellowship training programs. Of the 134 respondents, 90% were from academic practices. Ninety percent of respondents stated that their primary job was clinical anesthesia (vs. primary research). Sixty-four percent of respondents indicated support of accreditation. Over 80% of respondents indicated that 1 year of fellowship training in neuroanesthesiology would be optimal. In addition, the top 5 factors which were considered to be important to a neuroanesthesiology fellowship curriculum were (listed in descending importance): (1) career development/mentorship, (2) neurocritical care, (3) intraoperative neuromonitoring, (4) neuroradiology, and (5) resident and medical student teaching. These data can help guide the members of Society of Neuroscience in Anesthesiology and Critical Care and training program directors when structuring neuroanesthesiology fellowship training programs. Such structure and (possibly someday) accreditation are likely to be critical for the future recruitment of highly qualified physicians to neuroanesthesiology subspecialty training fellowships. Reporting data from respondents, who did not favor accreditation, may have proven interesting, although this perspective was not included in the Mashour et al⁶ report.

Clinical Trends

Understanding the trends in neurosurgical procedures and utilization is critical to both the training and allocation of anesthesia providers. Hughey et al⁷ analyzed neurosurgical utilization data from the Nationwide Inpatient Sample⁸ (a hospital discharge database used to track trends in healthcare) for the interval 1993 to 2007. In 2007, the most common neurosurgical procedure was spinal fusion, accounting for 54% of registered procedures, although it was not discernible whether these procedures were performed by neurosurgeons or orthopedic surgeons (a mix of providers seems likely). Spinal fusion also had the highest absolute growth rate over the study period (54,000 registered procedures in 1993 to 350,000 in 2007), with the rate of growth during the last 5 years at 14%. Although endovascular procedures of the head and neck (including carotid stenting) were the second most common procedure performed (accounting for 20% of neurosurgical procedures overall with 116,000 procedures registered in 2007), this procedure experienced...
a slight decrease over the last 5 years. Intracranial endovascular procedures (including aneurysm coiling and arteriovenous malformation embolization) had the highest rate of growth in the last 5 years (29%); however, only 849 procedures were registered in the database in 2007. Craniotomy performed for vascular disorders exhibited a slight decrease (4.2%) over the 15-year study period, but craniotomy performed for tumor resection (71,000 procedures performed in 2007) showed a steady 2.3% increase over the study period. The investigators hypothesize that this latter finding is due to an increase in the prevalence of brain cancer in the United States.9 Craniotomy performed for nonvascular, nontumor purposes (56,000 procedures registered in 2007) showed a 4.0% increase in the last 5 years. Collectively, 75,000 craniotomy procedures were registered in the database in 2007. Shunt procedures for hydrocephalus had a steady growth over the 15-year study period (1.3%) but showed a 6.6% reduction in the number or registered procedures over the last 5 years, possibly due to endoscopic alternatives to mechanical shunts for treatment of obstructive hydrocephalus. Deep brain stimulator (DBS) placement increased 12% over the entire study period with only a small increase (0.6%) over the last 5 years. This latter finding was surprising, given the apparent increase in publications in the medical and public literature and media addressing DBSs. As such, although craniotomy procedures are still commonly performed, spinal fusion and endovascular procedures of the head and neck represent the greatest number of neurological (or neurosurgical-like) cases performed in 2007.

Although implantation of DBSs represent a small fraction of neurological surgical procedures, this technique offers promise for the treatment of Parkinson disease, essential tremor, and depression in patients for whom medical therapy has failed. However, there are few published data on the long-term impact of DBS in patients with advanced Parkinson disease. Williams et al10 reported results from the PD SURG trial, which included patients for whom medical therapy was failing. Study patients were randomized to either receive continued “best” medical therapy alone (n = 183) or DBS implantation in addition to best medical therapy (n = 183). The primary outcome measure was score on the 39-item Parkinson disease questionnaire (PDQ-39), the most widely-used patient-reported rating scale for assessment of the severity of Parkinson disease.11–13 The PDQ-39 assesses functional performance (eg, mobility, communication, performance of activities of daily living), cognition, discomfort, and psychological factors (eg, emotional well-being, stigma, social support) on a scale of 0 (no deficit) to 100 (most severely affected by Parkinson disease). As such, a decrease in score represents improvement in condition. Mean PDQ-39 scores at baseline were 37.5 ± 14.6 and 38.7 ± 13.7 (mean ± SD) in the surgery and medical management groups, respectively. At 1 year, scores were 32.5 ± 15.8 and 38.1 ± 13.5, respectively, representing a mean improvement of 5.6 [95% confidence interval (CI), 2.4-8.9; P = 0.0008] points in patients who underwent surgery. Improvement was most significant in mobility, performance of activities of daily living, feelings of the social stigma from Parkinson disease, and bodily discomfort. No significant improvement in emotional well-being, social support, cognition, or communication was noted. Adverse events were more common in the surgery group: 96 events occurred in 65 patients (36% of patients) versus 29 events occurring in 26 patients (14% of patients) in the medical therapy group. Surgery-related events were infection (16 events), intracranial hemorrhage (4 events with 1 fatality), postoperative confusion (5 events), and urinary retention (4 events). In addition, there were 3 deaths during the study period: 1 due to hemorrhage and 1 due to pneumonia in the surgery group, and 1 stroke in the medical management group. One unsuccessful suicide attempt occurred in the surgery group. On balance, DBS implantation seems to offer benefits to patients with medically intractable Parkinson disease. However, this procedure is not without risks. We refer interested readers to a 2010 article in the New England Journal of Medicine by Follett et al14 in which 299 patients with severe Parkinson disease were randomized to receive stimulator lead placement into either the globus pallidus or the subthalamic nucleus. Although the groups did not differ in the degree of overall improvement of symptoms (P = 0.50), those who received subthalamic stimulation: (1) required a lower dose of additional anti-Parkinson medications to provide optimal symptom control, but (2) had greater worsening of visuomotor processing speed (P = 0.03), and (3) had worsened depression while those who had pallidal stimulation had improved depression scores (P = 0.02).

There was no difference in serious adverse events between groups.

Airway management in acromegalic patients can be complicated by macroglossia, progagism, and hypertrophy of pharyngeal and laryngeal tissues, making mask fit, mask ventilation, laryngoscopy, and correct tracheal tube placement difficult. Although no method of airway assessment is fool-proof for predicting the difficult airway, one of the most commonly accepted assessment techniques is the Mallampati classification,15 which is based on the anatomic structures visualized when patients open their mouths. The 4 Mallampati classes are: class I, full visibility of soft palate, tonsils, and uvula; class II, visibility of soft palate but only the upper portion of the tonsils and uvula; class III, only soft palate and base of the uvula are visualized; and class IV, only the hard palate is visualized. A Mallampati class of III or IV is predictive of airway management difficulty in acromegalic.16 An alternate airway assessment modality is the upper lip bite test (ULBT) in which a patient is asked to cover the vermilion of the upper lip with the lower incisors.17 The ULBT has 3 grades: grade 1, ability of lower incisors to fully cover the upper lip and extend superior to the vermilion border; grade 2, lower incisors can bite the upper lip but only inferior to the vermilion border; and grade 3, lower incisors are not able to bite the upper lip at all. A higher grade can be predictive of airway management.
Difficult airway management refers to the number of patients in each group in whom correct placement of the tracheal tube required >2 attempts and required a change of technique such as laryngoscope blade change, use of a bougie, or fiberoptic devices. 

See manuscript text for the description of the classification systems.

Difficult airway management refers to the number of patients in each group in whom correct placement of the tracheal tube required > 2 attempts and required a change of technique such as laryngoscope blade change, use of a bougie, or fiberoptic devices.

Adapted with permission from J Neurosurg Anesthesiol. 2010;22:138-143.

CL indicates Cormack and Lehane grade.

**TABLE 1. Airway Assessment and Management Data From Patients Having Pituitary Surgery Stratified Based on the Presence or Absence of Acromegaly**

<table>
<thead>
<tr>
<th></th>
<th>Acromegaly Group (n = 62)</th>
<th>Non-acromegaly Group (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL 1 or 2</td>
<td>CL 3 or 4</td>
</tr>
<tr>
<td>Mallampati class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>III or IV</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Upper lip bite test grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Difficult airway management</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

Data represents the number of patients in each group.

For Mallampati class was 0.581 and 0.765 in acromegalics and non-acromegalics, respectively, and for ULBT was 0.535 and 0.759 in acromegalics and non-acromegalics, respectively, indicating that both Mallampati Scoring and ULBT are less predictive of airway difficulty in acromegalics versus non-acromegalics.

**Physiology**

Endoscopically facilitated neurosurgical procedures offer a minimally invasive option for biopsy and resection of cysts and masses in the ventricular system and an alternative to ventriculoperitoneal shunting for the treatment of obstructive hydrocephalus (eg, third ventriculostomy, aqueductoplasty, aqueductal stenting). Major concerns with neuroendoscopic procedures are the intraoperative and postoperative complications. Cardiac arrhythmia and hemodynamic changes are most common, but cranial nerve dysfunction and intracranial hemorrhage can also occur. These cardiac and hemodynamic changes have been attributed to changes in intracranial pressure (ICP), possibly due to temporary obstruction of the outflow of irrigation fluid through the neuroendoscope. To confirm that the pressure recorded by the neuroendoscope correlates with ICP, Salvador et al measure both epidural pressure and the pressure transduced from the irrigating lumen of the neuroendoscope in 17 patients having neuroendoscopic procedures. The epidural pressure was measured by a transducer placed in the epidural space within the same burr hole used for the endoscopic procedure, and the epidural transducer was placed before dural opening for advancement of the endoscope. Of all data from all patients, the Pearson correlation coefficient was 0.59 (P = 0.001), suggesting moderate agreement. Lin concordance coefficients were calculated for epidural versus neuroendoscopic pressures. This analysis is used to assess the extent to which the correlation between 2 parameters deviates from the line originating at the origin (0,0) with a slope of 1. Lin coefficients exist in the range of 0 (no correlation) to 1 (perfect correlation). A Lin coefficient > 0.5 occurred in 9 (53%) of patients. Of all data in all patients, the Lin coefficient was 0.58 (CI, 0.577-0.592), also
suggesting moderate correlation. The agreement between the 2 pressures became more divergent at higher epidural pressures. Epidural pressure was higher than the pressure measured from the endoscope in 15 patients (88%). As such, the pressure transduced from the inflow port on the neuroendoscope may be useful for following trends, but in most circumstances this pressure is lower than the epidural pressure. Of note, the ability of inflow port pressures to predict absolute, or trends in, epidural pressures may become even less reliable at higher epidural pressure values.

Head-up positioning, including the sitting position, is used for procedures other than neurosurgery (eg, shoulder surgery). Cases of cerebral ischemia have been reported in non-neurosurgical patients during head-up positioning, and this finding was attributed to cerebral hypoperfusion secondary to reduced cerebral perfusion pressure (CPP), although some emphasize that global CCP may not be the only driving force of cerebral blood flow (CBF).24–28 Currently, it is unclear whether changes in posture influence cerebral perfusion enough to lead to a stroke. Murphy et al29 studied changes in regional cerebral oxygen saturation (rSO2) [by near-infrared spectroscopy with the FORE-SIGHT system (CAS Medical Systems, Inc., Bradford, CT)] during positioning in 124 patients having shoulder surgery by a standardized anesthetic in either the beach-chair or lateral decubitus position. Operative position was determined by surgeon preference. Although the anesthesia team was blinded to the rSO2 values (only directly observed by a research assistant), if a cerebral desaturation event (defined as a decrease in rSO2 by > 20% of baseline value or a decrease to < 55% for > 15 s) occurred, then the anesthesia team was instructed to treat the event by performing at least one of the following: (1) increase systemic blood pressure, (2) increase end-expired CO2 by decreasing minute ventilation, or (3) increase the fraction of inspired oxygen. Although there was no difference in heart rate or blood pressure between groups during position change, a significantly greater number of patients in the sitting position group (80%) developed cerebral desaturation events during positioning compared with the lateral position group (0%; P < 0.0001). Blood pressure was measured by an automated blood pressure cuff, obtained from the nonoperative arm, and without correction for vertical distance between the arm and the external auditory meatus (ie, the presumed level of the circle of Willis). No patient awoke from anesthesia with a new neurological deficit. These data suggest that cerebral hypoperfusion, when going from supine to sitting position, is common and may be, in part, independent of systemic blood pressure. It would have been interesting if the investigators had performed a correlation analysis between change in systemic blood pressure and change in cerebral rSO2 accompanying the change from supine to sitting position. Further, although the investigators provided some data on the cerebral desaturation events, it was difficult for the reader to appreciate the nature and time course of these events (eg, the duration in the sitting position after which the event occurred, the duration of the events, and the number of events per patient).

In addition to the risk of cerebral hypoperfusion, the sitting position, when used for open intracranial procedures, predisposes to pneumocephalus. The incidence of pneumocephalus can be as high as 100%; however, currently available data do not describe the characteristics of the supratentorial component of air. Sloan30 reported a retrospective analysis of data derived from 95 patients having intracranial procedures performed in the sitting position, in whom postoperative cranial imaging was performed. Supratentorial pneumocephalus was identified in 40 patients (42%) on imaging performed within 4 hours of surgery with an estimated volume range of 6 to 280 cm3. There was no significant difference in the incidence of air or estimated air volume between patients with or without either a ventriculoperitoneal shunt or an external ventricular drain (some have attributed the development of postoperative pneumocephalus to the presence of these devices).31,32 Specifically, the incidence and volume of air was 42% and 87 ± 91 cm3 in patients with either a shunt or a drain and 42% and 71 ± 79 cm3 in patients without either of these devices (P > 0.05 for both comparisons). No measurable pneumocephalus was noted in patients in whom surgery lasted ≤ 4 hours. No patient required postoperative surgical release of air; however, several patients were obtunded in the recovery room (number not stated). Head imaging was obtained on 5 patients on multiple days after surgery. Overall, there was a 24% reduction in air volume in the first day with a mean half-life of 1.5 days for the decrease in air volume. On the basis of these data, supratentorial air would be predicted to be less than 0.5 cm3 within 13 days. This research determined that supratentorial air is common after intracranial procedures performed in the sitting position and may account for altered mental status postoperatively.

Cerebral autoregulation and the responsiveness of the cerebral vasculature to changes in the partial pressure carbon dioxide in arterial blood (PaCO2) are important homeostatic mechanisms for the regulation of CBF. Induced changes in blood pressure and PaCO2 will have different effects on the cerebral vasculature depending on the baseline functional status of brain physiology. Both CBF autoregulation and the responsiveness to changes in PaCO2 can be attenuated by the presence of a brain tumor;33,34 however, whether the integrity of these systems is restored after tumor resection remains to be elucidated. Accordingly, Sharma et al35 evaluated the effect of tumor resection on parameters thought to be reflective of autoregulation of CBF and responsiveness to PaCO2 in 35 patients having supratentorial tumor resection. Cerebrovascular responsivity to blood pressure changes was assessed by the transient hyperemic response when the ipsilateral common carotid artery is compressed for 10 s and then released while simultaneously assessing changes in middle cerebral artery blood flow velocity (Vmca) by transcranial Doppler sonography (TCD). The transient hyperemic response ratio (THRR) was then
calculated as the Vmca after the release of compression divided by the Vmca before compression. Under normal conditions (i.e., intact autoregulation), the THR has the value 1.35 ± 0.09 as one would expect an increase in Vmca after the release of compression due to the presence of compression-induced cerebral vasodilation.36 To assess reactivity to changes in PaCO₂, patients were asked to spontaneously hyperventilate to achieve a 10 mm Hg decrease in PaCO₂ and CO₂ reactivity was estimated by:

\[ 100 - \left( \frac{100 \times Vmca_f}{Vmca_i} \right) / (PaCO_2_i - PaCO_2_f) \]

where Vmcai and Vmcaf are the Vmca values obtained before and after hyperventilation, respectively, and PaCO2i and PaCO2f are values of PaCO2 obtained before and after hyperventilation, respectively. A normal value for CO2 reactivity assessed by this method is 2.74 ± 1.0%/mmHg.37 The investigators found no difference between preoperative and postoperative (obtained 6 to 24 h after resection) THR (1.27 ± 0.10 vs. 1.30 ± 0.12 for preoperative and postoperative values, respectively; \( P = 0.11 \)) or the calculated reactivity of the cerebral vasculature to changes in CO2 (3.41 ± 0.46%/mm Hg vs. 3.60 ± 0.63%/mm Hg for preoperative and postoperative values, respectively; \( P = 0.07 \)). Seven patients (20%) had impaired blood pressure reactivity before surgery. Although the investigators did not specify the THR cutoff criteria to define impairment, these 7 patients all had impairment of blood pressure reactivity postoperatively (THR preoperative and postoperative were 1.07 ± 0.02 vs. 1.06 ± 0.01, respectively; \( P = 0.18 \)) but intact reactivity to CO₂ (3.39 ± 0.46%/mm Hg vs. 3.67 ± 0.24%/mm Hg for preoperative and postoperative values, respectively; \( P = 0.17 \)). Although the investigators also did not report the criteria used to define impairment of CO₂ reactivity, when comparing patients with and without impairment of blood pressure reactivity, the only 2 factors associated with impairment were a larger tumor size (100 ± 32 cm³ vs. 40 ± 8 cm³; \( P = 0.002 \)) and midline shift >5 mm (the percentage of patients having blood pressure reactivity impairment with midline shift >5 mm was 100% vs. 15% in those with a lesser or no midline shift; \( P < 0.001 \)); however, impairment was not associated with age, sex, the presence of peritumoral edema, or tumor type. We refer readers interested in these types of clinical measurements to a pilot investigation by Klein et al38 that showed the utility of a novel device for intraoperative monitoring of the cerebral microcirculation. The O₂C device (oxygen-to-see device, LEA Medizintechnik, Gies- sen, Germany) allows for the simultaneous assessment of surrogate parameters of the cerebral microcirculation such as regional capillary venous blood flow, rSO₂, and regional hemoglobin concentration (based on photometry and laser Doppler flowmetry measurements).

Although PaCO₂ is an important factor modulating cerebral vascular resistance, monitoring of end-expired (tidal) carbon dioxide (ETCO₂) is often used intraoperatively as a surrogate marker of PaCO₂. Although changes in minute ventilation are used to control ETCO₂, and thus PaCO₂, cardiac output variations can impact the relationship between ETCO₂ and PaCO₂. Cardiac output may correlate with systemic blood pressure during general anesthesia, but the true nature of the relationship between arterial blood pressure and the gradient between PaCO₂ and ETCO₂ is not well understood. Luostarinen et al39 reported a prospective analysis of the relation between blood pressure and PaCO₂ to ETCO₂ gradient in 72 patients having craniotomy. Blood pressure was obtained before induction of anesthesia and then again just before placement of pinions, at which point both PaCO₂ and ETCO₂ were measured. Blood pressure decrease was stratified based on the percentage decrease in blood pressure before pinion placement, using 4 categories: < 20%, 20% to 29%, 30% to 35%, and > 35% decrease. Although there was no difference in ETCO₂ among groups (31.6 ± 3.7 mm Hg, 31.2 ± 2.9 mm Hg, 31.7 ± 3.7 mm Hg, and 32.3 ± 2.9 mm Hg, respectively; \( P = 0.811 \)) during the conduct of the study, PaCO₂ was significantly higher with greater decreases in blood pressure from baseline awake values (35.7 ± 4.5 mm Hg, 36.3 ± 3.8 mm Hg, 38.0 ± 4.4 mm Hg, and 39.3 ± 2.8 mm Hg, respectively; \( P = 0.036 \)) despite no differences in other periprocedural factors, such as demographics, comorbid conditions, ventilatory parameters, anesthetic drug doses, or indication for craniotomy. As such, significant changes in arterial blood pressure during general anesthesia may reduce the reliability of ETCO₂ as a surrogate marker for PaCO₂.

The extent of cyclic variation in blood pressure relative to positive pressure breaths has been used as a metric of intravascular volume status with greater variation indicating hypovolemia.40-42 Qiao et al43 evaluated the correlation between systolic blood pressure variation (SPV), pulse pressure variation (PPV), and central venous pressure (CVP), with stroke volume variation (SVV) using a Vigileo Flo-Trac system (Edwards Lifesciences, Irvine, CA) in 26 patients having craniotomy. The Flo-Trac Vigileo system applies a proprietary algorithm to the contour of the arterial blood pressure waveform to estimate cardiac stroke volume. After induction of anesthesia and hemodynamic stabilization, all patients received an intravenous infusion of 6% hydroxyethyl starch at 30 mL/kg/h for 60 minutes to assess responsiveness of the study parameters to changes in intravascular volume status. There was good correlation between SPV expressed in mm Hg \( (r^2 = 0.76; P < 0.001) \), SPV expressed as percentage of mean systolic blood pressure \( (r^2 = 0.80; P < 0.001) \), and PPV expressed as a percentage of mean pulse pressure \( (r^2 = 0.77; P < 0.001) \) with estimated cardiac stroke volume. Formulas used to calculate these parameters were:

1. **SPV (mm Hg)** = \( SBP_{max} - SBP_{min} \), where \( SBP_{max} \) indicates maximum systolic blood pressure and \( SBP_{min} \) indicates minimum systolic blood pressure associated with the respiratory cycle.
2. **SPV (%)** = \( 200 \times (SBP_{max} - SBP_{min})/(SBP_{max} + SBP_{min}) \).
3. **PPV (%)** = \( 200 \times (PP_{max} - PP_{min})/(PP_{max} + PP_{min}) \), where \( PP_{max} \) and \( PP_{min} \) represent maximum and minimum pulse pressure, respectively, associated with the respiratory cycle.
Although there was a significant correlation found between each measured parameter and the volume of fluid administered intravenously, there was a great deal of variability in specific measurements at each increment of fluid administered, probably reflecting individual differences in baseline fluid status (Fig. 1). Using SVV as a gold standard, receiver operating characteristic curve analysis yielded an area under the curve of 0.937 (CI, 0.899-0.975) for SPV (%), 0.938 (CI, 0.901-0.974) for SPV (mm Hg), and 0.943 (CI, 0.907-0.909) for PPV (%). There were no significant differences in the area under the receiver operating characteristic curve among these variables (P = 0.110). In addition, sensitivities and specificities of SPV (%), SPV (mm Hg), and PPV (%) for predicting SVV (%) were above 80% for all 3 variables. As such, SPV and PPV are both strongly predictive of SVV, suggesting that standard arterial blood pressure monitoring by an arterial catheter and pressure transducer can be a good substitute for the more expensive Flo-Trac Vigileo monitor. However, we were surprised that the investigators did not report the comparison of these variables to CVP, as CVP was measured in this study and is often considered a standard for assessing trends in intravascular fluid volume.

Electrophysiologic Monitoring

Monitoring the status and integrity of the nervous system has become a common practice in a wide variety of surgical procedures. Examples include evoked potential monitoring during spine surgery, electromyography and brainstem auditory evoked potential monitoring during skull base surgery, and electroencephalography during carotid endarterectomy (CEA). Although monitoring the integrity of the primary motor pathway (ie, the corticospinal tract) has been commonly used during spine surgery, other types of surgical procedures pose risks to this extremely important pathway. Cerebral aneurysm clipping can put this tract in jeopardy by a variety of mechanisms including inappropriate clip placement on an artery supplying the neurons of the corticospinal tract (ie,
middle cerebral artery, anterior cerebral artery, anterior choroidal artery, lenticulostriate artery) or disruption of perforating arteries which supply this tract, most commonly seen during basilar tip aneurysm clipping (as the pontine segment of the corticospinal tract is supplied by small arteries derived directly off the basilar artery).44–47 The true sensitivity of intraoperative motor-evoked potential monitoring for reducing the risk of postoperative motor deficits in this setting is in need of further elucidation. Irie et al 48 reported on the outcome in 111 patients after cerebral aneurysm clipping with intraoperative motor-evoked potential monitoring. Monitoring was conducted by cutaneous electrical stimulation of the scalp, with recording in the thenar and adductor pollicis muscles bilaterally during a total intravenous anesthetic. Ninety-eight patients had no significant changes in evoked potential tracings, although 1 patient later developed low-density areas on postoperative computed tomographic (CT) scans of the head. Six patients, 4 of whom had aneurysms involving the anterior choroidal artery, developed evoked potential changes consistent with ischemia. In 4 of these 6 patients, the waveform returned to baseline within 5 minutes after clip adjustment. In one patient, recovery of signals took 50 minutes, and in the remaining patient the signals never recovered to baseline. Postoperative neurological deficits were noted in these last 2 patients. Another 6 patients had postoperative neurological deficits despite a lack of change in intraoperative motor-evoked potential. Five patients were undergoing treatment of middle cerebral artery aneurysms, and 1 had an anterior choroidal artery aneurysm. In 4 of these 6 patients, a motor deficit was apparent immediately upon emergence from anesthesia. In distinction, in the remaining 2 patients, a deficit developed over the course of 5 hours after emergence. It is worrisome that motor-evoked potential monitoring was unable to predict a deficit in 6 of 111 patients (5%) having cerebral aneurysm clipping and, overall monitoring had a disturbing rate of false positives and false negatives for adverse neurological outcomes. The investigators did not speculate on a mechanism that might account for these findings.

The application of a tetanic stimulus to a peripheral nerve before acquisition of motor-evoked potentials enhances the motor-evoked potential waveform and compensates for some of the suppressant effects of anesthetics.49 Repetitive tetanic stimuli can lead to fatigue of muscles and a decrease in motor responses,50 although the duration of potentiation was previously unknown. Yamamoto et al 51 evaluated posttetanic motor-evoked potential waveforms if at least 120 s is not allowed to pass to allow standard motor-evoked potentials were increased if the delay between each tetanic stimulus was 60% of initial response after 10 stimuli. In a second experiment, a standard motor-evoked potential was conducted with a variable amount of delay after a posttetanic motor-evoked potential. Amplitudes of standard motor-evoked potentials were increased if the delay after a posttetanic potential was < 120 s. As such, posttetanic motor-evoked potential waveforms can be affected by rapid and frequent stimulation cycles and may influence subsequent standard motor-evoked potential recordings if at least 120 s is not allowed to pass to allow for recovery from the posttetanic state. This posttetanic technique offers promise to compensate for the suppressant effects of anesthetic agents on motor-evoked potential recordings; however, further study will be required to determine the reliability of this technique for detecting intraoperative motor tract compromise.

Patients with intracranial lesions in close proximity to eloquent regions of cerebral cortex have often undergone awake cortical mapping, during surgical resection, to minimize the risk of developing a significant neurological deficit. When only motor, and not language, testing is required, patients may undergo resection under general anesthesia in conjunction with direct electrical stimulation of the cortex and assessment of gross motor function.52 Although many anesthesiologists have reported on sedation techniques for “awake” craniotomy, there is a paucity of literature describing anesthetic techniques that allow for successful motor mapping during general anesthesia. Conte et al 53 reported on their experience with intraoperative cortical mapping. During the period of 2005 to 2008, patients at their institution underwent awake craniotomy if language assessment was required (n = 135) and “asleep” craniotomy if intraoperative mapping only involved identification of the motor cortex (n = 103). All procedures were performed with an infused propofol-remifentanil anesthetic and without neuromuscular blocking drugs. For awake craniotomies, the mean propofol and remifentanil doses were 125 ± 35 µg/kg/min and 0.11 ± 0.03 µg/kg/min during surgical opening; however, only remifentanil was administered during mapping and closure at doses of 0.05 ± 0.03 µg/kg/min and 0.07 ± 0.06 µg/kg/min, respectively. For asleep mapping, propofol and remifentanil doses were 107 ± 30 µg/kg/min and 0.11 ± 0.08 µg/kg/min during opening, 63 ± 28 µg/kg/min and 0.11 ± 0.05 µg/kg/min during mapping, and 93 ± 30 µg/kg/min and 0.11 ± 0.09 µg/kg/min during closure, respectively. Median bispectral index was 41 (range, 22 to 64), 55 (range, 20 to 82), and 48 (range, 23 to 73) during the maintenance portions of opening, mapping, and closure in this group. The investigators reported a significantly
lower intraprocedural complication rate in patients who underwent asleep mapping (41%) versus those having awake mapping (57%) \( (P < 0.01) \), although many intraprocedure complications in the asleep group were precluded by general anesthesia. The most common complications noted in the asleep group were: seizures (31%), hypotension (5%), and hypertension (3%). In the awake group, the common complications were: hypertension (27%), seizures (16%), hypotension (10%), vomiting (7%), agitation (6%), need for emergency airway management (5%), and apnea (4%). Although the investigators describe an anesthetic technique that is apparently compatible with cortical mapping in patients during general anesthesia, they do not report the incidence of postoperative complications, especially new-onset neurological deficits. As such, whether outcomes are impacted by a propofol/remifentanil-based general anesthetic during procedures involving motor mapping requires further investigation.

**Anesthetic Techniques and Pharmacology**

Dexmedetomidine offers many advantages for sedation and as an adjunct during general anesthesia for patients undergoing neurosurgery. Specifically, dexmedetomidine has a short effective half-life, allowing for rapid titratability, and both antihypertensive and analgesic effects without significant respiratory depression.\(^6\) However, one primary concern is that, in animal models, dexmedetomidine is reported to decrease CBF without affecting cerebral metabolic rate, thus potentially decreasing oxygen and nutrient supply more than demand.\(^5,6\) As in animal models, dexmedetomidine reduces CBF in humans\(^7,8\); however, data from one investigation showed that in humans, dexmedetomidine produces a parallel decrease in cerebral metabolism.\(^9\) Drummond and Sturaitis\(^10\) questioned whether, in the setting of impaired flow-metabolism coupling, the cerebral vasoconstrictive effects of dexmedetomidine predominate. Five patients having craniotomy for vascular lesions, 2 with arteriovenous malformations and 3 with cerebral aneurysms and preoperative neurological deficits secondary to their lesions, were included in this case series. All 5 patients had brain tissue parenchymal oxygen probes (Licox, Integra Neurosciences, Plainsboro, NJ) placed before commencement of surgery in the territory felt to be at greatest risk from pending surgery. Anesthesia was maintained with inhaled sevoflurane (0.4% to 0.8% end-expired) and 50% nitrous oxide, and intravenous sufentanil (0.15 to 0.5 \( \mu \)g/kg/h). After attaining stable blood pressure and heart rate with constant anesthetic concentrations, dexmedetomidine was administered as a 1 \( \mu \)g/kg bolus over 5 to 10 minutes followed by an infusion at 0.5 to 0.7 \( \mu \)g/kg/h without altering the doses of the other anesthetic agents; however, surgery was started after completion of the loading dose, so data acquired during the infusion may have been subject to the effect of surgical intervention. During the loading dose, there was a 4.5% increase in mean arterial pressure (MAP) \( (P = 0.041) \) vs. pressure before institution of the loading dose and an 11.1% increase in brain tissue oxygen tension \( (P = 0.015) \). As such, these data support other findings in humans that dexmedetomidine probably does not adversely affect cerebral oxygen supply-demand relationships.

Relative or absolute hypotension can occur during many neurosurgical procedures either as a side effect of drugs used in the perioperative period (eg, anesthesia induction agents, excessive \( \beta \)-adrenergic-blocker administration) or as a result of hypovolemia due to bleeding or diuretic use. Maintenance of adequate cerebral perfusion is critically important. Phenylephrine, an \( \alpha \)-adrenergic receptor agonist, is a commonly used pressor in the perioperative period. Some data suggest that acidosis may attenuate the vasoconstrictive response of phenylephrine.\(^6\) To determine whether the pressor response to phenylephrine is affected by the alkalosis associated with hypocapnia, Schwartz and Adams\(^52\) measured the amount of phenylephrine required to increase systemic blood pressure by 33% and 66% in 6 monkeys receiving isoflurane anesthesia during both normocapnia \( (\text{PaCO}_2, \text{35 to 44 mm Hg}) \) or hypocapnia \( (\text{PaCO}_2, \text{23 to 29 mm Hg}) \). Ventilation was adjusted to achieve hypocapnia and held constant; carbon dioxide was added to the inspired gas mixture to achieve normocapnia. To increase systemic blood pressure by 33%, 2.4 ± 0.9 \( \mu \)g/kg/min and 1.7 ± 0.9 \( \mu \)g/kg/min phenylephrine were required in the normocapnia and hypocapnia groups, respectively \( (P < 0.05) \). To increase systemic blood pressure by 66%, 4.9 ± 2.4 \( \mu \)g/kg/min and 3.1 ± 1.7 \( \mu \)g/kg/min phenylephrine were required in the normocapnia and hypocapnia groups, respectively \( (P < 0.05) \). The investigators hypothesize that either an alkalosis-induced increase in \( \text{Ca}^{++} \) currents in vascular smooth muscle, or an increase in the ionized fraction of phenylephrine leading to an increased proportion of molecules interacting with the \( \alpha \)-adrenergic receptors, may account for these effects.\(^6\) As such, the dose of phenylephrine may need to be decreased in patients who are undergoing hyperventilation.

Hypertension is common during intracranial procedures, and 60% to 90% of patients undergoing craniotomy require treatment with antihypertensive medications.\(^64-66\) Currently available intravenous antihypertensive medications are limited by either a long half-life (eg, labetolol), minimal effect on elevated systemic vascular resistance (eg, esmolol)—the primary cause of hypertension after craniotomy, or adverse effects on intracranial blood volume (eg, sodium nitroprusside, hydralazine). Clevidipine is a calcium channel antagonist that lowers blood pressure by reducing systemic vascular resistance. Clevidipine is rapidly metabolized by plasma esterases, resulting in an effective half-life of \(< 1 \) minute, and this drug does not predominantly rely on the liver or kidney for metabolism and elimination. As such, clevidipine has significant advantages over currently available injectable antihypertensive medications. Bekker et al\(^67\) prospectively evaluated clevidipine in 21 patients having craniotomy who required pharmacologic treatment for hypertension.
in the perioperative period. The primary goal of hemodynamic management was a systolic blood pressure of 90 to 130 mm Hg and a heart rate of 40 to 90 beats/ min. Blood pressure control was defined as maintaining a systolic blood pressure < 130 mm Hg. The infusion was most commonly instituted during emergence from anesthesia, occurring in 13 patients (62%). Once instituted, blood pressure was reduced to < 130 mm Hg within 5 minutes in 50% of cases, with only 11% of cases requiring at least 30 minutes to attain blood pressure control. There were only 2 episodes of hypotension (systolic blood pressure < 90 mm Hg) that occurred after institution of the clevidipine infusion, and both resolved rapidly by temporary termination of the clevidipine infusion and administration of a pressor (ie, ephedrine or phentylephrine). No other adverse events were attributed to clevidipine. Further study will be required to determine whether clevidipine has any effect on intracranial blood volume and operating conditions.

As the brain itself does not have sensory or pain receptors, there is a common misperception that patients having brain surgery do not have, or experience minimal, pain. However, the skin, periosteum of the skull, and the meninges are innervated with nerves responsible for sensory and pain transmission. Currently, few data exist to describe the incidence and severity of pain after craniotomy. Mordhorst et al68 prospectively assessed the incidence, severity, and risk factors for pain in 243 patients having craniotomy at a single institution. All patients underwent craniotomy without local anesthetic infiltration at the operative site. Patients received either sevoflurane or a propofol infusion in addition to either sufentanil or a remifentanil infusion for maintenance of general anesthesia. In all patients who received remifentanil, and in some who received sufentanil, the μ-opioid receptor agonist piritramide was administered 30 minutes before the end of surgery. Seventy percent of patients received piritramide and 73% received nonopioid analgesics, such as paracetamol, metamizole, and diclofenac. Postoperative pain was assessed by a numeric rating scale (NRS) where 0 indicates no pain and 10 indicates maximum pain. At 24 hours after surgery, 13% had no pain (NRS = 0), 32% had mild pain (NRS = 1 to 3), 44% had moderate pain (NRS = 4 to 7), and 11% had severe pain (NRS ≥ 8). Younger age (P = 0.05), but not the presence of nausea (P = 0.13) or vomiting (P = 0.21), was associated with increased pain scores. Increased postoperative pain was more common in patients who received sevoflurane versus propofol; however, 93% of patients in the propofol group received piritramide versus only 55% in the sevoflurane group. Although no surgical factors were associated with pain severity, the administration of intraoperative corticosteroids for the prevention or treatment of cerebral edema was beneficial as 24% of patients who received a corticosteroid complained of moderate-to-severe pain (NRS = 4 to 10) versus 64% in the group that did not receive corticosteroids (P < 0.001 although this value was not reported in study). Clearly, postoperative pain after craniotomy is a common occurrence that warrants further study.

Of note, local infiltration of the surgical site is often performed to either minimize hemodynamic responses to craniotomy or for postoperative pain control. We refer the interested reader to a review article pertaining to the “scalp block.” Osborn and Sebe69 review the history of scalp infiltration and scalp block, the relevant anatomy, and common complications. They also describe specific techniques for performing blocks of individual nerves and address potential applications for these blocks.

Before turning from general to more specific topics relevant to neurosurgical anesthesiology, we refer readers to the October, 2010 issue of the Journal Current Opinion in Anesthesiology. That issue published several articles that review neuroanesthesiology topics and provide interpretations of the contemporary literature. Topics included glucose management,70 nitrous oxide use,71 postcraniotomy pain,72 thromboprophylaxis in neurosurgical patients,73 antiepileptic drug use,74 neuroendoscopic procedures,75 cerebral oximetry,76 and ischemic optic neuropathy.77

**INTRACRANIAL HEMORRHAGE**

**General Management Issues**

In 2005, the results of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) were published.78,79 One thousand patients with recent aneurysmal subarachnoid hemorrhage (SAH) and normal or near-normal neurological status were randomized to systemic hypothermia (target core temperature of 33°C) or normothermia (36.5°C) for aneurysm clipping. No difference was found between groups with respect to long-term gross neurological or cognitive outcome. One of the major criticisms of IHAST is that, given the diversity among the study patients, there was the possibility that hypothermia benefited some specific subset of patients but not others.

Temporary arterial occlusion is sometimes performed to facilitate permanent aneurysm clip placement. This is because temporary cessation of blood flow in the vessel “feeding” the aneurysm allows for a decrease in tension in the aneurysm wall and may theoretically reduce the risk of rupture during permanent clip placement. However, temporary occlusion is not a benign technique; it can produce cerebral ischemia that, in turn, may lead to stroke.80–82 Cerebroprotective drugs, such as thiopental, may attenuate the adverse effect of temporary clipping.83 Hindman et al84 performed a post hoc analysis of data obtained from 441 patients from the IHAST investigation in whom temporary arterial occlusion was used. Data were stratified first based on duration of temporary clipping (ie, ≤ 10 min, 11 to 19 min, ≥ 20 min). Permanent aneurysm clip placement was judged by the surgeons to be difficult or very difficult more frequently in patients with a longer temporary clip time: 39%, 48%, and 72% for temporary occlusion durations of ≤ 10 minutes, 11 to 19 minutes, and ≥ 20 minutes, respectively (P < 0001). Despite the greater use of neuroprotective drugs in

© 2011 Lippincott Williams & Wilkins www.jnsa.com | 75
patients with longer temporary clip durations (33%, 53%, and 52% for durations of ≤10 min, 11 to 19 min, and ≥20 min, respectively; P < 0.001), postoperative cerebral infarction was more common in patients with an occlusion duration of ≥20 minutes (45%) versus ≤10 minutes (27%) or 11 to 19 minutes (26%) (P < 0.05 for both comparisons). Using multivariate logistic regression analysis, when comparing the influence of various factors on the rate of a good outcome (ie, Glasgow outcome score = 1) at 3 months, neither hypothermia [odds ratio (OR) = 1.043; CI, 0.678-1.606; P = 0.85] nor use of cerebral protective drugs [OR = 1.048; CI, 0.674-1.631; P = 0.84] impacted the odds of a good outcome (OR significantly >1 indicates increased odds of a good outcome). Compared with those in whom temporary occlusion duration was ≤10 minutes, those with a duration of ≥20 minutes (OR = 0.53; CI, 0.281-0.989; P = 0.046), but not 11 to 19 minutes (OR = 0.920, CI, 0.542-1.562, P = 0.76), were at decreased odds of a good outcome. As such, the investigators conclude that neither hypothermia nor the use of protective drugs influences long-term gross neurological outcome in patients who received temporary arterial occlusion during cerebral aneurysm clipping surgery. Prolonged temporary occlusion was associated with poor outcome.

Vasospasm and cerebral infarction are both common sequelae after SAH, and patients who develop either of these complications are at risk for worse outcome. Data describing the relationship between aneurysm treatment and risk of developing subsequent vasospasm are inconclusive. Specifically, one could reason that removal of blood at the time of craniotomy may reduce the triggering effect of abluminal oxyhemoglobin on the major cerebral arteries, thus reducing the risk of vasospasm. Similarly, aneurysm clipping involves less external manipulation of the major cerebral arteries, thus clipping may reduce the risk of vasospasm relative to coiling. Current data either support no difference in the incidence of vasospasm between techniques or a greater risk in patients who have undergone surgical clipping. Dumont et al performed a post hoc analysis of data from the Clazosentan to Overcome Neurologic Ischemia and Infarction After SAH trial to determine whether aneurysm treatment method had an impact on the risk of developing vasospasm or cerebral infarcts. The Clazosentan to Overcome Neurologic Ischemia and Infarction After SAH trial showed a dose-dependent reduction in the risk of vasospasm by clazosentan, an endothelin-1 receptor antagonist. Aneurysm treatment (ie, clipping vs. coiling) was decided by the treating physician. After multivariate analysis correcting for factors thought to impact outcome, propensity matching, and adjusting for baseline risk factors between clipping and coiling, patients who underwent clipping were 3.89 (CI, 1.75-8.63; P = 0.0008) times more likely to develop angiographic vasospasm; however, there was no impact of treatment type on risk of delayed ischemic neurological deficits, vasospasm-related cerebral infarction, or Glasgow outcome score at 6 weeks after initial hemorrhage. When interpreting these data it should be kept in mind that some patients have aneurysms which, based an anatomy, are not safely amenable to coiling. As such, the decision to clip versus coil an aneurysm should be made on a case-by-case basis.

Anemia is a common finding after intracranial hemorrhage, occurring in up to 50% of patients. The etiology of anemia is probably multifactorial, with critical illness, iatrogenic hemodilution (eg, as associated with “ triple-H therapy involving hemodilution or fluid resuscitation), and multiple blood draws contributing. Patient risk factors for anemia after SAH include low baseline hematocrit, female sex, history of hypertension, poor clinical aneurysmal grade, presence of systemic inflammatory response syndrome, and surgical aneurysm treatment. There is concern that the associated derangements in cerebral hemodynamics that can occur after SAH, (ie, decreased CBF as a result of vasospasm or elevated ICP) can impair oxygen delivery to the brain. Additional decreases in the oxygen content of blood, resulting from anemia, can further impair oxygen delivery. Understanding the relationship between hemoglobin concentration and cerebral oxygen delivery is currently limited. Kurtz et al reviewed the records of 34 consecutive patients with SAH who underwent simultaneous monitoring of ICP, brain tissue oxygen partial pressure (PbrO2), and cerebral microdialysis to assess metabolic intermediate concentrations to determine the effect of anemia on cerebral hemodynamics and metabolism. Hemoglobin concentrations were obtained in these 34 patients; median value was 9.7 g/dL (interquartile range, 8.8 to 10.5). Hemoglobin concentration was ≤10 g/dL in 54% of samples. Values for PbrO2 indicating cerebral hypoxia (PbrO2 < 15 mm Hg) were more common in patients with a hemoglobin ≤9 g/dL (25%) versus a hemoglobin 9.1 to 10 (12%), 10.1 to 11 (9%), and > 11 g/dL (4%), respectively (P values not reported). The highest incidence of recordings indicating metabolic distress (ie, microdialysate lactate-to-pyruvate concentration > 40—an indicator of increased anaerobic metabolism) occurred in the cohort of patients with hemoglobin ≤9 g/dL (45%). Fractions of readings indicating metabolic distress were 25%, 15%, and 23% in patients with a hemoglobin 9.1 to 10, 10.1 to 11, and > 11 g/dL, respectively (P values not reported). Compared with those with a serum hemoglobin of 10.1 to 11 g/dL, those with a hemoglobin of 9.1 to 10 g/dL and ≤9 g/dL were 1.9 (CI, 1.1-3.3) and 3.8 (CI, 1.5-9.4) times more likely to have a lactate-to-pyruvate ratio > 40, indicating metabolic distress and inadequate oxygen delivery (P < 0.05 for both comparisons to the group with a hemoglobin concentration of 10.1 to 11 mg/dL). Although there are risks associated with blood transfusion in patients with SAH, these data support the avoidance of anemia. There are 2 major limitations of this investigation that are worth mentioning. First, patients in whom multimodal monitoring was used were more likely to have more severe injury. In addition, 47% of patients included in this investigation had a Hunt Hess grade of 5 (ie, severe SAH).
and there were no patients with a Hunt Hess grade \(< 3\) (ie, mild to moderate SAH). In addition, data analysis was by hemoglobin values and not per patient. As such, patients with greater severity of injury and greater metabolic derangement were probably more likely to have been monitored for a longer period of time, thus increasing the number of measurements indicating adverse oxygen delivery. Of note, in a pilot investigation by Naidech et al,\(^96\) patients with SAH were randomized to a target hemoglobin of either 10.0 to 11.5 g/dL or \(> 11.5 \text{ g/dL}\). Their data suggested a trend toward reduced cerebral infarctions and improved functional neurological status in patients in the higher hemoglobin group.

Aberrations in serum glucose concentration in the setting of neuronal insult can have a profound impact on overall outcome. Studies in both animal models and humans have shown that elevated serum glucose concentration is associated with poor outcome after ischemic brain injury.\(^57-100\) However, attempts to strictly control glycemia increase the risk of hypoglycemic episodes.\(^101,102\) In addition, in some circumstances such as traumatic brain injury (TBI), the brain may become increasingly metabolically active (often considered to be a ramification of glutamate release and excitotoxicity and other mechanisms). In these circumstances, blood glucose concentrations in the euglycemic or mild hypoglycemic range may not allow for adequate substrate delivery to compensate for a hypermetabolic brain.\(^103\) Helbok et al\(^104\) correlated serum glucose concentration with cerebral microdialysis data obtained from 28 comatose patients with SAH. Metabolic crisis was defined as the simultaneous occurrence of glucose \(< 0.7 \text{ mmol/L}\) and a lactate-to-pyruvate ratio \(> 40\) in the dialysate fluid. Nineteen patients (68%) developed 54 episodes of metabolic crisis at some point during monitoring, with the greatest prevalence occurring on day 4 after hemorrhage. Changes in cerebral glucose mirrored changes in systemic glucose. Serum glucose concentration decreased from 148 ± 32 mg/dL (obtained 2 h before onset of metabolic crisis) to 124 ± 34 mg/dL at the onset of metabolic crisis \((P < 0.001)\). Similarly, the lactate-to-pyruvate ratio increased from 45 ± 16 (obtained 2 h before onset of metabolic crisis) to 54 ± 17 with the onset of metabolic crisis \((P < 0.02)\). A reduction in serum glucose \(> 25\%\), but not absolute glucose concentrations, was associated with the new onset of metabolic crisis \((\text{OR} = 2.8; \text{CI}, 1.7-4.5; P < 0.001)\) and a \(> 25\\%\) increase in lactate-to-pyruvate ratio \((\text{OR} = 1.6; \text{CI}, 1.1-2.4; P = 0.01)\) after adjusting for CPP and Glasgow coma score. As such, close to “normal” blood glucose concentrations may be associated with reduced brain glucose and an increase in the lactate-to-pyruvate ratio obtained from microdialysis in patients with SAH.

Naidech et al\(^105\) retrospectively obtained blood glucose concentrations from 172 patients managed with a strict glycemic management protocol (ie, target blood glucose of 80 to 110 mg/dL) and correlated outcome with respect to blood glucose concentrations. Patients with a more severe hemorrhage, based on the World Federation of Neurological Surgeons scale, had greater serum glucose variability with a greater maximum glucose \((P < 0.001)\), greater mean glucose \((P < 0.001)\), and lower nadir glucose \((P = 0.03)\). The investigators did not comment on whether a single episode of severe hypoglycemia (blood glucose \(< 40 \text{ mg/dL}\)) and other, less severe, episodes of hypoglycemia were directly attributable to insulin administration. Those with symptomatic cerebral vasospasm \((n = 30, 17\%)\) had lower nadir glucose versus those without vasospasm \((78 ± 12 \text{ mg/dL vs. } 84 ± 16 \text{ mg/dL}; P = 0.04)\), but there was no difference in initial, mean, or maximum blood glucose concentrations. Similarly, those with cerebral infarction \((n = 91, 53\%)\) had lower nadir glucose versus those without infarction \((81 ± 15 \text{ mg/dL vs. } 87 ± 16 \text{ mg/dL}; P = 0.02)\), but there was no difference in initial, mean, or maximum blood glucose concentrations. Although the investigators showed statistical significance in the 2 comparisons, the clinical importance of a difference in blood glucose concentration of 6 mg/dL is unclear. However, 3-months modified Rankin score was related to nadir glucose in that, with the exception of patients that died (ie, modified Rankin score = 6), progressively decreased nadir glucose was associated with progressively worse outcome \((P < 0.001)\) as shown in Figure 2. Accordingly, the investigators conclude that, even in the absence of severe hypoglycemia, a strict glycemic control protocol may put patients at risk for poor outcome after SAH. Further study will be required to confirm these findings.

**Pharmacologic Interventions in SAH**

Owing to its direct vasodilatory effects and antagonism of the N-methyl-d-aspartate receptor, magnesium sulfate has been investigated as a potential treatment for patients with SAH. Small investigations in this setting have reported trends toward reduced vasospasm and improved overall outcome; however, many of these “pilot” investigations lack the power to provide a

![FIGURE 2. Mean nadir blood glucose concentrations versus 3-month modified Rankin scale score in patients with subarachnoid hemorrhage. With the exception of patients who died (modified Rankin score = 6), decreasing nadir glucose was associated with a poorer modified Rankin score \((P < 0.001)\). Adapted with permission from *Neurocrit Care*. 2010;12:181–187.](image-url)
definitive effect of magnesium sulfate in this setting. In addition, magnesium may reduce headache and subsequent analgesic requirements associated with SAH. However, magnesium sulfate can increase the risk of hypotension, cardiac arrhythmias, respiratory dysfunction, and muscular weakness. As such, it is unclear, in the setting of SAH, whether elevated serum magnesium concentrations would be associated with benefit or increased risk for adverse outcomes. Unlike many earlier investigations in which magnesium sulfate was administered by a set dose, Westermaier et al randomized patients with SAH to receive either placebo or intravenous magnesium sulfate, adjusted to maintain a serum concentration of 2.0 to 2.5 mmol/L, continued for 10 days or until vasospasm resolved, followed by an oral taper of magnesium over 12 days. Data from 107 patients were included in the analysis, and 54 received magnesium. Daily administration of 140 ± 51 mmol magnesium was required to maintain appropriate serum concentrations in the study group. No episodes of profound bradycardia or hypotension were noted. During the intravenous administration phase, serum magnesium concentrations were maintained within the predefined range; however, once oral supplementation was instituted, serum magnesium concentrations were similar between groups (ie, oral magnesium had no meaningful effect on serum magnesium concentrations). There were fewer cases of delayed ischemic infarction (ie, cerebral parenchymal hypodensities appearing between day 3 and the end of the study period on CT scans), the primary study endpoint, in the magnesium group (22% vs. 51% in the placebo group, \( P = 0.002 \)). However, the incidence of vasospasm, as detected by either TCD or cerebral angiography, was reduced in the magnesium group (67%) compared with the placebo group (85%) (\( P = 0.028 \)). Further, there was no difference between groups with respect to the rate of a good outcome (ie, Glasgow outcome score of 4 to 5 at 3 mo; 63% vs. 51% for magnesium and placebo groups; \( P = 0.210 \)) or overall mortality at 3 months (11% vs. 19% for magnesium and placebo groups; \( P = 0.260 \)). The investigators conclude that a serum magnesium-guided protocol was effective at reducing vasospasm and infarction after SAH. However, this protocol resulted in no significant impact on mortality or overall outcome based on the Glasgow outcome score.

In the multicenter Intravenous Magnesium Sulfate for Aneurysmal SAH investigation, Wong et al randomized 327 patients with SAH to receive either placebo or intravenous magnesium sulfate, adjusted to maintain a serum magnesium concentration twice their individual baseline value but < 2.5 mmol/L for up to 14 days after initial hemorrhage. There was no difference between groups with respect to favorable outcome at 6 months (primary outcome measure; extended Glasgow outcome score of 5 to 8; 64% vs. 63% for the magnesium and placebo groups, respectively; \( P > 0.05 \)). In addition, there was no difference between groups in the incidence of clinical vasospasm (25% vs. 18% for the magnesium and placebo groups, respectively; \( P > 0.05 \)), fraction with a modified Rankin score of 0 to 2 (57% vs. 58%, respectively; \( P > 0.05 \)), fraction of patients able to perform activities of daily living at 6 months (Barthel Index > 85; 57% vs. 61%, respectively; \( P > 0.05 \)), or overall mortality (10% vs. 12%, respectively; \( P > 0.05 \)). Unlike the investigation by Westermaier et al, this investigation by Wong et al did not support a beneficial effect of serum magnesium concentration-targeted therapy to improve outcome after SAH.

These conflicting findings derived from relatively similar investigations reflect earlier reports on the use of magnesium sulfate after SAH. Ma et al performed a meta-analysis of those prospective studies. The investigators identified 6 investigations performed at different medical centers and time points. The relative risk for poor outcome at 12 months (defined differently among the investigations) was 0.62 (CI, 0.46-0.83) for all investigations and 0.67 (CI, 0.49-0.93) for high-quality investigations, favoring the use of magnesium sulfate. Similarly, magnesium sulfate reduced the risk of delayed cerebral ischemia [relative risk = 0.73 (CI, 0.53-1.00) for all reporting investigations and relative risk = 0.64 (CI, 0.44-0.94) for high-quality investigations]. On the basis of 3 investigations, use of magnesium was associated with an increased risk of study withdrawal [relative risk = 9.98 (CI, 3.04-32.74)] with the most common side effects making patients discontinue intervention being hypotension, hypermagnesemia, cardiac arrhythmia, renal failure, respiratory arrest, myocardial infarction, and phlebitis. As such, the investigators conclude that magnesium may be of benefit in patients with SAH, but may not be well tolerated in individual patients due to adverse effects.

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (ie, the “statins”), in addition to their beneficial effect on reducing cholesterol biosynthesis, also increase endothelial nitric oxide biosynthesis, thus reducing vascular tone. Many investigators have examined this latter effect as a potential treatment modality for vasospasm after SAH. Kramer and Fletcher performed a meta-analysis of investigations describing new-onset statin use after SAH, and they excluded studies designed to assess outcome in patients taking chronic statins before SAH. Twelve studies were identified: 6 randomized controlled trials, 5 cohort investigations, and 1 case-control study. Definitions for delayed ischemic neurologic deficits and vasospasm, and metrics of outcome, varied among the investigations; each study’s individual definitions were used to define these events. The 6
randomized controlled trials collectively contained 309 patients. In these investigations, statins were found to reduce the odds of delayed ischemic neurological deficits (OR = 0.38; CI, 0.23-0.65; P < 0.001), but had no significant effect on the presence of vasospasm (OR = 0.98; CI, 0.35-2.78; P = 0.97), odds of a poor outcome (OR = 0.81; CI, 0.49-1.32; P = 0.39), or mortality (OR = 0.51; CI, 0.25-1.02; P = 0.06). When data from all 12 investigations were collectively analyzed, consisting of 1851 patients with statins administered either before or after vasospasm, statin use had no effect on the odds of developing delayed ischemic neurological deficits (OR = 0.80; CI, 0.61-1.05; P = 0.10), poor outcome (OR = 1.05; CI, 0.79-1.40; P = 0.75), or mortality (OR = 0.89; CI, 0.56-1.40; P = 0.61). As such, better quality data suggest that statins reduce the risk of developing delayed ischemic deficits; however, there may be no major effect on long-term outcome. The investigators warn of limitations that may have affected these findings: (1) there was heterogeneity among the investigations, (2) patients not treated with statins had an unusually high rate of delayed ischemic neurological deficits (48% overall), and (3) with the inclusion of lesser quality data, any significant benefit from statins was lost.

A mainstay treatment for patients with vasospasm refractory to conservative means (eg, nimodipine, triple-H therapy) involves administration of vasodilators directly into vasospastic arteries; however, there are no major effects on long-term outcome. The investigators warn of limitations that may have affected these findings: (1) there was heterogeneity among the investigations, (2) patients not treated with statins had an unusually high rate of delayed ischemic neurological deficits (48% overall), and (3) with the inclusion of lesser quality data, any significant benefit from statins was lost.

A mainstay treatment for patients with vasospasm refractory to conservative means (eg, nimodipine, triple-H therapy) involves administration of vasodilators directly into vasospastic arteries; however, there are currently few data describing the systemic hemodynamic consequences of this intervention. Schmidt et al retrospectively reviewed hemodynamic data, vasopressor requirements, and systemic complications (which may be attributed to systemic hypotension or vaspressors) in patients who received either nicardipine or milrinone into the cerebral arterial circulation. One hundred sixty endovascular treatments were performed in 73 patients; 96 received nicardipine only, 5 received milrinone only, and 59 received both drugs. Despite an increase in the dose of either phenylephrine (63% increase), norepinephrine (104% increase), or vasopressin (240% increase) required to maintain an “appropriate” systemic blood pressure, mean systemic blood pressure decreased by 13% after treatment. One patient with preexisting cardiac disease had a postprocedural elevation in serum troponin concentration without other adverse cardiac sequelae. Clinicians should be aware that hemodynamic changes are possible, and can be clinically significant, after intraarterial administration of vasodilators. However, it remains unclear whether this decrease in blood pressure is solely due to a systemic effect of these drugs or if this change is a normal physiologic response to restoration of CBF in previously hypoperfused regions of brain in vasospastic vascular territories.

The etiology of cerebral vasospasm is likely multifactorial and is believed to be at least partially the result of peroxides and reactive oxygen species associated with abluminal oxyhemoglobin. The trace element selenium is a cofactor for antioxidant enzymes responsible for reducing peroxides (eg, glutathione peroxidase). In a rabbit model of SAH and vasospasm, Kocaogullar et al randomized animals to receive either placebo or sodium selenite, 0.05 mg/kg intraperitoneally, administered daily starting after the induction of SAH. Sodium selenite is a common human food additive. Digital subtraction angiography was performed before and 72 hours after SAH (ie, the time of peak vasospasm in rabbits) to assess basilar artery diameter. The animals were then immediately killed for anatomic analysis of basilar artery diameter and determination of the thickness of the arterial muscular layer. Angiographic vessel diameter was reduced approximately 40% in control animals, but was unchanged from pre-SAH diameter in animals that received selenium (P < 0.001). Vessel lumen diameter and thickness of muscle layer, both assessed in gross specimens, were 100% greater (P < 0.005) and 62% smaller (P < 0.005) in animals that received intraperitoneal selenium, respectively. One major concern with regard to selenium in humans is toxicity. A recommended dose in humans for supplementation of this trace nutrient is 7.5 µg/kg/d. This dose, if given for many days, can become toxic, and a single dose of 5 mg can be lethal.

As such, if this therapy is ever applied to humans, a much lower dose than that used in the Kocaogullar et al animal model will need to be investigated.

Intravenous adenosine has a short-duration negative chronotropic effect on the cardiac sinoatrial node and slows electrical conduction in the atrioventricular node. As such, brief bradycardia and rhythm pause, with a subsequent brief decrease in cardiac output, results. This brief adenosine-induced cardiac rhythm interruption and blood flow diminution makes possible a therapeutic maneuver to facilitate cerebral aneurysm clipping. Further, intravenous adenosine boluses may help supplant some requirements for traditional circulatory arrest, and they may have utility in managing acute intraoperative aneurysm rupture as well. Currently, most evidence of this use of adenosine occurs in single-case reports and small case series that offer few insights into effective dose ranges, duration of asystole, and complications. Bebawy et al retrospectively reported on a series of 24 cases in which adenosine was used intraoperatively, with 14 patients receiving more than 1 dose of adenosine. Repeat doses of adenosine were administered after the return of stable systemic hemodynamics, and no apparent tachyphylaxis was noted. One patient, despite receiving 3 doses of adenosine [0.3, 0.4, and 0.5 mg/kg ideal body weight (IBW)], did not achieve asystole, but had a significant duration of hypotension to facilitate the placement of multiple aneurysm clips. Adenosine was used more commonly in cases in which the aneurysm was located on either the carotid or basilar arteries. Thirteen patients had hemodynamic data specifically recorded by a dedicated observer. In these patients, a median adenosine dose of 0.34 mg/kg IBW (range, 0.29 to 0.44 mg/kg IBW) resulted in a systolic blood pressure of < 60 mm Hg for a median of 57 s (range, 26 to 105 s). Two patients developed atrial fibrillation after adenosine: one spontaneously converted to sinus rhythm and the other required...
treatment with amiodarone. Two patients developed an increase in serum troponin (>0.03 ng/mL), neither with echocardiographic evidence of myocardial dysfunction. Three patients developed new postoperative neurological deficits. There were no pulmonary complications observed. Of note, adenosine was not used in patients having severe coronary artery disease, atrioventricular conduction defects, electronic pacemakers, or severe reactive airway disease.

In a similar report, Powers et al.135 reported their experience with adenosine-induced asystole to facilitate aneurysm clipping in 6 successful cases. They provide a useful “rule of thumb” that for each 1 s of expected asystole, 1 mg of adenosine should be administered. For example, to attain 30 s of asystole, 30 mg of adenosine is a reasonable approximate dose. The investigators also state that a standard practice at their institution is to apply cutaneous pacing pads in the event of sustained bradycardia or asystole, but the pacemaker has never been required.

CAROTID ARTERY DISEASE

Surgical treatment of atherosclerotic disease of the carotid artery has previously been reported to be superior to medical management alone in reducing the risk of stroke and death. Despite an increase in complications in the periprocedural period, the long-term risk of stroke is significantly reduced after revascularization, even after 10 years, in patients who were initially asymptomatic.136 However, these data, reported in 1998, preceded the current advances in medical therapy.137,138 As such, the medical versus invasive treatment debate must continue to take into account evolving treatment options.139,140 Currently, the 2 treatment options for patients with carotid artery disease are CEA and carotid angioplasty with stenting. Earlier data comparing outcome after these 2 procedures suggested that the overall risk of both short- term and long-term stroke or death is similar; however, restenosis is more common after stenting, whereas minor-to-moderate complications (eg, hematoma, cranial nerve injury) are more common after endarterectomy.141–146 These data were updated by 2 recent short-term outcome studies published in 2010, both involving large, randomized, multicenter trials; the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and the International Carotid Stenting Study (ICSS).

CREST147,148 involved 117 centers in the United States and Canada and enrolled 2505 patients who had either symptomatic or asymptomatic carotid artery disease. All procedures were performed by certified proceduralists. The primary outcome metric was the combined rate of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed. At 30 days, there was no difference in the combined incidence of stroke, death, or myocardial infarction at 30 days after treatment or ipsilateral stroke within 4 years. The 4-year outcome data from patients lost to follow-up were imputed.

### TABLE 2. Outcome Data From 2 Investigations Comparing Carotid Endarterectomy With Carotid Stenting for the Treatment of Carotid Atherosclerotic Disease

<table>
<thead>
<tr>
<th></th>
<th>Endarterectomy</th>
<th>Stenting</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST—30 day outcome data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1240</td>
<td>1262</td>
<td></td>
</tr>
<tr>
<td>Combined rate of stroke, death, or myocardial infarction</td>
<td>56 (4.5%)</td>
<td>66 (5.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.3%)</td>
<td>9 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Any stroke</td>
<td>29 (2.3%)</td>
<td>52 (4.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>29 (2.3%)</td>
<td>52 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>28 (2.3%)</td>
<td>14 (1.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>(4.7%)</td>
<td>(0.3%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hematoma</td>
<td></td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>CREST—4 year outcome data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined rate of stroke, death, or myocardial infarction</td>
<td>76 (6.8%)</td>
<td>85 (7.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>83 (12.6%)</td>
<td>94 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral stroke</td>
<td>50 (4.7%)</td>
<td>72 (6.2%)</td>
<td>0.049</td>
</tr>
<tr>
<td>ICSS—120 day outcome data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>857</td>
<td>853</td>
<td></td>
</tr>
<tr>
<td>Combined rate of stroke, death, or myocardial infarction</td>
<td>44 (5.2%)</td>
<td>72 (8.5%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death</td>
<td>7 (0.8%)</td>
<td>19 (2.3%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Any stroke</td>
<td>35 (4.1%)</td>
<td>65 (7.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (0.6%)</td>
<td>3 (0.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>45 (5.3%)</td>
<td>1 (0.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hematoma</td>
<td>50 (5.8%)</td>
<td>30 (3.1%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data reported as number within group (percentage).
CREST indicates Carotid Stenting Versus Endarterectomy for Carotid Artery Stenosis trial; ICSS, International Carotid Stenting study; NS, not significant.
1.11-3.21; \( P = 0.02 \)), this finding was not different at the 4-year assessment (hazard ratio = 1.37; 95% CI, 0.90-2.09; \( P = 0.14 \)). Stenting had greater efficacy in younger patients (ie, < 70 y), a finding consistent with other research.\(^{149}\) The authors attributed this finding to increased vascular tortuosity and calcifications in older patients (which may make angioplasty and stenting technically more difficult). There was a higher incidence of stroke at 30 days after stenting versus endarterectomy in symptomatic patients; however, no difference was found at either time point for any other metric assessed in this investigation when stratified based on symptom status before randomization. As such, the investigators conclude that for carotid revascularization, either procedure is safe if performed by qualified proceduralists. Unfortunately, the rates of restenosis were not reported in this study.

The ICSS\(^{150}\) is an international multicenter investigation (involving 50 centers in Europe, Australia, New Zealand, and Canada) in which patients who were recently (ie, within 12 mo of randomization) symptomatic from carotid artery atherosclerotic disease were randomized to receive either stenting or endarterectomy. Similar to CREST, proceduralists and centers were certified to assure experience and expertise, and the primary endpoint was the combined rate of stroke, death, or myocardial infarction. Stents were used from a variety of manufacturers, with distal protection devices used in 72% of stented patients, unlike CREST where stents were supplied by a single manufacturer and distal protection devices were used in 96.1% of cases. The 120 day results from the intention-to-treat population are provided in Table 2. The combined rate of stroke, death, or myocardial infarction was significantly greater in the stent versus endarterectomy group. This outcome pattern was also observed in the 30-day data analysis in which combined rate of stroke, death, or myocardial infarction was 7.4% and 4.0% in the stented and endarterectomy groups, respectively (\( P = 0.003 \)). There were 3 fatal myocardial infarctions in the stented group versus 5 nonfatal myocardial infarctions in the endarterectomy group. Three times as many patients in the stenting group had evidence of a new ischemic brain lesion on posttreatment diffusion-weighted magnetic resonance imaging (MRI) scans compared with those who underwent endarterectomy.\(^{151}\) Both hematomas and cranial nerve injuries were more common in endarterectomy patients. Post hoc subgroup analysis suggested that the risk of the primary outcome event was probably similar between groups among women, but stenting was much more hazardous than endarterectomy in men.

Using data derived from investigations published before CREST and ICSS, Young et al\(^{152}\) performed a cost-effectiveness analysis of endarterectomy versus stenting. Using a hypothetical 70-year-old cohort over a lifetime and a Markov model to reflect the outcomes of clinical trials, they found that the lifetime costs of CEA were $35,200 versus $52,900 for stenting. In addition, the quality-adjusted life years were 9.64 years versus 8.97 years for endarterectomy and stenting, respectively. Sensitivity analysis showed that the lifetime risk of stroke or mortality influenced these results. Accordingly, the Investigators concluded that, “…with 59% probability, CEA will be the optimal intervention when all of the model assumptions are varied simultaneously.” On the basis of the results of earlier randomized trials and the outcome from this cost analysis, these investigators suggest that, “…given the uncertainty about the effectiveness and cost-effectiveness of carotid artery stenting versus CEA, (stenting) should remain limited to randomized trials or select populations of patients with carotid stenosis.”

Despite the contradictory finding of the similar primary outcome measure from these 2 recent prospective, randomized, controlled investigations, both CEA and stenting as options for the treatment of carotid stenosis will continue to be used, as there are specific contraindications to each technique. Specifically, patients with very heavy plaque burden may benefit more from endarterectomy, whereas those with earlier neck surgery, neck radiation, contralateral recurrent laryngeal nerve palsy, or a high carotid bifurcation may benefit more from stenting. The results of these clinical investigations, although they may not have clearly and consistently identified a benefit of one technique, do help physicians better understand the risks associated with these procedures and may allow for a more well-informed decision for each individual patient who presents with carotid artery disease. We refer readers to a special article by Perkins et al\(^{139}\) (with an accompanying editorial by Adams\(^{140}\)) in the December issue of the Mayo Clinic Proceedings. The investigators provide a detailed review and synthesis of data derived from investigations (including CREST and ICSS) that evaluated the effectiveness of CEA and those that compared CEA with carotid angioplasty. In addition, the investigators provide recommendations for applying these data to patient care. Perkins et al\(^{139}\) and Adams\(^{140}\) also emphasize the role that evolving medical treatment and reimbursement mechanisms will have on future choices in treating carotid artery atherosclerosis.

The application and design of distal protection devices, and their efficacy in preventing intraprocedural embolization of plaque, will likely have an important role in the future success and desirability of carotid stenting procedures. There currently exists no good-quality evidence to support the use of distal protection devices, and using stroke as an endpoint would require a large study population to identify benefit. Macdonald et al\(^{153}\) randomized patients undergoing carotid stenting to have their procedures filter protected or unprotected. The presence of emboli on diffusion-weighted MRI (DW-MRI: a technique with greater sensitivity at detecting emboli than clinical examination for stroke) was used, thus reducing the number of patients needed to supply adequate statistical power for the investigation. Thirty symptomatic patients were randomized and underwent DW-MRI both preprocedurally and then again 1 to 3 hours, 24 hours, and 30 days after stenting. TCD was conducted during the procedure to assess for evidence of emboli in real time. Surprisingly, the investigators
found a numerically higher (but statistically insignificant) incidence of new DW-MRI lesions in scans from patients in whom distal protection devices were used both within 24 hours of their procedure [7 of 24 scans (29%) vs. 4 of 22 scans (18%) for unprotected; \( P = 0.4 \)], and within 30 days of their procedure [9 of 33 scans (27%) vs. 4 of 33 scans (12%) for unprotected; \( P = 0.1 \)]. Unfortunately, the investigators did not report the fraction of patients in whom new lesions were found. Although there was merely a tendency toward a greater frequency of embolic events determined by TCD during embolicigenic phases (ie, predilatation, stent deployment, postdilatation) in patients in whom distal protection was used (138 vs. 80 events in unprotected patients; \( P > 0.05 \)), there were significantly more events in patients with distal protection both during advancement of the catheter through the atherosclerotic plaque and filter deployment (138 vs. 16 events in unprotected patients; \( P < 0.01 \)) and during the entire procedure (428 vs. 165 events in unprotected patients; \( P = 0.03 \)). The majority of emboli seemed to be particulate in nature (vs. gaseous emboli, based on sample volume length\(^{154,155} \)). Two patients (one in each group) developed new neurological deficits (ie, stroke) after the procedure. As such, the investigators concluded that embolic phenomena are more common in carotid stenting procedures when distal protection is used and the impact of this finding on the risk of stroke and clinical practice requires further study.

During CEA-associated carotid occlusion (ie, cross-clamping), cerebral hypoperfusion may lead to ischemia. Although routine shunting may reduce the risk of hypoperfusion, the use of a shunt is associated with risk of embolic stroke and cognitive deficits postoperatively.\(^{156-158} \) As such, selective shunting is often performed in conjunction with monitoring for cerebral hypoperfusion by a variety of modalities. Monitoring for the development of gross neurological deficits in an awake patient is considered to be the gold-standard technique; however, this can only be accomplished during regional anesthesia. For patients in whom general anesthesia is used, other modalities (eg, electroencephalography, stump pressure, somatosensory evoked potentials, cerebral oximetry) must be relied upon to detect cerebral hypoperfusion. To compare these techniques with the gold standard requires an awake patient, and general anesthetic-induced changes in cerebral hemodynamics and other effects can alter the extrapolation of awake data of patients receiving general anesthesia. Moritz et al\(^{59} \) randomized patients having CEA to receive either general or regional anesthesia. In those having general anesthesia, maintenance was by inhaled sevoflurane [1.0 minimum alveolar concentration (MAC) without nitrous oxide], with as-needed intravenous injections of fentanyl and ventilation was adjusted to maintain a PaCO\(_2\) of 37 to 43 mm Hg. A shunt was placed if patients having regional anesthesia developed new neurological deficits and was placed in those having general anesthesia if the somatosensory evoked potential N20/P25 amplitude decreased to 30% of the baseline value. All patients underwent monitoring for cerebral ischemia through continuous TCD of \( V_{MCA} \), regional cerebral oximetry through near-infrared spectroscopy, stump pressure, and somatosensory evoked potential recording through the contralateral median nerve. Ninety-six patients completed the investigation: 48 patients in each group. Mean stump pressure after occlusion was not different between groups [52 ± 20 mm Hg and 50 ± 21 mm Hg in the general and regional anesthesia groups, respectively (\( P = 0.4 \))]. These values were still not different even after correction for systemic blood pressure (MAP was 11.8 mm Hg higher in the regional anesthesia group; \( P < 0.001 \)). Graphical comparison of monitoring data (not corrected for MAP) between groups are provided in Figure 3. There was no significant difference in percentage change in \( V_{MCA} \) from baseline (\( P = 0.795 \), \( P = 0.885 \)), N20/P25 amplitude (\( P = 0.294 \), \( P = 0.317 \)), or percentage change in rSO2 (\( P = 0.177 \), \( P = 0.166 \)) (values given for unadjusted and after adjustment for MAP, respectively for linear regression analysis of data over the entire study period). Absolute \( V_{MCA} \) was higher before clamping and during reperfusion in the regional anesthesia group (Fig. 3A), and values were significantly higher over the study period both before (\( P < 0.01 \)) and after (\( P < 0.01 \)) correction for MAP in the regional anesthesia group; however, there was no difference during occlusion. rSO2 from the ipsilateral hemisphere was significantly higher at all time intervals in patients having regional anesthesia both before (\( P < 0.01 \)) and after correction for MAP (\( P < 0.01 \)). These data support the notion that monitoring modalities used to detect cerebral hypoperfusion during CEA are minimally affected by general anesthesia versus values obtained in awake patients. Two major limitations of this investigation, both addressed by the investigators in the study, are that these data may not be transferable to patients having general anesthesia by other drugs (eg, propofol). In addition, the investigators did not determine how each monitoring modality compared with the awake neurological examination at detecting cerebral ischemia—only trends in data from each modality were assessed over the course of the procedure, independent of whether ischemia developed and whether a shunt was used in an attempt to restore adequate cerebral perfusion in patients showing poor oxygen delivery.

Airway management for CEA patients requiring postoperative neck hematoma evacuation can provide major challenges for anesthesia providers. Shakespeare et al\(^{160} \) performed a retrospective review of patients having CEA during a 10-year period at a single institution. Forty-four of 3225 patients (1.4%) developed a neck hematoma requiring evacuation within 72 hours after surgery, and 42 of these 44 patients required airway management before hematoma evacuation (the tracheal tube was not removed after CEA in 2 patients). An awake fiberoptic technique was attempted in 20 patients and was successful in 15; the remaining 5 patients were successfully intubated by direct laryngoscopy. Direct laryngoscopy was the initial technique used in the remaining 22 patients and was successful in 18 patients. In the remaining
4 patients, direct laryngoscopy was facilitated by rapid opening of the incision allowing decompression of the hematoma in 3 patients, and 1 patient required an emergency tracheostomy at the bedside in the intensive care unit. In 36 of the 44 patients (82%), the tracheal tube was removed uneventfully in < 24 hours. There were no other adverse events attributed to airway management or any deaths within 2 weeks after hematoma evacuation. The investigators recommend an attempt at awake fiberoptic intubation in stable patients, as it offers the advantage of the patient being able to maintain his own airway patency and ventilation during intubation. In cases with acute airway compromise, direct laryngoscopy may be faster and, if this technique fails, release of the hematoma may help facilitate direct laryngoscopy.

We refer interested readers to a review article in the *British Journal of Anaesthesia* by Erickson and Cole[161] on carotid artery disease. The investigators address pathophysiology and diagnosis of carotid disease, treatment options (specifically focusing on CEA vs. stenting), and anesthetic techniques for both CEA and stenting procedures.

**SPINE SURGERY**

Spine operations are performed to address a variety of malignant and nonmalignant maladies. These procedures...
have inherent risks such as bleeding, infection, the development of new neurological deficits (including blindness and positioning-related injuries), and complications related to preexisting comorbidities. The incidence of preexisting comorbidities at the time of surgery is generally greatest in the elderly. Deyo et al162 performed a retrospective analysis of Medicare claims for surgical procedures performed to treat lumbar spinal stenosis in elderly patients between the years 2002 and 2007. Overall, the rate of spine surgery per 100,000 Medicare beneficiaries decreased from 137.4 in 2002 to 135.5 in 2007. Despite this, the rate of complex spine fusion (ie, >2 disk levels fused or patients having combined anterior and posterior approach) increased 15 fold from 1.3 to 19.9 per 100,000 beneficiaries, but still accounted for only <2% of the surgeries. Overall, major medical complications in beneficiaries were reported in 3.1%, wound infections were reported in 1.2%, and death occurred within 30 days in 0.4%. Those having complex fusion procedures had a 3-fold increase in the odds of having a life-threatening complication compared with those having decompression alone. Further, adjusted mean hospital costs were 3.4-times greater for a complex fusion ($80,888) than for decompression alone ($23,724). As such, the investigators suggest considering more conservative surgical options, if feasible, in elderly patients with spinal stenosis.

In patients having surgery on the cervical spine by an anterior approach, an estimated 7% to 13% will acquire new-onset recurrent laryngeal nerve injury. Often asymptomatic, vocal cord dysfunction can also cause hoarseness, stridor, or even frank airway compromise. Although the cause is probably multifactorial, both direct pressure on the recurrent laryngeal nerve during surgical retraction and compression of submucosal branches of the nerve by the endotracheal tube may contribute. In the latter case, the tracheal tube is fixed in position at the mouth and at the inflated cuff such that when the airway is retracted, pressure is thought to be exerted by the tracheal tube on the convex aspect of the airway. In addition, retraction can cause the pressure within the tracheal tube cuff to increase, thereby potentially increasing pressure on submucosal branches of the nerve. Accordingly, deflation of the cuff after surgical retraction, and cuff reinflation until no gas leak is present (or at least reduction of the pressure within the cuff), may reduce tension on the tracheal wall. To determine the influence of side of surgery, and cuff pressure on postoperative recurrent laryngeal nerve dysfunction in patients having cervical fusion, Jung and Schramm163 reduced tracheal tube cuff pressures to <20 mm Hg in 149 of 242 study patients having a left-sided anterior approach to surgery. Cuff pressure was not reduced in the remaining 93 cases “...for anesthesiological reasons or was forgotten.” Data obtained from these patients were compared with other published data from another investigation by the investigators where patients underwent a right-sided approach.164 A summary of data from this investigation is given in Table 3. In patients having a left-side approach, reduction of tracheal tube cuff pressure to <20 mm Hg resulted in a lower incidence of vocal cord paresis in the first week after surgery. However, there was no difference associated with reduced cuff pressure in patients having a left-sided approach at 3 months. When comparing surgical approach, right-sided surgery resulted in an increased incidence of vocal cord paralysis within a week of surgery when compared with a left-sided approach, but there was no difference at 3 months after surgery. Performing both interventions (ie, right-sided approach and reduced tracheal tube cuff pressure) led to a significant decrease in both short-term and long-term vocal cord dysfunction. Another interesting finding was that in patients with fiberoptic laryngoscopy-confirmed vocal cord dysfunction (regardless of surgery or anesthetic management), hoarseness occurred in only 33% and 25% of patients at 1 week and 3 months, respectively. Therefore, the clinical finding of hoarseness underestimates the rate of injury after anterior cervical spine surgery. Given the findings of numerous earlier investigations, these results are not surprising but serve to reinforce the multifactorial etiology of nerve dysfunction. In interpreting these data, some elements of the study design deserve comment. The “control” group (ie, left-side approach with no tracheal tube cuff pressure adjustment) consisted of patients in whom “...it was impossible to reduce the cuff pressure for anesthesiological reasons or (it) was forgotten.” Although the investigators did not state the reason for the former element, it potentially introduced selection bias in the study results. In addition, it was unclear when cuff pressure was adjusted (ie, before or after retraction). Finally, throughout the study, the investigators drew conclusions from

### TABLE 3. Incidence of Vocal Cord Dysfunction After Cervical Spine Surgery Through the Anterior Approach

<table>
<thead>
<tr>
<th>Surgical Approach</th>
<th>Reduced Tracheal Tube Cuff Pressure*</th>
<th>N</th>
<th>Incidence of Vocal Cord Dysfunction—Within 1 wk</th>
<th>Incidence of Vocal Cord Dysfunction—at 3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Paresis Paralysis</td>
<td>Total Paresis Paralysis</td>
</tr>
<tr>
<td>Left</td>
<td>Yes</td>
<td>142</td>
<td>4 (2.7%)	extsuperscript{1,2} 1 (0.7%)	extsuperscript{1} 3 (2.0%)	extsuperscript{1}</td>
<td>2 (1.3%)	extsuperscript{1} 1 (0.7%)	extsuperscript{1} 1 (0.7%)	extsuperscript{1}</td>
</tr>
<tr>
<td>Left</td>
<td>No</td>
<td>93</td>
<td>13 (14%) 7 (7.5%) 6 (6.6%)</td>
<td>6 (6.5%) 2 (2.2%) 4 (4.3%)</td>
</tr>
<tr>
<td>Right</td>
<td>No</td>
<td>120</td>
<td>29 (24.2%) 4 (3.3%) 25 (20.8%)</td>
<td>16 (13.3%) 8 (6.6%) 8 (6.6%)</td>
</tr>
</tbody>
</table>

Vocal cord dysfunction was assessed by indirect laryngoscopy, observing vocal cord mobility where paresis represents decreased movement and paralysis represents no vocal cord movement.

Adapted with permission from J Neurosurg. 2010;67:10–15.

*For patients in whom tracheal tube cuff pressure was reduced, the cuff pressure was decreased to 20 mm Hg.

†P < 0.05 versus left-side approach and no reduction in cuff pressure (ie, 1 intervention).

‡P < 0.05 versus right-side approach and no reduction in cuff pressure (ie, 2 interventions).
their data, but it was not clear whether any of the data in this investigation were subject to statistical analysis (we performed the statistical analysis of the categorical data shown in Table 3). Noting that this is an “observational study” does not obviate the need for formal statistical analysis, especially given that the study groups contained 93 to 142 patients and should have provided reasonable statistical power.

**Spinal Cord Injury**

After induction of general anesthesia, direct laryngoscopy and tracheal tube placement will generally cause an increase in sympathetic activity, manifested as an increase in blood pressure, heart rate, and circulating catecholamine concentrations. The presence of spinal cord injury can have a profound impact on autonomic function, but it is unclear whether it impacts the hemodynamic responses to direct laryngoscopy. Yoo et al prospectively assessed the impact of the level of spinal cord injury (i.e., quadriplegia with a lesion above C7 or paraplegia with a lesion below T5) and the time interval since injury on hemodynamics in 214 patients. Twenty patients without spinal cord injury served as controls. Patients were excluded if they: (1) had a prior history of cardiac arrhythmias, (2) required medications that influence autonomic function, (3) were in spinal shock, or (4) were anticipated to be difficult to ventilate by mask. Anesthesia was induced with intravenous sodium thiopental and muscle relaxation was facilitated with succinylcholine in all patients. Heart rate, systolic blood pressure, and serum catecholamine concentrations were evaluated before and after direct laryngoscopy. As shown in Figure 4, systolic blood pressure increased similarly in controls and paraplegic patients in whom duration of injury was < 10 years; paraplegics with an injury duration ≥10 years exhibited an exaggerated increase in blood pressure compared with controls. All quadriplegic patients had a significantly blunted systolic blood pressure response to laryngoscopy compared with controls. Heart rate response to laryngoscopy was blunted only in acute quadriplegics. Finally, a rise in serum norepinephrine concentration was attenuated in patients with quadriplegia but not in those with paraplegia. Some study design elements deserve comment. First, the investigators stated that patients with spinal shock (including those not requiring pressor support of blood pressure) were excluded from the investigation. However, the investigators included 27 quadriplegic patients in their analysis with a complete spinal cord injury at a level higher than C7 who were within 4 weeks of their injury at the time of their inclusion into the investigation. It is unclear whether and why these patients differed mechanistically and physiologically from those having clinical spinal shock. Second, the investigators’ decision to administer succinylcholine may not be advisable for all patients, given that paralysis can predispose some patients to life-threatening hyperkalemia.

Patients with spinal cord injury often have significant functional limitations and a variety of associated medical comorbidities, often leading to significant cost and resource utilization. Transplantation of stem cells at the site of injury has promise for restoring some spinal cord function; however, this technique has limitations, as reviewed by Sahni and Kessler. There are ethical issues surrounding the acquisition of human fetal stem cells. Neural stem cells undergo replicative senescence, and stem cells derived from bone marrow have limited differentiation capacity, although this latter effect may be attenuated by the coadministration granulocyte colony-stimulating factor. Hu et al reported on the implantation of human umbilical cord mesenchymal stem cells 1 day after spinal cord injury in rats. The advantages of using this cell line are greater ex vivo proliferation and lower immunogenicity than bone marrow-derived stem cells. Further, these cell lines are...
derived from human tissues that are usually discarded immediately after delivery, thus posing no threat to mother and fetus. In animals that received human stem cell transplantation, hind limb motor function was significantly improved at 5 weeks after experimental spinal cord injury versus animals that received vehicle at the site of injury. Histologic assessment showed stem cell survival and migration, increased growth-cone structures at the site of injury, and a reduced glial scar. The stem cells produced a significant amount of glial cell line-derived neurotrophic factor and neurotrophin-3, possibly attenuating astrocyte reactivity and scar formation. Additional research is needed to further explore the potential of stem cell transplantation in central nervous system neuronal repair or regeneration after injury.

Pain After Spine Surgery

Postoperative pain is common after surgery on the spine and can limit activity, thus hindering physical and occupational rehabilitation. Reduced physical activity can increase the risk for medical complications, such as pneumonia, venous stasis and thromboembolism, and urinary tract infection. Collectively, these factors can lead to prolonged care facility stay, psychological stress, and reduced patient satisfaction. Perioperative narcotics are generally the mainstay treatment for pain after spinal surgery; however, other analgesic modalities are currently under investigation.

Gabapentin, an orphan drug originally used as an antiepileptic, is effective for both the treatment of neuropathic pain and for acute postsurgical pain. In addition, the preoperative administration of gabapentin to patients who are to undergo lumbar spine surgery reduces acute postoperative narcotic requirements; however, these data are obtained from adult patients. Rusy et al performed a prospective, randomized investigation in children, age 9 to 18 years, having spinal fusion who received either gabapentin or placebo orally before surgery. In the postoperative period, intravenous morphine was administered by a protocol (ie, intermittent, weight-based boluses in the recovery room and by patient-controlled analgesia afterward). Patients randomized to receive gabapentin preoperatively also received gabapentin orally (5 mg/kg/dose) 3 times per day for 5 days starting the day after surgery; patients randomized to the placebo group received a placebo tablet or elixir by a similar schedule. Data from 59 patients were included in the final analysis (29 received gabapentin). Compared with those who received placebo, total daily morphine consumption was lower in the gabapentin group in the post anesthesia recovery unit (0.044 ± 0.17 vs. 0.064 ± 0.031 mg/kg/h; P = 0.003), and on postoperative day 2 (0.036 ± 0.016 vs. 0.047 ± 0.019 mg/kg/h; P = 0.018) with a trend toward reduced morphine requirement on postoperative day 1 (0.046 ± 0.0160 vs. 0.055 ± 0.017 mg/kg/h; P = 0.051); no difference was noted on days 3 to 5. Verbal numeric pain scores (ie, 0 to 10) were lower in the gabapentin group both in the post anesthesia recovery unit (2.5 ± 2.8 vs. 6.0 ± 2.4; P < 0.001) and on the morning after surgery (3.2 ± 2.6 vs. 5.0 ± 2.2; P < 0.001) compared with placebo; pain scores were not different at any other time point up to postoperative day 5. Further, there was no difference between groups with respect to morphine-related side effects (ie, duration of supplemental oxygen or urinary catheter requirements, time to first bowel movement or transition to oral analgesics, or number of doses administered of either ondansetron, diphenhydramine, or diazepam). The investigators concluded that gabapentin, when given preoperatively and for 5 days postoperatively, will reduce morphine requirements for up to 2 days and pain score immediately after pediatric spinal fusion. This is not a sustained effect despite continued administration of gabapentin.

Ketamine is another nonopioid analgesic that can be used in addition, or as a supplement, to opioids for pain control in the perioperative period. Patients with subacute or chronic spine disease often have subacute or chronic pain treated with multiple analgesics, and little is known about the use of ketamine in opioid-tolerant patients with chronic pain who undergo surgery. To determine whether perioperative use of ketamine is beneficial in this patient population, Loftus et al randomized 52 patients with a > 6-week history of daily opioid use and chronic back pain for > 3 months to receive either ketamine (0.5 mg/kg upon induction of anesthesia followed by a continuous infusion at 10 mg/kg/min, terminated at wound closure) or saline placebo bolus and infusion during elective major lumbar spine surgery. Providers and patients were blinded to treatment, and the anesthetic and postoperative pain protocols were standardized. Demographics and operative characteristics were similar except patients in the ketamine group: (1) received more nonsteroidal anti-inflammatory agents preoperatively (26% vs. 6% for placebo; P = 0.006) and (2) required less narcotic (in terms of morphine equivalents) intraoperatively (51 ± 27 mg morphine equivalents vs. 67 ± 44 mg for placebo; P = 0.034). Total narcotic consumption was reduced 48 hours after surgery in patients receiving ketamine (195 ± 111 mg morphine equivalents vs. 309 ± 341 mg for placebo; P = 0.029), and this difference remained even after multivariate statistical analysis to correct for nonsteroidal anti-inflammatory administration (P = 0.045). At 6 weeks after surgery, patients who received ketamine intraoperatively had lower pain scores (recorded on a visual analog scale of 0 to 10; 3.1 ± 2.4 vs. 4.2 ± 2.4 for placebo; P = 0.026) and lower daily opioid consumption (converted to mg/h of a continuous intravenous morphine infusion; 0.8 ± 1.1 mg/h vs. 2.8 ± 2.4 mg/h; P = 0.041). Similarly, Amr showed that an intermittent intravenous ketamine infusion (80 mg over 5 h every day for 1 wk) was effective, for up to 2 weeks after termination of infusion, at reducing pain scores in patients with chronic spinal cord injury.

Elder reported on the effect of bupivacaine 0.5%, infused through a catheter placed intraoperatively into the subfascial paravertebral space, in patients having posterior cervical spine fusion. All 24 patients received an ON-Q PainBuster (I-Flow Corporation, Lake Forest, CA)
delivery system at the time of surgery. This system consists of an elastomeric pump that delivers a continuous infusion of medication through a catheter placed at the time of surgery. Although the study did not standardize the anesthetic or analgesic plan, the investigators reported that, “...there were no fundamental differences in the (anesthesia) team’s technique or types of medications used...” All pumps delivered 2 mL/h of 0.5% bupivacaine for a total of 72 hours. For a comparison group, the investigators identified 24 historical controls matched for age, diagnosis, and levels fused. Patients in the study group had a significantly lower consumption of morphine equivalents of narcotic on each of the first 4 days after surgery [range, 24.4% reduction (P = 0.048) to 58.1% reduction (P = 0.009) on days 1 and 4, respectively, vs. controls]. The investigators also reported that study patients were more likely to have a bowel movement, ambulate, and be discharged home earlier than those in the control group. Further, there were no complications attributed to the use of this technique. There was no mention of how the local anesthetic infusion impacted postoperative neurological assessment.

Transcutaneous electrical stimulation (TENS) is a commonly used electroanalgesia modality, delivering a mild (and essentially painless) electrical current through skin electrodes. TENS reportedly provides a reduction in perceived pain. Although the mechanism of action is still unclear, TENS is believed to affect the pain response by activating small, low-threshold myelinated peripheral afferent nerve fibers. These, in turn, inhibit central transmission of afferent pain impulses through unmyelinated C-fibers within the dorsal horn of the spinal cord. In addition, TENS stimulates the release of endogenous opioids within the brain and spinal cord. TENS also reduces postoperative narcotic requirements after abdominal and shoulder, but not knee, surgery, although in the investigation of knee surgery, the specific setting of the TENS unit were not supplied in the study. To determine whether a TENS-associated reduction of postoperative pain has utility after lumbar spine fusion, Unterrainer et al studied 38 patients having lumbar spine fusion. Four TENS electrodes were applied preoperatively such that one electrode was placed 4 cm to the left and the right side of both the superior and inferior aspects of the planned surgical incision site. Patients were then randomized into 3 groups; (1) TENS unit was activated for 30 minutes before incision, for 8 hours after skin closure, and for 30 minutes on the first postoperative day, (2) TENS was activated only 8 hours after skin closure and for 30 minutes on the first postoperative day, and (3) the TENS was not activated. All patients received standardized patient-controlled analgesia with piritramide, a synthetic opioid with 70% of the potency of morphine. During the first 24 hours after surgery, the group in whom TENS was initiated before incision had reduced piritramide consumption (0.158 ± 0.051 mg/kg for 24 h) compared with those in whom the stimulation was initiated after surgery (0.221 ± 0.066 mg/kg; P = 0.011). Those in whom the TENS unit was never activated had the highest 24 hours piritramide consumption (0.583 ± 0.167 mg/kg; P < 0.0005 for comparison with the other 2 groups). As such, the investigators showed that TENS can effectively reduce postoperative systemic narcotic requirements after surgery with minimal (if any) adverse effects.

**TRAUMATIC BRAIN INJURY**

Increased ICP is a common finding after TBI, and the presence, frequency, and severity of increased ICP is associated with poor outcome. There are sparse data describing the time course of the development of elevated ICP and how these changes are associated with outcome. Bremmer et al retrospectively reported on 221 patients with severe TBI (ie, Glasgow Coma Score < 8 with abnormalities noted on CT scan of the head upon hospital admission) requiring ICP monitoring. Elevated ICP was defined as an ICP > 20 mm Hg for > 5 minutes. Maximal therapy for elevated ICP included: (1) sedation and analgesia alone (29% of patients), (2) cerebrospinal fluid drainage (26%), (3) mannitol or hypertonic saline (28%), and (4) barbiturates and other second-tier therapies (17%). ICP profiles were stratified into the following categories based on the first day at which the highest mean ICP was noted: (1) early rise, highest mean ICP on days 1 to 2 occurring in 70 patients (32%); (2) intermediate rise, highest pressure on days 3 to 5 occurring in 74 (34%) patients; and (3) late rise, highest pressure after day 5 occurring in 75 patients (34%). In 13 patients, a bimodal spike in ICP was noted. In these 13 patients, the first increase was noted before day 5 and the second increase was noted after day 9. Use of mannitol, hypertonic saline, and/or second-tier therapies to control elevated ICP was required in 65% of patients in the late-rise group versus only 33% of patients in the early and intermediate-rise groups combined (P < 0.001). In patients not lost to follow-up, outcome was stratified based on the Glasgow outcome score at 1 year after injury and was as follows: good recovery (15%), moderate disability (28%), severe disability (21%), vegetative state (4%), and death (32%). For those who had a good recovery, 56% were in the early rise group, 36% in the intermediate rise group, and 8% in the late rise group (P < 0.005 for comparisons of late group with both early and intermediate groups; P > 0.05 for early vs. intermediate group comparison). In addition, mortality was 25% in the early group, 30% in the intermediate group, and 41% in the late rise group (P < 0.02 for early vs. late rise groups; P > 0.05 for all other comparisons). As such, in patients with severe TBI, a late rise in ICP is predictive of more refractory intracranial hypertension and a poorer prognosis. These data also support the notion that lower ICPs, obtained early after TBI, do not always predict a more favorable course and may support the need for a longer duration of ICP monitoring. However, further study will be required to identify the mechanisms accounting for these findings. Of note, these data were limited to those with severe TBI on admission. These results probably

© 2011 Lippincott Williams & Wilkins
Loss of heart rate variability was initially used to assess fetal well-being and has also been reported to correlate with outcome after myocardial infarction and to predict brain death.\textsuperscript{190–193} Traditionally, assessing heart rate variability involved complex mathematical modeling; however, Mowery et al\textsuperscript{194} described a simpler technique where the variability of heart rate can be accurately estimated by collecting values over a 5-minute epoch and determining the standard error among those values. A reduction in these integer heart rate variabilities (HRVi) in trauma patients was associated with autonomic dysfunction and subsequent poor outcome. As there are dynamic changes in autonomic function after TBI, Kahraman et al\textsuperscript{195} applied the technique of Mowery et al to determine whether an association exists between HRVi, integer pulse pressure variability (PPVi; standard deviation of pulse pressure obtained during 5-minutes epochs), and changes in ICP and CPP, in 25 patients with severe TBI (Glasgow coma score on admission < 9 plus need for ICP monitoring). Patients were excluded from data analysis if they required treatment with drugs that affect autonomic function (eg, dopamine, epinephrine, atropine, dexmedetomidine), high-dose vasopressin for blood pressure support, or thiopental for sedation. In addition, an autonomic index was calculated as HRVi \times PPVi for each patient, derived from each 5-minute epoch. As shown in Figure 5, HRVi, PPVi, and especially autonomic index increased with increasing ICP until ICP was > 50 mm Hg, at that point all 3 parameters significantly decreased to values significantly less than those obtained during periods of normal ICP. Accordingly, these data suggest that as ICP rises, initially there is increased activity of the autonomic nervous system reflected in increase variability in heart rate and pulse pressure. However, when ICP is excessively elevated (ie, > 50 mm Hg in this investigation), there is failure of the autonomic nervous system reflected as a decreased variability in heart rate and pulse pressure.

Hypertonic saline is an accepted treatment for intracranial hypertension after TBI, and it improves cerebral hemodynamics and brain tissue oxygenation.\textsuperscript{196–198} One major limitation is the development of hyperchloremic metabolic acidosis and associated renal impairment.\textsuperscript{199–202} In 10 patients with severe TBI, Bourdeaux and Brown\textsuperscript{203} treated intracranial hypertension with 85 mL of sodium bicarbonate 8.4%, instead of 100 mL of sodium chloride 5%—the latter being the standard practice at their institution. These 2 doses contain a similar solute load (170 mOsm). The infusion was instituted if ICP was > 20 mm Hg for > 5 minutes, and the volume was delivered over 30 minutes through a pump into a central venous catheter. If ICP increase to > 20 mm Hg again within 6 hours, a second dose was administered. Treatment was considered a failure if the patient did not respond with a decrease in ICP to < 10 mm Hg after 2 doses of sodium bicarbonate plus the initiation of other standard conservative measures. Mean ICP was 28.5 ± 2.6 mm Hg before instituting the sodium bicarbonate infusion and decreased to 10.3 ± 1.9 mm Hg within 15 minutes after beginning the infusion (\(P < 0.01\)). ICP was < 20 mm Hg in all patients for 5 hours after initiating the infusion. Although MAP was unchanged during the 5 hours study period, CPP increased from 62 ± 4 mm Hg to 80 ± 3 mm Hg (\(P < 0.01\)). There was a statistically significant, but probably not clinically consequential: (1) increase in serum sodium concentration from 145 ± 6 mmol/L to 147 ± 6 mmol/L (\(P < 0.01\)), (2) decrease in serum chloride concentration from 119 ± 7 mmol/L to 118 ± 6 mmol/L (\(P < 0.01\)), and (3) increase in serum pH from 7.45 ± 0.05 to 7.50 ± 0.05 (\(P < 0.01\)). Limitations of this investigation include a small sample size and failure to comment on adverse effects attributable to hypertonic sodium bicarbonate infusion (although it is possible that no adverse effect was noted). We refer the reader with additional interest in TBI to recent review articles. The journal \textit{Brain Injury} recently published a series of 3 review articles by Meyer et al\textsuperscript{204–206} that address TBI topics in an evidence-based manner. In the first article,\textsuperscript{204} the usefulness of individual nonpharmacologic interventions, such as hypothermia, hyperbaric oxygen, cerebrospinal fluid drainage, and decompressive craniectomy are addressed. In the second article,\textsuperscript{205} data supporting (or refuting) the utility of various pharmacologic treatments are addressed. These drugs include sedative/hypnotics (eg, barbiturates and propofol), opioids, osmotic agents, and corticosteroids. In the third article,\textsuperscript{206} the investigators address interventions that have been alleged to promote arousal from coma after TBI, including dopaminergic drugs (eg, bromocriptine, levodopa), amantadine, sensory stimulation, median nerve stimulation, and music therapy. In all 3 review articles, the investigators include well-organized tables summarizing the current literature. We also refer readers to a series of 2 brief editorials that debate the
optimal environment for caring for TBI patients. Teig and Smith argue that patients should be managed in a specialty neurocritical care unit, whereas Petsas and Waldmann comment on quality management in a general critical care unit.

NEUROTOXICITY AND NEUROPROTECTION

When neural tissue is at risk for, or has sustained, injury, the primary goal of care is to optimize oxygen and nutrient delivery to the endangered brain, spinal cord, and peripheral nerves by assuring adequate oxygenation and perfusion (ie, through the ABCs of airway, breathing, and circulation support). In addition to these interventions, other “neuroprotective” strategies may be warranted. In 2010, a number of review articles addressed adult pharmacologic neuroprotection and the effect of anesthetics on apoptosis, and neuroprotective strategies in neonates experiencing hypoxic or ischemic brain insults. In the remainder of this section, we will highlight some other articles published in 2010.

Volatile Anesthetics and Injury

The association between volatile anesthetic use and long-term neuronal degeneration has been characterized in a variety of animal models for almost a decade. Recently, other research has determined that in susceptible individuals (ie, the very young and very old) anesthetic exposure may adversely impact long-term cognitive function and behavior, hypothetically as a result of changes in neuronal chloride ion gradients due to anesthetic-induced neurotoxicity. Specifically, exposure to a variety of common anesthetic drugs during the period of rapid synaptogenesis activates apoptosis in neurons, and inhibition of apoptotic mechanisms may confer a protective benefit. As this is a very young field of investigation, there remain many unanswered questions such as are certain anesthetic agents more likely to cause injury by apoptosis, and are there other mechanisms by which anesthetic drugs can produce long-term cognitive and behavioral changes?

To determine whether isoflurane and sevoflurane exposure differentially impact neurodegeneration, Liang et al exposed 7-day-old mice to 0.5 MAC of either isoflurane or sevoflurane (0.75% and 1.1%, respectively) for 6 hours. In mice, the first 2 weeks after birth represents a time of rapid synaptogenesis. The investigators found that, compared with mice not exposed to a volatile anesthetic, isoflurane caused a 2-fold increase in serum S100β protein, an intracellular neuronal protein that enters the systemic circulation after neuronal injury and disruption of the blood-brain barrier. In contrast, sevoflurane did not produce a significant increase in serum S100β. Isoflurane also caused a 4-fold and 6-fold increase in cleaved caspase-3, a biomarker of apoptosis, in the hippocampal CA1 region and cerebral cortex, respectively (P < 0.05 for both comparisons with control animals). Sevoflurane exposure had no significant effect on hippocampal cleaved caspase-3, but caused a 3-fold increase (P < 0.05) in cleaved caspase-3 in the cortex. Despite these findings, no impairment of learning or memory was identified in either group, when compared with similar animals not exposed to an anesthetic.

As documented by Liang et al, an increase in biomarkers of apoptosis does not always strongly correlate with clinical manifestations, such as cognitive deficits. Although there are multiple explanations for this finding (ie, low sensitivity of cognitive testing in this setting, inherent differences in study methodology), an alternate explanation may be that mechanisms other than those resulting in increases in apoptotic biomarkers account for long-term anesthetic-induced cognitive and behavioral changes. Briner et al evaluated the effect of 3 volatile anesthetics on neuronal architecture in 16-day-old rats to determine whether these drugs induce structural changes in neurons, specifically dendritic spines (which are regions on a neuronal dendrite that receive input from another neuron by a single synapse). Rats received 1 MAC of either isoflurane, sevoflurane, or desflurane for 30, 60, or 120 minutes. Animals were then killed and, in addition to staining layer 5 of the medial prefrontal cortex (ie, a region of brain critical to the control of high-order cognitive functions) to detect necrosis and apoptosis (by Fluoro-Jade B and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labeling), ionotrophic injections were carried out in individual neurons to visualize the dendritic arbor and assess changes in dendritic spines. Although there was no difference in cell death (which was not surprising as anesthetic-induced neuroapoptosis is less prevalent in 16-day-old rats vs. younger rats), there was an increase in dendritic spine density after exposure to all 3 volatile anesthetics. However, the timing of changes differed according to anesthetic; significant increases in spine density were seen after 30, 60, and 120 minutes, with sevoflurane, isoflurane, and desflurane, respectively. As such, the investigators conclude that volatile anesthetics may alter synaptogenesis independent of their effect on neuronal apoptosis.

Binding of γ-aminobutyric acid (GABA) to the GABA receptor induces the opening of a chloride channel where chloride ions flow along their concentration gradient. The GABA receptor is also a primary site of action of volatile anesthetics and may indirectly modulate volatile anesthetic-associated neuronal apoptosis. The GABA receptor has 2 isoforms: GABA and GABA. Initially, the GABA isoform is present but, at some point during development, there is a transition such that GABA receptors containing primarily the GABA isoform predominate. In rats, that transition occurs at approximately postnatal day 7. A similar transition occurs in humans as well; however, the timing of this transition in humans is not as clearly known. In younger animals, opening of the GABA chloride channel results in an efflux of chloride from neurons, thus causing neuronal depolarization. In adult animals, opening the GABA chloride channel results in chloride influx and thus neuronal hyperpolarization. This change in GABA function is likely to be the result of changes in neuronal chloride ion gradients due to changes in chloride transporters at different stages of
development.\textsuperscript{226,227} Piehl et al\textsuperscript{228} exposed hippocampal slices obtained from 4, 7, and 14 postnatal rats (these dates corresponding to pre- \textit{GABA}_A, during, and post-\textit{GABA}_A \(\alpha\)-subunit transition) to either 2% sevoflurane or air for 5 hours. They then evaluated cell death, the presence of activated caspase-3, and both isoforms of the \(\alpha\)-subunit of \textit{GABA}_A receptors immediately after and again at both 24 hours and 72 hours after treatment (ie, sevoflurane vs. air). Neuronal death was assessed using Sytox staining, a nucleic acid stain that only enters cells with disrupted cell membranes (ie, dead or dying cells); hence Sytox staining is not specific for apoptosis. Results are summarized in Table 4. In postnatal day 4 and day 7 rats, increased cell death was observed in the sevoflurane group only 72 hours after exposure (ie, delayed cell death) despite increased activated caspase-3 occurring only immediately after exposure. Early cell death was noted in postnatal day 14 sevoflurane-treated rats. Further, sevoflurane induced significant changes in the expression of the 2 isoforms of the \(\alpha\)-subunit of \textit{GABA}_A receptor. It is, however, difficult to interpret how, and whether, these latter changes impacted the differences observed in the timing of neuronal demise, as one of the primary limitations of this investigation is that concurrent changes in chloride ion flux were not determined (a limitation addressed by the investigators in the study). As such, it is unclear from these data whether alterations in chloride ion flux, concurrent with changes in the \(\alpha\)-subunit of \textit{GABA}_A receptor, contributed to the differences in early versus late neuronal death as a function of age (observed in this model).

As discussed earlier, in addition to an age-related change in the isoform of the \(\alpha\)-subunit expressed in the \textit{GABA}_A receptor, there is a change in expression of an ion transporter which may impact the function of the \textit{GABA}_A receptor. Chloride currents in immature neurons are in part governed by an isoform of the Na\textsuperscript{+}-K\textsuperscript{+}-2Cl\textsuperscript{−} cotransporter (NKCC1), which is considered the driving force for neuronal depolarization after \textit{GABA}_A stimulation. Peak expression of NKCC1 occurs around postnatal days 5 to 7 in rats.\textsuperscript{229} In older animals, a different chloride transporter isoform—K\textsuperscript{+}-Cl\textsuperscript{−} cotransporter—is expressed and is considered to be one of the factors responsible for a change in the response of neurons from excitation to inhibition upon activation of \textit{GABA}_A receptors. Data from Edwards et al\textsuperscript{230} suggest that alterations in chloride currents, likely to be associated with changes in chloride transporters, may be critical in modulating cell death in neonatal rat neurons after sevoflurane exposure. Either bumetanide (a selective NKCC1 antagonist) or saline was administered to postnatal day 4 to 9 rats before 60 minutes of sevoflurane (2.1%) anesthesia. Seizures during induction of anesthesia were significantly reduced in animals that received bumetanide (9% vs. 62% in the placebo group; \(P = 0.01\)). The investigators state that, in older rats (postnatal days 10 to 17), seizures were more common during emergence from anesthesia, and prior administration of bumetanide was not effective at reducing seizure frequency in older animals (specific data not reported in the study). As observed in Figure 6, in young rats (postnatal day 4), sevoflurane caused a significant increase in activated caspase-3 in brain, a response significantly attenuated in rats that received bumetanide. Although these data do not reflect changes in cleaved caspase-3 in specific regions of brain, the results of Edwards et al suggests that ionic currents probably play a role in mediating anesthetic-induced changes in the apoptotic pathway. Further experimentation will be needed to determine whether these changes in ionic currents are responsible for an increase in cell death, as Edwards et al did not assess the extent of cell death in specific brain regions.

In addition to changes in \textit{GABA}_A receptor morphology and neuronal chloride transporters, anesthetics may alter neuronal gene expression and, in turn, cognitive and neurobehavioral function in at-risk patients. Although animal age was not specifically stated in their study, Kalenka et al\textsuperscript{231} administered isoflurane to rats and characterized hippocampal protein expression compared with unanesthetized animals. Eighteen proteins were differentially expressed after isoflurane exposure. We refer the reader to the study for the identity of these specific proteins (many of which are altered or differentially expressed in humans having other forms of cognitive dysfunction, most notably Alzheimer disease).

We refer readers with further interest in the topic of anesthetic-induced neurotoxicity to a review article by Stratmann et al.\textsuperscript{232} This brief but focused study addresses topics such as the relationship between cell death and subsequent development of cognitive dysfunction, specific effects of isoflurane on the hippocampus, and the effect of isoflurane on neurotransgenesis.

### TABLE 4. Effect of Sevoflurane on Cell Death, Activated Caspase-3 Staining, and the Nature of the \textit{GABA}_A Receptor \(\alpha\) Subunit in Rat Hippocampal Slices

<table>
<thead>
<tr>
<th>Postnatal Day Number</th>
<th>Cell death</th>
<th>Activated caspase-3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate</td>
<td>After 24 h</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Cell death assessed by Sytox staining. Adapted with permission from J Neurosurg Anesthesiol. 2010;22:220–229. + indicates significant increase in sevoflurane group versus air group; –, significant decrease in sevoflurane group versus air group; 0, no significant difference between sevoflurane and air groups; \textit{GABA}_A, type \(\alpha\)-\(\gamma\)-aminobutyric acid.
Novel Nonanesthetic Neuroprotectants

In addition to reducing serum cholesterol concentrations, thus decreasing stroke secondary to reduced vascular plaque accumulation or embolization, the statin drugs have multiple downstream and cholesterol-independent effects that can protect the brain from injury. Specifically, statins induce endothelial nitric oxide synthase and inhibit inducible nitric oxide synthase. Nitric oxide derived from endothelial nitric oxide synthase has a protective role as it mediates the paracrine function of the vascular endothelium, such as inhibition of leukocyte and platelet adhesion and vasodilation. Conversely, nitric oxide and other oxidative by-products derived from inducible nitric oxide synthase in astrocytes after ischemia are thought to contribute to the adverse oxidation of neuronal structural proteins. This may account for the observation that statins have a protective role in stroke; however, their effect on outcome after peripheral nerve injury is unknown. Pan et al randomized 144 rats to receive either atorvastatin (5 mg/kg orally) or placebo for 7 days before sciatic nerve insult induced by application of a vessel clamp to the nerve for 20 minutes during isoflurane anesthesia. Atorvastatin attenuated sciatic nerve injury based on functional assessment, electrophysiology, and histology. The extent of sciatic neuronal apoptosis (assessed by Fluoro-Jade B and terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labeling and cleaved caspase-3 staining) and inflammation (assessed by inflammatory cell counts, myeloperoxidase staining, and interleukin-1β staining) were also decreased in the group that received atorvastatin. As such, these results suggest that statins may be protective if given before peripheral nerve insult.

The nonselective β-adrenoreceptor antagonist, propranolol, provides neuronal protection from focal ischemic injury. Further, there exists limited data describing the outcome after cerebral ischemia associated with selective β1-adrenoreceptor antagonists. Iwata et al administered either propranolol, esmolol, and landiolol (esmolol and landiolol are selective antagonists for the β1-adrenoreceptor), or saline to isoflurane-anesthetized rats either 30 minutes before or 60 minutes after 8 minutes of cerebral ischemia induced by bilateral carotid occlusion with simultaneous systemic hypotension (MAP goal of 35 mm Hg). All study drugs were administered continuously through intravenous infusion for 5 days after reperfusion, at which point the animal underwent neurological testing followed by histologic analysis of the brain. In animals that received treatment before ischemia, there was no difference in functional outcome nor in the fraction of nonviable neurons (identified based on presence of cytoplasmic eosinophilia, loss of Nissl substance, and pyknotic nuclei). Despite no difference in functional performance among groups, animals that received a selective β1-antagonist (ie, esmolol or landiolol) after ischemia had significantly fewer dead hippocampal neurons versus the saline group. However, the number of dead neurons was not attenuated by propranolol. In addition, there were no differences in systemic blood pressure or heart rate among groups in any protocol. These data are consistent with the research of Umehara et al who reported that both esmolol and landiolol, when administered before and continued for 24 hours after spinal cord ischemia, resulted in a significant attenuation of functional and histologic injury. Further research will be required to validate these findings and identify operant mechanisms.

Nonpharmacologic Protection

Hypothermia has been explored as a neuroprotectant in a variety of clinical situations, some showing promise, some showing harm, and some showing an equivocal effect. One subgroup of patients who may benefit from the use of mild to moderate hypothermia is those neonates who have experienced a hypoxic-ischemia injury during birth. Of note, perinatal asphyxia is an important cause of neonatal morbidity and mortality accounting for about 20% of cases of cerebral palsy. Rutherford et al performed a post hoc analysis of patients included in the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial to determine whether hypothermia in this setting reduced the number of ischemia regions in the brain based on MRI. In the TOBY trial, neonates with perinatal asphyxia were randomized to receive either normothermic (goal temperature 37°C) or hypothermic (goal temperature 33 to 34°C for 72 h) management. The investigation showed no difference in death at 18 months, but there was a reduced rate of cerebral palsy in infants who received
hypothermia. One hundred thirty-one patients from the TOBY trial had suitable imaging studies available with a median age at the time of imaging of 8 days (range 2 to 30 d). Baseline demographics of this subset of patients did not differ between treatment groups, including Apgar score at 10 minutes or amplitude-integrated electroencephalographic findings. Cooled infants were more likely to be lesion-free in the basal ganglia and thalami [26 of 64 (40%) vs. 14 of 67 (21%) in non-cooled; P = 0.01], posterior limb of the internal capsule [which contains the corticospinal tract; 34 of 64 (53%) vs. 23 of 67 (34%) in non-cooled; P = 0.03], and generalized white matter [23 of 64 (36%) vs. 11 of 67 (16%) in non-cooled; P = 0.01]. As such, these data further support an attenuation of brain injury by the use of moderate hypothermia in neonates after perinatal asphyxia.

Preconditioning refers to a strategy where some intervention (ie, ischemia, administration of a drug) is administered before a test insult. This intervention may induce a change in physiology or gene expression and regulation such that the tissue sustains a lesser injury as a result of the test insult. Initially, this was shown in myocardium where a subinjurious period of ischemia was induced before a more severe ischemic insult, resulting in an attenuation of injury from the second insult.\(^{251,252}\) Later, ischemic preconditioning was found to protect against injury to neural tissues.\(^{253–255}\) Recently, exposure of a tissue remote to the site of expected ischemic insult has been reported to cause attenuation of injury—a concept which has been referred to as remote ischemic preconditioning (RIPC).\(^{256}\) Hu et al\(^{257}\) performed a small-scale, prospective, randomized, controlled trial in humans to cervical spinal cord insults to determine whether RIPC can impact changes in biochemical markers of neuronal injury. This approach was used to determine whether a larger-scale investigation, with neurological function as a primary endpoint, would be feasible. Forty patients with radiologic evidence of cervical spinal cord compression undergoing surgical decompression and fusion were included in the investigation. Those randomized to receive RIPC (n = 20) had three 5-minutes cycles of right arm ischemia induced by blood pressure cuff inflation to 200 mm Hg, with 5 minutes reperfusion between cycles; those randomized to the control group had a blood pressure cuff placed on their arm with no inflation. RIPC was conducted after induction of anesthesia but before commencement of surgery. The patients, surgeons, and anesthesia providers were unaware of group assignment. All patients underwent a standardized anesthetic consisting of maintenance with propofol and remifentanil; no volatile anesthetic or nitrous oxide was used. Blood samples for determination of S-100B and neuron-specific enolase, 2 serum biomarkers of neuronal injury, \(^{223,258}\) were obtained before induction of anesthesia, intraoperatively both before and after surgical decompression of the spinal cord, and then at 6 hours, 1, 3, 5, and 7 days after surgery. In addition, gross neurological function was assessed by the Japanese Orthopedic Association (JOA) criteria,\(^{259}\) which assesses 6 individual parameters, with a maximum score of 17 indicating best outcome. To account for preoperative deficits, the investigators calculated a recovery ratio as postoperative JOA score – preoperative JOA score/ (17 – preoperative JOA score), where higher values indicated better functional recovery. Recovery ratio and serum biomarker data are reported in Figure 7. Patients who underwent RIPC had improved recovery ratios at 7 days, 1 month, and 3 months, but not at 6 months after surgery. In

![FIGURE 7. Outcome after remote ischemic preconditioning in patients with cervical myelopathy. A, Recovery ratio, (B) serum S-100B concentration, and (C) Neuron-specific enolase concentration at various time points after surgery. See manuscript text for details pertaining to the calculation of the recovery ratio. All data represented as mean ± standard deviation. \(^{*} P<0.05\) compared with control value at the same time point. NSE indicates neuron-specific enolase; PO, postoperative; POD, postdecompression but before emergence from anesthesia; PreD, post anesthesia induction but before decompression; PreO, preoperative; RIPC, remote ischemic preconditioning. Adapted with permission from J Neurosurg Anesthesiol. 2010;22:46–52.](image-url)
addition, the investigators reported that, despite no difference in either serum biomarker before surgery, RIPC attenuated an increase in both S-100B and neuron-specific enolase after surgery. These data support the need for further testing of the potential benefit of RIPC. Further study of the mechanism accounting for RIPC is also needed. Preliminary data suggest that upregulation of non-neuronal antioxidant production\(^\text{260}\) and p38 mitogen-activated protein kinase-induced upregulation of heat-shock protein \(^\text{70}\)\(^\text{261}\) may play a role.

**REFERENCES**


245. Yenari MA, Temmen TM. Therapeutic hypothermia for brain ischemia: where have we come and where do we go? Stroke. 2010;41:572–574.


Introduction

Aneurysmal subarachnoid haemorrhage (SAH) accounts for approximately 85% of all episodes of non-traumatic subarachnoid haemorrhage. Bleeds from arteriovenous malformations in the brain and the spine account for a further 5%. The remainder are due mainly to intracerebral haemorrhages. Acute SAH is associated with a high mortality. Even for those who survive the acute event, the associated morbidity is significant. Involvement in the management of a patient who has suffered an aneurysmal SAH will depend on each anaesthesiologist's individual practice profile. For many anaesthesiologists, this may be restricted to the immediate preoperative, intra-operative and postoperative care of the patient. For anaesthesiologists involved in critical care medicine, the care period may extend right from the initial resuscitation and investigation on admission to the management of vasospasm postoperatively.

Regardless of the degree of involvement, a clear understanding of the underlying pathophysiology of the disease process is essential in order to manage SAH patients appropriately and effectively. This review will be restricted to the discussion of aneurysmal SAH.

Epidemiology

The estimated incidence of intracranial aneurysm (ICA) in North America is 2 000 per 100 000, or 1 in 50 of the population. The annual incidence of rupture of ICA leading to SAH is, however, only 10.5 to 12 per 100 000. This translates to an overall estimate of 30 000 Americans being affected by SAH disease each year. Figures from the UK are marginally lower at 8 - 10 per 100 000. The mean age of patients suffering an acute SAH is 55 years, with most patients presenting in the fifth and sixth decades. A female preponderance of between 1.6:1 to 2:1 exists. Twice as many black people develop SAH as white people.

Pathophysiology

The aetiology of intracranial aneurysms is multifactorial. Genetic factors are implicated in intracranial aneurysms, with a seven-fold increase in risk noted in first degree relatives of patients. Smoking is associated with a staggering eleven-fold increased risk, while...
hypothesis only carries a three-fold increased risk. Along with alcohol abuse, all of these factors contribute to weakening arterial tunica media. Chronic subjection to intravenous she stress results in pouting of the weakened wall, particularly in the vicinity of bifurcations where turbulent flow is prominent. La Place’s law applies to aneurysmal wall tension and predisposes to continued growth in size of the aneurysm. The annual risk of rupture increases with the size of the aneurysm, rising from 0.05% in aneurysms less than 10 mm, to 6% for those greater than 25 mm.

The majority of cases arise from the anterior carotid circulation (anterior and posterior communicating and middle cerebral arteries), with only 10 - 20% arising from the posterior vertebrobasilar circulation.

Following rupture of the aneurysm wall, blood continues to be pumped into the subarachnoid space until the pressure gradient has equalised, with pressure within the subarachnoid space now equalling systemic arterial pressure. This phase is short-lived, lasting several minutes only. The sudden rise in pressure accounts for the excruciating headache that accompanies SAH. Other important sequelae include cerebral oedema and hydrocephalus, the latter resulting from decreased absorption of cerebrospinal fluid (CSF) due to blood clots on the subarachnoid granulations, and/or blood clot obstruction to CSF drainage from the ventricles. The presence of blood in the subarachnoid space is associated with meningeal irritation and meningism. The blood and breakdown products of haemoglobin in the subarachnoid space are thought to provide the stimulus for vasospasm. The degree of vasospasm accompanies SAH. Other important sequelae include cerebral oedema and hydrocephalus, the latter resulting from decreased absorption of cerebrospinal fluid (CSF) due to blood clots on the subarachnoid granulations, and/or blood clot obstruction to CSF drainage from the ventricles. The presence of blood in the subarachnoid space is associated with meningeal irritation and meningism. The blood and breakdown products of haemoglobin in the subarachnoid space are thought to provide the stimulus for vasospasm. The degree of vasospasm accompanies SAH.

The three main predictors of mortality and dependence after SAH are:
1. An impaired level of consciousness on admission (see Table I and II);
2. Advanced age;
3. A large volume of blood on the initial cranial CT scan (see Table III).

### Table I: Hunt and Hess grading scale for subarachnoid haemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic or minimal headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>III</td>
<td>Drowsiness, confusion, or mild focal deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Stupor, moderate to severe hemiparesis, and possibly early decerebrate rigidity and vegetative disturbances</td>
</tr>
<tr>
<td>V</td>
<td>Deep coma, decerebrate rigidity, and moribund appearance</td>
</tr>
</tbody>
</table>

### Table II: World Federation of Neurological Surgeons (WFNS) grading scale for aneurysmal subarachnoid haemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glasgow Coma Scale score</th>
<th>Motor deficit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>Absent</td>
</tr>
<tr>
<td>II</td>
<td>13 or 14</td>
<td>Absent</td>
</tr>
<tr>
<td>III</td>
<td>13 or 14</td>
<td>Present</td>
</tr>
<tr>
<td>IV</td>
<td>7 – 12</td>
<td>Present or absent</td>
</tr>
<tr>
<td>V</td>
<td>3 – 6</td>
<td>Present or absent</td>
</tr>
</tbody>
</table>

*Excludes cranial neuropathies, but includes dysphasia

### Table III: Fisher Grading Scale of Cranial Computerised Tomography

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings on Cranial computerised tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No subarachnoid blood detected</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse or vertical layers &lt; 1 mm</td>
</tr>
<tr>
<td>3</td>
<td>Localized clot and/or vertical layer &gt; 1 mm</td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral or intraventricular clot with diffuse or no SAH</td>
</tr>
</tbody>
</table>
Grading scales such as these above are utilised to standardise clinical assessment and estimate prognosis. The higher clinical scales are associated with a higher incidence of complications, such as cerebral vasospasm, elevated ICP, impaired cerebral auto-regulation, impaired vascular CO₂ reactivity, cardiac arrhythmias and dysfunction, hypovolaemia, and hyponatraemia.¹

Medical complications of subarachnoid haemorrhage

The complications of subarachnoid haemorrhage are not confined to the central nervous system (CNS). Medical complications other than those of the CNS contribute significantly to morbidity and overall mortality. In a large multicentre study involving 41 neurological centres in the United States and Canada, with a total of 457 patients with SAH enrolled, major non-neurological medical complications accounted for 23% of deaths.² Compare this to 19% attributed to the direct effects of the initial hemorrhage, 22% due to rebleeding and 23% due to vasospasm. 40% of patients were found to have experienced at least one life-threatening medical complication. Major cardiovascular complications accounted for most of the medical complications, with a 23% incidence of pulmonary oedema (PE). Interestingly, the association of PE was significant in relation to the timing of the surgery (p < 0.05), but not the use of triple-H therapy (p = 0.1).¹²

In addition to PE, the other common cardiovascular complications associated with SAH were marked systemic and pulmonary hypertension and myocardial dysfunction, including cardiac arrhythmias and myocardial damage. ECG abnormalities have been reported at anywhere between 25 - 100% of SAH patients. Elevation of cardiac enzymes was not uncommon, with 17 - 28% demonstrating elevated cardiac troponin and 37% showing elevation in creatine kinase MB isoenzyme.³ The syndrome of neurogenic stunned myocardium is the most severe form of cardiac injury associated with SAH, and is characterised by reversible left ventricular systolic dysfunction, cardiogenic shock and PE.³

The underlying mechanism for the apparent myocardial dysfunction is thought to be a massive myocardial release of catecholamines from sympathetic nerve terminals, causing calcium overload and myocyte necrosis. SAH is associated with elevated sympathetic tone and increased plasma concentrations of catecholamines. Interestingly, the degree of myocardial dysfunction correlates more with the neurological deficit than the severity of ECG abnormalities.⁵

This association between neurological deficit and myocardial dysfunction is demonstrated in Table IV. The data is derived from a study investigating ECG and echocardiographic changes in patients with intracranial aneurysms.²

The dilemma for the anaesthetist or intensivist is how to interpret these signs of myocardial injury associated with SAH and how to manage them, as they do not necessarily correlate with similar findings in a primary myocardial injury unassociated with SAH. It would, however, seem prudent in the presence of signs of cardiac dysfunction or myocardial injury to very carefully consider the possible risks before embarking on triple-H therapy, bearing in mind the therapeutic goals of increased blood pressure and cardiac filling.⁶

Cerebral vasospasm

In 60 – 70% of patients, SAH is complicated by cerebral vasospasm. Although the cause of this phenomenon is still unknown, a longstanding theory holds that the balance between endothelin and nitric oxide is disturbed by free oxyhaemoglobin in the CSF, leading to prolonged vasoconstriction.³

Vasospasm is a major contributor to morbidity and mortality in SAH. The effects of the resultant cerebral ischaemia may vary from subtle neurological signs to frank cerebral infarction and, in up to one third of patients, death. It usually develops within the first week, with peak incidence at 7 - 10 days post-SAH. Resolution occurs within three weeks.

Noninvasive sequential transcranial Doppler detection of blood velocity changes is used to detect vasospasm in asymptomatic patients. Normal cerebral blood flow velocity is 80 – 100 cm/s, and any measurement that is greater than 50 cm/s above baseline is predictive of vasospasm.¹ However a high level of sensitivity and specificity for the detection of vasospasm can only be achieved in experienced hands, and then only of the middle cerebral artery. It is significantly less successful for detecting vasospasm in the anterior cerebral artery and posterior circulation.² Although cerebral angiography for vasospasm will be positive in up to 70% of cases, only 20 - 30% of these will be symptomatic.⁵

Treatment modalities for cerebral vasospasm

Nimodipine

Therapy with nimodipine has been shown to improve the outcome of SAH if it is initiated on admission and continues for 21 days.¹³ Although nimodipine can be administered both orally or intravenously, the preferred route of administration is per os or nasogastric tube. The recommended oral/nasogastric dosage is 60 mg every 4 hours, with a maximum daily dose of 360 mg. Nimodipine should be administered for the full 21 days.

The intravenous administration of nimodipine as a continuous infusion is associated with a high incidence of hypotension, and is no more effective than when given orally. The recommended intravenous dose is 1 mg per hour during the first 6 hours. In the

---

Table IV: Number of SAH patients without heart disease with abnormalities of the ECG and echocardiogram (ECHO)²

<table>
<thead>
<tr>
<th>Neurological grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG normal ECHO normal</td>
<td>7</td>
<td>13</td>
<td>3</td>
<td></td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>ECG acute change ECHO normal</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>ECG acute change ECHO motion abnormality</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>21</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>41</td>
</tr>
</tbody>
</table>
absence of hypotension, the dosage may be gradually increased as follows:

- Increased to 1.5 mg per hour for the next 6 hours;
- Increased to the maximum dose of 2 mg per hour thereafter.

The following additional recommendations apply to intravenous infusion of nimodipine:

- Nimodipine should be administered via a central line to avoid thrombophlebitis.
- The administration system must be protected from light.
- An adequate systolic blood pressure of 130 – 150 mm Hg takes priority over nimodipine administration, and it should be discontinued if a stable blood pressure cannot be maintained.

This hypotensive effect is more pronounced in the presence of hypovolaemia and with the induction of anaesthesia. The beneficial effects of nimodipine may be based more on a general brain protective mechanism, as there is no evidence to suggest that it relieves angiographically documented vasospasm.5

**Triple-H therapy**

Triple-H therapy is a combination of induced hypertension, hypervolaemia, and haemodilution. The indications for initiating triple-H therapy in SAH patients include a noted increase in transcranial Doppler velocities and/or the development of new neurological deficits. Increases in transcranial Doppler velocities are seen as an indication of cerebral vasospasm. The underlying theory is that, during vasospasm, cerebrovascular resistance is determined by blood vessels that lack effective autoregulation. Hence cerebral blood flow (CBF) now becomes pressure-dependent. The aim of therapy is therefore to reverse cerebral ischaemia by increasing perfusion pressure, while at the same time decreasing the blood viscosity. Thereby, CBF is effectively increased to the affected areas.

Blood pressure elevation is achieved via fluid administration and cardiovascular drugs. Commonly used drugs include dopamine, noradrenaline and metaraminol.5,14 In a study utilising xenon-enhanced CT to measure CBF before and after dopamine administration, improved CBF flow to ischaemic areas and reduced flow to hyperaemic areas in response to dopamine administration was demonstrated.15 Generally, aggressive fluid loading with hetastarch solutions or albumin should precede the administration of dopamine or norepinephrine.

The targets for triple-H therapy are as follows:5

- Systolic blood pressure elevation to approximately 120 – 150 mm Hg in unclipped, and 160 – 200 mm Hg in clipped, aneurysms.
- Central venous pressure of 8 – 12 mm Hg, or pulmonary artery wedge pressure of 15 – 18 mm Hg.
- Haematocrit of 30 – 35%.

Before proceeding to triple-H therapy, we need to be aware of its probable limitations and associated risks. To start with, most neurosurgeons do not recommend triple-H therapy in unclipped aneurysms. Furthermore, although it will reverse neurological symptoms in up to 70% of patients with vasospasm, triple-H therapy has not proved effective in reducing the incidence of delayed ischaemic neurological deficits or death after SAH, and it may actually increase patient mortality.5 The serious complications that are associated with this form of therapy include PE, myocardial ischaemia, respiratory failure and electrolyte disturbances such as hyponatraemia. The latter may develop in SAH in the absence of triple-H therapy, and is likely to be the result of cerebral salt-wasting syndrome (CSWS) or the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). Triple-H therapy in the presence of cardiac dysfunction is not advised. Nevertheless, should the decision be made to undertake triple-H therapy in this setting, consideration should only be given after confirming the transcranial Doppler-detected vasospasm with catheter angiography. Full invasive haemodynamic monitoring, including pulmonary artery catheterisation or transoesophageal echocardiography or both, is considered mandatory under these circumstances.

**Balloon angioplasty**

A more recent development in the management of vasospasm is the use of balloon angioplasty, often combined with the intra-arterial administration of papaverine. Before embarking on balloon angioplasty in patients with persistent new neurological deficits that are unresponsive to medical therapy, the following investigations must be performed:

- Urgent catheter angiography to confirm segmental stenosis which reflects vasospasm of the distal carotid artery, the proximal M1 and A1 segments, or the vertebral and basilar artery;
- Cranial CT must be performed to rule out infarction in the area supplied by the spastic vessels.

Transluminal balloon angioplasty of the vasoconstricted vessels may then be performed, with or without the concomitant intra-arterial administration of papaverine.5

**Intra-arterial papaverine**

Intra-arterial papaverine, up to 300 mg per hemisphere, has been utilised for more distal segment vasospasm.16 However, when balloon angioplasty is feasible, it is considered the more effective treatment option. Papaverine is neurotoxic and may result in blindness, seizures, coma and irreversible brain damage.17

**Hydrocephalus**

Hydrocephalus should be excluded by CT scan, in the presence of deteriorating neurological signs, before a diagnosis of vasospasm is made. Both communicating hydrocephalus, the result of reduced CSF absorption, and non-communicating hydrocephalus, the result of CSF drainage obstruction, are encountered in SAH (see Pathophysiology...
above), and may require external ventricular drainage. Continuous ICP monitoring should be considered in poor grade patients with hydrocephalus.

Hypertension

The dangers of causing possible cerebral ischaemia need to be carefully considered when treating hypertension in SAH. Systolic pressures in excess of 180 mm Hg despite nimodipine therapy may, however, be considered suitable for antihypertensive treatment with labetalol or ACE inhibitors.

Seizures

These may occur at the time of rupture, as a result of hypoxia. SAH patients will remain seizure-prone for 18 months thereafter.

Electrolyte disturbances

Hyponatraemia, hypokalaemia, hypocalcaemia and hypomagnesaemia are common in SAH, and should be monitored and treated appropriately.

The differentiation between the two most common causes of hyponatraemia in this setting can be made on fluid balance:
- **Cerebral salt wasting syndrome**, due to the secretion of brain and atrial natriuretic hormone, is accompanied by a negative sodium balance and an intravascular volume depletion;
- **SIADH** is accompanied by the accumulation of an excess of free water with a high central venous pressure (CVP).

Timing of surgery

There are advantages and disadvantages to early and late surgery. Early surgery reduces the risk of a further bleed, but has the disadvantage of being associated with poor operating conditions. Late surgery has the advantage of providing excellent operating conditions but, as was shown in the co-operative study on the timing of aneurysm surgery, 30% of the patients randomised to undergo late surgery did not survive until the planned surgical intervention. The period from 7 to 10 days post SAH, which represents the peak period for vasospasm, has been associated with the poorest outcome for surgery.

Anaesthesia for the clipping of intracranial aneurysms

Aims of anaesthesia

There are certain broad principles or goals that apply to the anaesthetic management of intracranial aneurysm surgery. The actual techniques employed are of lesser importance.

The primary goals should be:

- The control of the transmural pressure gradient (TMPG) across the aneurysm wall, as this is paramount to the prevention of inadvertent aneurysm rupture;
- The optimisation of cerebral oxygenation and perfusion;
- The optimisation of ICP, and the avoidance of large and sudden fluctuations in ICP;
- The provision of cerebral protection during ischaemic periods;
- The provision of optimal operating conditions, and surgical exposure with the least brain retraction.

Other issues that need to be taken into consideration, and that may contribute to the achievement or form part of the above, include:

- The optimisation of ventilation to achieve:
  - Low mean airway pressure, to avoid increasing ICP;
  - Normocapnia, at around 4.5kPa:
    - The avoidance of hypocapnia to prevent cerebral vasoconstriction and resultant ischaemia;
    - The avoidance of hypercapnia to prevent cerebral vasodilatation and resultant increased ICP.
- The prevention or treatment of cerebral oedema. This can be achieved with careful fluid administration, including the avoidance of excessive crystalloid infusion.
- Adequate preparation to manage potential intra-operative problems, such as aneurysm rupture.
- Provision of adequate analgesia to obtund painful stimuli, such as intubation of the trachea and head pin placement.
- Provision for rapid emergence, to facilitate early postoperative neurological assessment.

Preoperative assessment

These patients will require a very thorough preoperative assessment. In addition to the standard considerations, careful attention must be paid to the cardiovascular status of the patient, as this is most likely to be affected. (see Pathophysiology above.)

Fluid Management

Careful consideration of the patient’s hydration status is essential. The vomiting associated with SAH, reduced fluid intake and the diuretic effect of contrast injections, coupled with the vasodilatory effects of nimodipine, can produce significant relative hypovolaemia. In poor grade patients, CVP monitoring of fluid status is essential. In addition to fluid volume derangements, electrolyte disturbances (see above) are common and need to be monitored and corrected preoperatively.

Premedication

Poor grade patients should not receive any premedication. Good grade patients, in addition to reassurance, may require mild benzodiazepine premedication. Sedation is not encouraged, as it may mask underlying neurological deterioration preoperatively.
Induction of anaesthesia

The main aim of the induction is to provide a very smooth transition from the awake state to the anaesthetised state, without incurring significant haemodynamic changes. No specific technique has been shown to have an outright advantage. Popular combinations are thiopentone/propofol with fentanyl/alfentanil, or propofol with remifentanil. The latter combination is preferred as part of a total intravenous anaesthesia (TIVA) technique.

Monitoring

In addition to the standard monitoring (including ECG, pulse oxymetry, NIBP and capnography), the placement of an intra-arterial line pre-induction is recommended. The main reason for placing the line awake is to be able to rapidly address any haemodynamic changes during induction.

The need for CVP monitoring will be very much dependant on the patient’s general status. Although CVP, and even pulmonary artery monitoring, was considered essential in SAH, this practice has largely been discontinued as the added risk of placing a central line probably outweighs any benefit for the majority of patients. However, in poor grade patients or patients with significant cardiovascular dysfunction, CVP monitoring is considered essential.

Bispectral index (BIS) monitoring will be required if brain protection with doses of thiopentone or propofol, sufficient to produce significant burst suppression, are being considered.

Neuromuscular relaxation should be monitored continuously to avoid the disaster of a patient moving or coughing during the procedure. This can have catastrophic results in terms of a rupture of the aneurysm, or a sudden increase in ICP.

Choice of technique for the maintenance of anaesthesia

There is currently no evidence to suggest that a propofol TIVA-based anaesthetic has any advantage over an isoflurance/sevoflurane inhalational-based anaesthetic, in terms of patient outcome. Nitrous oxide was used as part of maintenance of anaesthesia for intracranial aneurysm surgery in the IHAST study, and is used in centres such as Helsinki University Central Hospital. An inhalational technique is usually supplemented with fentanyl or remifentanil. My personal opiate of choice is sufentanil. Although this has only been associated with increased CBF when compared to fentanyl, this only applies when dosages much higher than those normally required in intracranial neurosurgery have been administered. In a study looking at continuously measured middle cerebral blood flow, there was no difference between recorded blood flows when comparing fentanyl 25 µg/kg with sufentanil 3 µg/kg. Increased flow was only demonstrated in the group receiving sufentanil 6 µg/kg.

If higher doses of fentanyl or sufentanil are to be avoided, it becomes essential to supplement painful events, such as the head pin placement, with 1 mg of alfentanil. In patients receiving remifentanil, a small bolus of the drug can be given immediately before the pins are placed. In my experience, other techniques, such as local infiltration or deepening the level of anaesthesia, are not adequate to blunt the hypertensive response that accompanies head pin placement.

More importantly, the goals of maintenance of a compliant brain and maintenance of cerebral perfusion Pressure (CPP) will dictate the technique.

Cerebral protection

The use of mild hypothermia for cerebral protection was, until recently, a very popular technique in intracranial aneurysm surgery. That was until the IHAST study, conducted in 30 centres and 1 001 patients, demonstrated that neurocognitive improvement was not effected by the use of intra-operative hypothermia in good grade patients with SAH.

Despite the lack of any substantial evidence of its benefit, the administration of either propofol or thiopentone to achieve near burst suppression remains popular during temporary clipping.

Temporary Clipping

Over two decades ago, temporary clipping of feeder vessels replaced the use of global hypotension as a means of reducing the pressure gradient across the aneurysm wall during surgical dissection. Good communication between the surgeon and the anaesthetist during this period is of paramount importance.

Anaesthetic recommendation during clipping include:

- Blood pressure maintained at high normal levels, to provide for adequate collateral circulation during periods of clamping;
- Brain protection in some form (e.g. propofol, barbiturates), administered prior to clipping;
- FiO₂ increased, possibly to 100%, as the administration of 100% O₂, coupled with brain protection, may have a beneficial effect during temporary clipping;
- The clamp time should be carefully monitored by stopwatch and the surgeon kept abreast of the elapsed time. Guidelines for clamp times vary but a maximum of 15 - 20 minutes is generally recommended.

Intra-operative aneurysmal rupture

Intra-operative rupture of an ICA represents one of the major complications that should be anticipated in all cases. Rupture carries a high morbidity and mortality. It can occur at any time during the procedure, and is usually associated with an abrupt increase in the aneurysm’s TMPG. This could be secondary to a sudden increase in BP, a sudden decrease in ICP or due to surgical manipulation or dissection. Rupture during induction, while the skull is closed, carries a worse prognosis than a rupture occurring after the dura
has been opened. Intra-operative rupture occurs ten times more frequently in previously ruptured aneurysms than in unruptured aneurysms. Bleeding can, in 8% of ruptures, be so severe as to result in haemorrhagic shock.20

The actual anaesthetic management of a rupture varies from centre to centre. The maintenance of normovolaemia should be the primary haemodynamic goal. Surgical management will largely be dictated by the size of the rupture, the stage of the dissection and the ability of the surgeon to occlude the blood vessels proximally and distally by the size of the rupture. In Helsinki, a very aggressive approach has been adopted.18 Cardiac arrest is induced by a rapid IV bolus administration of 12 mg of adenosine into a large vein. During the short period of arrest (= 10 seconds), the operative field is suctioned and temporary clips (so-called “pilot” clips) are placed. Normal rhythm is reportedly returned without any need for medical intervention. It has, however, been recommended that controlled studies are needed to validate the appropriateness of this intervention before making it a recommendation.

Controversy still surrounds blood pressure management during rupture. Wherever possible, temporary vessel occlusion is the preferred technique to gain control of bleeding. When this is not readily possible, mean arterial pressure (MAP) should be transiently decreased to 40 – 50 mm Hg, in order to facilitate surgical occlusion of the rupture. The real danger in the face of continuing major blood loss, if surgical control cannot be rapidly established, is that the combination of hypotension and hypovolaemia can result in profound cerebral ischaemia.5

Emergence

Although fast-tracking techniques aimed at rapid emergence are beneficial in terms of early postoperative neurological assessment, this practice must be balanced against adequate analgesia, if postoperative hypertension and undue agitation are to be avoided.

Analgesic strategies usually include intravenous paracetamol and codeine (see below). Long-acting opioids, such as morphine, should be used with great care in view of their respiratory depressant effect, which can result in hypercapnia and resultant cerebral vasodilation, sedation interfering with neurological assessments and an increased risk of postoperative nausea and vomiting (PONV).

Consideration should be given to the administration of anti-emetic prophylaxis for high-risk groups. Ondansetron is presently favoured.

Postoperative care

Postoperative controlled ventilation should not be considered in good grade patients who were subjected to only brief periods of temporary clipping, as this practice has been shown to adversely affect patient outcome following aneurysm surgery.18 Patients should generally be extubated as soon as they are adequately awake. In patients requiring postoperative controlled ventilation due to complications, or those more severely affected by SAH, propofol sedation should be administered. In addition, continuous ICP monitoring should be initiated. Several centres recommend the addition of jugular bulb saturation monitoring, which is now an established, routine monitoring technique in sedated ventilated postsurgical patients in neuro-intensive care.5

Postoperative monitoring should include frequent neurological assessments.1

Patients should be provided with adequate postoperative analgesia. Paracetamol 1 gm should be given by intravenous infusion, starting intra-operatively and continuing 6 to 8 hourly, to provide analgesia and to prevent and treat hyperthermia. Oxycodone 2 to 3 mg given intravenously can be used to supplement analgesia.18

Prophylactic antiepileptic medication should be considered for cases involving temporal or frontal haematomas.

In some centres, such as Helsinki, anxiolysis with benzodiazepines or haloperidol is used.18

Delayed cerebral ischaemia due to arterial vasospasm is one of the major complications of the postoperative period, occurring up to 14 days after the bleed. Special attention must be paid to its prevention and treatment. The maintenance of systolic blood pressure and normo- to hypervolaemia are important preventative measures. In patients at high risk, systolic blood pressure should be maintained above 140 - 160 mm Hg.18 Nimodipine administration may be accompanied by temporary hypotension. The simultaneous administration of etilefrine (Effortil®) 10 to 20 mg orally with nimodipine tablets is one possible solution. The most common vasoactive drugs employed to maintain blood pressure are phenylephrine, dopamine and noradrenaline.

Serum electrolyte balance should be monitored, as hyponatraemia commonly occurs.

Anesthesia for interventional radiological treatment of intracranial aneurysms

Interventional neuroradiology (INR) has seen major developments in the past decade. Presently there is evidence that coiling has a benefit over clipping. The ISAT trial published in the Lancet in 2002, investigating both options, demonstrated a marginally improved outcome in WFNS grade I or II SAH patients for coiling of small aneurysms in the anterior circulation.22 Coiling has also established itself as the preferred modality for the treatment of posterior circulation aneurysms.22 With the considerable developments that have taken place over the last few years in the field of endovascular technology, the application of interventional radiological treatment has expanded even further.

Radiation safety

For the anaesthesiologist who only occasionally visits the angiography suite, the usual lead apron will probably suffice. However, for those
who are regularly required to provide anaesthesia or sedation in these radiation hazard environments, additional radiation protection by means of a thyroid shield is recommended.22

Radiological vascular access

The interventional radiologist usually selects the transfemoral arterial approach, placing a large 6,0 French gauge sheath. However, in special circumstances, direct carotid or brachial puncture may be done.22

Materials used for embolisation or infusion

Coils are the most commonly employed technique for aneurysm obliteration. Detachable coils are introduced through a microcatheter, using a pusher wire. Once satisfactorily positioned, they are detached either by electrical or mechanical means. Recent advances have included specialised coatings to encourage thrombus formation and epithelial growth. The success rate of occlusion with coils is dependent on the width of the neck of the aneurysm, with a much greater success rate (up to 85%) being achieved in aneurysms with a neck of less than 4mm.22 Other invasive radiological substances are used in aneurysms, although their usage is more commonly associated with the treatment of arteriovenous malformations and tumour embolisations. These substances include:

- Cyanoacrylates (Histoacryl®, B. Braun) are rapidly polymerising adhesives. The polymerisation process is exothermic, resulting in heat liberation into the surrounding tissues during embolisation, and requires immediate catheter withdrawal after cyanoacrylate injection, because of its adhesive nature.
- Onyx® (Microtherapeutics Inc) is a biocompatible liquid embolic agent consisting of polyvinyl alcohol particles (Contour®, Boston Scientific). Unlike the cyanoacrylates, Onyx® is nonadhesive and the catheter is left in place as the controlled injection and filling of the vascular abnormality takes place over several minutes.

Anaesthetic considerations

Invasive neurological suites are often situated some distance from the operating theatres. This must be taken into consideration when preparing to provide anaesthesia in a remote setting.

In addition to the limited space, the need for the table to be moved frequently requires care in terms of endotracheal tube and intravenous line fixation. The positioning of the anaesthetic machine itself is important to avoid inadvertent disconnections. The imaging equipment must also be mobile around the patient’s head. Further anaesthetic considerations for patients undergoing INR procedures include maintaining patient immobility, and providing haemodynamic manipulation of systemic and regional blood flow and heart rate. As with the clipping of aneurysms, it is important to be prepared for complications that may occur during the procedure. Inadvertent cooling is a problem encountered in the angio suite.

General anaesthesia

Propofol, sevoflurane and desflurane are all used to provide anaesthesia in this environment. Desflurane may have the disadvantage of increasing CBF. Because of the haemodynamic disturbances associated with intubation and extubation, some anaesthesiologists prefer the use of laryngeal mask airways (LMA) with muscle relaxants in appropriately selected patients.22

Sedation

Sedation is occasionally utilised because of the advantage of being able to perform neurological evaluations during the procedure. However, sudden movement of the patients and accidental hypoxaemia tend to make the use of sedation less attractive.

Anticoagulation

To avoid the complications of thrombo-embolic phenomena, these patients should all be anticoagulated with heparin to achieve a 2- to 3-fold increase in Activated Clotting Time (ACT). This is usually achieved by injecting 70 units of heparin per kg. ACT should be monitored hourly and heparin titrated accordingly.

Complications of INR procedures

These may be both rapid and catastrophic, and can be classified into CNS and non-CNS complications.

CNS complications can be divided into either haemorrhagic (aneurysm rupture or vessel dissection) or occlusive (coil displacement into a parent vessel, thrombo-embolic phenomenon and vasospasm) complications.

Non-CNS complications include contrast medium reactions (fatal contrast reactions occur in 1 in 10 000 exposures) and contrast nephropathy, and haematomas at the puncture site, usually in the groin or retroperitoneally.22

Postoperative care of INR patients

A smooth and rapid recovery from anaesthesia, to facilitate neurological examination, is important. Blood pressure maintenance should be approached similarly to that of patients undergoing clipping of aneurysms with vasospasm, requiring elevated systolic pressures. Treatment with nimodipine, likewise, should continue for 21 days. Patients with a large exposure of coils to the parent vessel may require long term aspirin, 75 mg daily for 3 months post procedure. In these cases, heparinisation may have to be maintained in the immediate post-operative period.

The osmotic diuretic effects of contrast medium should not be overlooked, and adequate hydration must be maintained.PONV
is also a problem that should be actively managed, and may be precipitated by both contrast and anaesthetic agents.

Careful neurological evaluations must be performed continuously to identify neurological deterioration as early as possible.

**Cost effectiveness of clipping versus coiling of intracranial aneurysms**

A study was recently undertaken to compare the clinical outcomes, resource consumption, and cost-effectiveness of endovascular treatment vs. surgical clipping in a developing country.

The study was conducted prospectively from January 2004 to June 2007. Of the patients with ruptured intracranial aneurysms, 24 were treated with interventional coils and the remainder by clipping. A modified Rankin scale was utilised to measure clinical outcome at 6 months, while the total cost of treatment related to all aspects of the inpatient stay were evaluated in both groups.

The average age of the patients in the endovascular group was 38 years, whereas, in the surgical group, it was 45 years. The majority of patients (43) were classified as grades 1 and 2. 18 received coils, and 25 were clipped. Clinical outcomes were similar in both groups. The average total cost for patients undergoing coiling was $5,080, and the total cost with surgical clipping was $3,127.

The higher cost of consumables needed for coiling was not sufficiently offset by shorter hospital stays, and proved the more expensive treatment option without any additional benefit in terms of outcome. However, the lack of outcome benefit, as assessed in such a small number of patients, should be viewed with scepticism. One should rather look to larger clinical trials, such as the ISAT study, when considering outcome-related issues.

**Conclusion**

SAH remains a devastating disease, affecting many other organs in addition to the central nervous system. The main aim of therapy is to prevent rebleeding by either clipping or coiling the aneurysm. Vasospasm is a major contributor to postoperative morbidity and mortality in patients with SAH, and should be actively sought and aggressively managed. Anaesthesiologists have a very important role to play in the overall management of these patients.

**References:**

Acute Subarachnoid Hemorrhage:
Anesthetic Management of Endovascular Aneurysm Coiling

Kenneth J. Van Dyke, M.D. Madison, Wisconsin

OBJECTIVES
As a result of this activity, participants will be able to:

1. Describe the physiologic derangements that can accompany subarachnoid hemorrhage, and how to tailor a preoperative assessment with these in mind.

2. Describe the physiologic goals one must keep in mind when anesthetizing a patient for intracranial aneurysm coiling, as well as the monitoring and techniques utilized to reach those goals.

3. Manage problems that can arise during intracranial aneurysm coiling.

4. Describe the challenges encountered when emerging from general anesthesia after coiling of an intracranial aneurysm and discuss appropriate management of these challenges.

STEM CASE - KEY QUESTIONS
A fifty-seven year old woman presents to the emergency department complaining of “the worst headache of her life” that developed suddenly after watching the latest barrage of political advertisements. The patient is alert, neurologically intact, and her only current complaints are of a severe headache and nuchal rigidity. The patient’s co-morbidities include longstanding hypertension and a sixty pack-year smoking history. A non-contrast head CT is quickly performed and a diagnosis of subarachnoid hemorrhage is made. A subsequent CT-angiogram confirms that a ruptured aneurysm of the posterior communicating artery is the likely cause. The interventional neuroradiologist calls you to ask what further studies she should perform before bringing this patient to the interventional neuroradiology suite for coiling of the aneurysm.

What grade on the Hunt and Hess scale would you give this patient?

Why do you care about the Hunt and Hess grade?

What further studies should be performed?

What electrolyte disturbances would you expect to see?

Why is a chest X-ray helpful?

What ECG abnormalities would you expect to see and how might this affect your management?

After an appropriate pre-procedural assessment and workup, the patient is brought to the interventional neuroradiology suite for coiling of the aneurysm.
What are the pitfalls of premedication with sedatives in this patient population?

Would MAC or general anesthesia be most appropriate for this case?

What types of monitoring and vascular access would be most appropriate for this patient?

What are your hemodynamic and ICP goals for this patient?

What anesthetic agent would you choose for maintenance?

Induction of general anesthesia and intubation are uneventful. Initial angiography confirms the presence of a 7mm posterior communicating artery aneurysm that has anatomy appropriate for coiling. During coiling of the aneurysm the neuroradiologist notices significant vasospasm and decides to treat this with intra-arterial verapamil.

What are you watching out for after injection of the verapamil?

How will you treat this?

The vasospasm resolves and the procedure continues. The patient remains stable. As the neuroradiologist is placing “one last coil” she informs you that she may have punctured the aneurysm and requests reversal of the heparin that has been administered since before she started coiling. 10,000 units have been given over the last two hours.

How much protamine will you give?

What will you be watching out for?

Upon further review, the neuroradiologist decides that she didn’t actually puncture the aneurysm and that, in fact, the coils look to be perfect and the procedure is complete.

Will you plan to extubate now or wait until later?

What are your concerns with this patient at the time of emergence and extubation?

What are some techniques that could help produce a smooth emergence?

If anti-hypertensive agents are indicated, what would you choose?

**Problem Based Learning Discussion**

**Demographics**

Subarachnoid hemorrhage is a devastating occurrence that carries a very high rate of morbidity and mortality. Mortality rates are estimated at 32-67%.(5) 20-30% of survivors are left with
significant disabilities and less than 1/3 of the patients will regain their previous level of neurologic function. Of the patients that survive to reach a tertiary care center for treatment, 1/4 will die from complications within two weeks (2).

Presentation

The typical presentation for subarachnoid hemorrhage includes the sudden onset of a severe headache often described by patients as the “worst headache of my life” that often develops during or after strenuous activity or a stressful situation. Concurrent symptoms can include nausea and vomiting, decreased or loss of consciousness, photophobia, meningismus, focal cranial nerve or other neurologic deficits, low back pain, ocular hemorrhage, and even psychiatric disturbances. The presence and severity of these signs/symptoms varies with the severity of the initial bleed and is commonly described with the Hunt and Hess grading system:

Grade Description
0 Unruptured Aneurysm
1 Asymptomatic or mild HA and slight nuchal rigidity
2 Mod to severe HA with nuchal rigidity, no neurologic deficit other than CN palsy
3 Lethargy and confusion, or mild focal deficit
4 Stupor, moderate to severe hemiparesis, possible early decerebrate posturing
5 Deep coma, decerebrate rigidity, moribund appearance.

Determining a Hunt and Hess grade is useful not only for standardization of communication between care providers, but also as an indicator of the degree of neurologic injury and thus a predictor of the likelihood and expected severity of the physiologic derangements that typically accompany subarachnoid hemorrhage.

Physiologic Derangements

Common physiologic derangements that accompany subarachnoid hemorrhage include cardiac dysfunction with or without pulmonary edema, electrolyte disturbances, elevated intracranial pressure, seizures and cerebral vasospasm leading to cerebral ischemia or infarction.

Cardiac

Cardiac rhythm disturbances have been reported in up to 90% of patients after subarachnoid hemorrhage and elevated CK-MB levels are seen in almost all patients with ECG evidence of wall motion abnormalities (4). Elevated troponin levels can be seen in up to 17% of patients (4). ECG changes can range from QRS, ST or T wave abnormalities to ventricular fibrillation. Many of these changes can appear similar to ECG changes seen in the setting of myocardial infarction, but postmortem studies of many of these patients have shown no evidence of coronary artery disease (4). This can be an important consideration when faced with the decision of whether to delay treatment of the aneurysm for further cardiac workup. In addition to ECG changes, echocardiography of these patients can reveal hypokinesis and a reduced ejection fraction. This
reduced ejection fraction, especially in the presence of disproportionately low serum troponin levels, is commonly referred to as neurogenic stunned myocardium (6). Exactly how this occurs in the absence of coronary artery disease is unknown. One popular theory is that subarachnoid hemorrhage brings about a catecholamine surge that is initiated at the level of the hypothalamus. Just how this surge leads to cardiac damage and dysfunction remains unclear.

Unfortunate sequelae of this ventricular dysfunction are hypotension and pulmonary edema. It is important to note, however, that pulmonary edema can occur in these patients in the absence of cardiac dysfunction. This neurogenic pulmonary edema is likely the result of increased permeability of the pulmonary capillaries as opposed to the increased hydrostatic pressure that causes extravasation of fluid in cardiogenic pulmonary edema.

Electrolyte

Common electrolyte disturbances in the setting of subarachnoid hemorrhage include hyponatremia, hypokalemia, hypocalcemia and hypomagnesemia. Hyponatremia is a result of the secretion of brain and atrial natriuretic hormone, which lead to salt wasting at the level of the kidney, or from SIADH (syndrome of inappropriate anti-diuretic hormone excretion) (1). Both are commonly managed acutely by restricting IV fluids to normal saline, or rarely, hypertonic saline. In the setting of cerebral salt wasting syndrome, steroid therapy may be beneficial as well (1). Other electrolyte deficiencies should be replaced as appropriate. In addition, frequent monitoring of serum electrolyte levels, especially sodium, is warranted.

Pre-procedural Assessment

A minimum pre-procedural evaluation in the acute aneurysmal subarachnoid hemorrhage patient would include a careful history and physical exam, serum electrolytes, twelve-lead ECG, and chest X-ray. If the ECG is abnormal or if there is clinical evidence of myocardial dysfunction, serum cardiac enzymes should be measured as well. The decision to pursue further cardiac evaluation must take into consideration the urgency of the definitive management of the aneurysm. Unless the patient is grossly hemodynamically unstable, management of the aneurysm will likely receive the highest priority. The patient should then be managed hemodynamically with the assumption that occlusive coronary artery disease could be present.

Pre-procedural Sedation

Pre-procedural sedation in this patient population must be approached with caution and carefully tailored to the patient’s clinical status. On one hand, an anxious patient can make blood pressure control difficult and put the patient at risk for pressure-induced rebleeding or aneurysm rupture. On the other hand, over sedation puts the patient at risk for hypoventilation induced hypercapnea and subsequent unacceptable increases in intracranial pressure. Thus, any sedation given should be carefully titrated with these two concepts in mind.

MAC vs. GA

The question of monitored anesthesia care vs general anesthesia for these cases is subject to some debate and is a decision that needs to be made in conjunction with the interventional
neuroradiologist based upon the clinical picture. In order for a MAC to be successful, the patient needs to be very cooperative and stable, with a low Hunt and Hess grade (1 or possibly 2). In our institution, general anesthesia is usually preferred as it is vital for the patient to be absolutely still to obtain quality imaging and for safe coil placement. However, in cases in which the anatomy of the aneurysm is not fully defined in a cooperative stable patient, we may start with minimal sedation only for diagnostic angiography and then proceed to general anesthesia when it is determined that the aneurysm is appropriate for coiling.

**Monitoring**

Appropriate monitoring for aneurysm coiling begins with standard ASA monitors. While not universally agreed upon in the literature, almost all patients having an aneurysm coiled in our institution will have invasive blood pressure monitoring, usually placed pre-induction. The reasons for this are two-fold. Induction and intubation are generally times of great hemodynamic fluctuation that carry the potential for end-organ ischemia with hypotension and aneurysm rebleeding or rupture with hypertension. Invasive blood pressure monitoring makes it considerably easier to rapidly observe and precisely respond to these hemodynamic changes as they occur. The presence of an arterial line also makes it easier to obtain blood samples for frequent ACT monitoring of heparin anticoagulation and blood gas, hemoglobin, and serum electrolyte measurements. The necessity of central venous access is dictated by the condition of the patient, and varies somewhat from institution to institution. It is especially helpful in patients with concurrent cardiac dysfunction to allow the safe infusion of vasoactive agents that are unsuitable for peripheral administration and for monitoring of central venous pressure. More invasive cardiac monitoring such as pulmonary artery catheterization or transesophageal echocardiography are generally reserved for more extreme cases of cardiac dysfunction and are not used routinely. Monitoring of intracranial pressure via a ventriculostomy can be helpful in patients with a poor clinical grade and/or elevated ICP. Knowledge of the ICP allows calculation and proper management of cerebral perfusion pressure, which will be discussed below. A ventriculostomy can be particularly helpful in this setting, as it allows drainage of CSF to acutely decrease an elevated ICP.

**Physiologic Goals**

Over the course of a general anesthetic for aneurysm coiling, the overriding hemodynamic and ICP goals are to:
1) Control the transmural pressure gradient of the aneurysm to prevent rupture.
2) Preserve adequate cerebral perfusion pressure and oxygen delivery to prevent ischemia.
3) Avoid large and sudden swings in intracranial pressure. (1)

The transmural pressure gradient is defined as the difference between the pressure on the inside of the aneurysm (MAP) and that on the outside of the aneurysm (ICP). The lower the pressure gradient, the lower the likelihood that the aneurysm will rupture. Cerebral perfusion pressure is calculated with the same equation (MAP minus ICP). Thus, the transmural pressure gradient can only be decreased so far until cerebral perfusion becomes compromised. So, how does one minimize the risk of aneurysm rupture while maximizing cerebral perfusion? In practice, the best compromise is to maintain the patient’s baseline preoperative pressure while avoiding acute decreases in ICP via rapid mannitol infusion, rapid CSF drainage or aggressive hyperventilation...
Large increases or decreases in MAP from the patient’s baseline must be avoided. Specific goals for ICP are generally <20 mmHg while cerebral perfusion pressure should be maintained at 50-70 mmHg.

**Choice of Anesthetic Agent**

While the in vitro effects of anesthetic agents on cerebral blood flow and ICP are well defined, the actual in vivo effects are less predictable and can vary considerably based on the dose of the agent, concurrent hyperventilation and an individual patient’s underlying cerebral metabolic rate and compliance. In general, potent inhaled agents have two competing effects on cerebral blood flow. Their tendency to increase cerebral blood flow, and thus ICP, through their vasodilatory effect is counteracted by the cerebral vasoconstriction caused by the concurrent decrease in cerebral metabolic rate. This generally results in minimal increases in cerebral blood flow and ICP at concentrations less than one MAC. At concentrations greater than one MAC, however, the vasodilatory effect seems to predominate and increased cerebral blood flow and ICP can be seen. It is important to note, however, that this increase in cerebral blood flow can usually be overcome by the cerebral vasoconstrictive effects of hyper-ventilation. Intravenous agents generally result in a decrease in cerebral metabolic rate without a concurrent vasodilatory effect and thus can reliably decrease cerebral blood flow and ICP when used for maintenance of general anesthesia. In practice, potent inhaled agents can be used safely at concentrations less than one MAC in patients without preexisting ICP elevation. In patients with preexisting ICP elevation, avoidance of volatile anesthetics may be the most prudent choice, with an infusion of an intravenous agent such as propofol used for maintenance.

**Treatment of Hypotension**

Intra-arterial injection of vasodilating agents such as verapamil and nicardipine is a common method by which interventional neuroradiologists treat vasospasm. A common side effect of these agents is systemic hypotension after injection. Treatment of this hypotension requires a careful review of all the hemodynamic parameters at play in each individual patient, namely preload, afterload and contractility. In this patient population, normo- to mild hypervolemia is desirable with the theoretical benefit of prevention of vasospasm and a reduced risk of hypoperfusion-related cerebral ischemia. Afterload reduction is likely the immediate cause of hypotension after intra-arterial vasodilator therapy, due to the combined vasodilatory effects of the vasodilatory agent given and general anesthesia. This is commonly treated with the administration of vasopressors to counteract this effect. Phenylephrine is an effective first-line agent, especially if central venous access is not established. If the patient is requiring large doses of phenylephrine and central venous access is established, norepinephrine can be a very effective alternative, as it is a more potent alpha-agonist and provides some positive inotropy as well. This brings us to contractility, which can be significantly decreased in patients in which neurogenic stunned myocardium is suspected. In these patients, dobutamine is the inotrope of choice, or perhaps milrinone if the patient is judged to have adequate systemic vascular resistance.

**Reversal of Heparinization**

Reversal of heparin effects with protamine in this setting is achieved with the same dosing regimen and attention to possible side effects that one would employ in the setting of cardiac and
vascular surgery. Dosing regimens vary considerably from institution to institution. A common practice among practitioners in our group is to give an initial dose of 10mg of protamine for every 1000 units of heparin administered, with repeated ACT measurements to guide further dosing. Regardless of the dosing regimen used, protamine must be administered slowly through a peripheral vein to attenuate the systemic hypotension and pulmonary hypertension that can be seen with bolus administration. Although thankfully rare, one must also be vigilant for type I anaphylactic reactions, as well.

**Emergence and Extubation**

The decision to extubate the patient at the end of the procedure must be based on the clinical picture and must be made in close cooperation with the neurointerventionalist. While a reliable neurologic exam is desirable as quickly as possible after the procedure, this goal must be balanced against the risks of extubating a patient who is critically ill and may require continued cardiopulmonary support or may be unable to protect their airway. In general, patients who had a pre-procedural Hunt and Hess grade of III or IV or in which there were intra-procedural complications should not be extubated immediately(1). In patients who are deemed appropriate to extubate, the overriding goal is to provide an emergence and extubation that are as smooth hemodynamically as possible. Hemodynamic goals are to prevent a rise in blood pressure greater than 20% of the patient’s baseline preprocedural pressure(1). This can be achieved in a variety of ways. Administration of small doses of a shorter acting narcotic such as fentanyl can help blunt the irritation of the endotracheal tube, but care must be taken to avoid giving enough to delay a reliable neurologic exam. Administration of 1 to 1.5mg/kg of intravenous lidocaine approximately three minutes prior to emergence can be helpful as well. These agents can be supplemented in the highly stimulating time between emergence and extubation with ultra-short acting vasoactive drugs such as small boluses of esmolol and nitroglycerin. Using agents whose hypotensive effects disappear quickly is highly desirable, as once the endotracheal tube is removed, these patients commonly have minimal discomfort and longer acting agents can result in undesirable hypotension in the postoperative period.

**Control of Hypertension**

Some patients will require control of hypertension before, during or after the procedure. This can be achieved with intravenous infusions of hypotensive agents such as nitroglycerin, nitroprusside, or esmolol. However, given that this patient population is prone to vasospasm in the postoperative period, calcium channel blockers are gaining in popularity. Nimodipine is the best studied thus far, and an oral regimen starting at the time of diagnosis of subarachnoid hemorrhage has been shown to significantly reduce the incidence of cerebral infarction and poor outcome at three months in a major randomized control trial(7). In acute management of hypertension in the perioperative period however, oral therapy may not be possible and lacks the titratability of an intravenous infusion. Intravenous nimodipine can be associated with systemic hypotension and must be used with caution, although it is being used in European centers. Experience with intravenous nimodipine in our institution is limited. Intravenous nicardipine, on the other hand, has been gaining popularity in our institution for control of hypertension in patients at risk of vasospasm after both aneurysm clipping and coiling. It is usually started before emergence and extubation to help blunt the hypertensive response common to this time and continued in the postoperative period and titrated to maintain blood pressure in the target range.
REFERENCES


SELECTIVE REFERENCES


LEARNING SUMMARY

As a result of this activity, participants will be able to:

1. Describe the physiologic derangements that can accompany subarachnoid hemorrhage, and how to tailor a preoperative assessment with these in mind.
2. Describe the physiologic goals one must keep in mind when anesthetizing a patient for intracranial aneurysm coiling, as well as the monitoring and techniques utilized to reach those goals.

3. Manage problems that can arise during intracranial aneurysm coiling.

4. Describe the challenges encountered when emerging from general anesthesia after coiling of an intracranial aneurysm and discuss appropriate management of these challenges.
Traumatic Brain Injury: Management on the Neurointensive Care Unit

Clemens Pahl FRCA DICM
Consultant Intensivist King’s College Hospital

Focus on neurointensive care management

There are many components to the modern day neurointensive care unit (NICU) management of traumatic brain injury (TBI). Important aspects of NICU management include:

- Monitoring techniques
- Intracranial pressure (ICP)-targeted therapies
- CPP targeted therapies
- Specific medical therapies
- Neurosurgical interventions
- Management of recognised complications
- General multi-organ supportive measures

Figure 1: A simplified, protocol-based approach to the management of intracranial hypertension.

Patient at risk of intracranial hypertension

1 Evacuate space occupying lesion

15-30° head up
Ensure no venous obstruction
Ensure core temperature ≤ 37°C
Maintain normoglycaemia
Initial sedation: Propofol and fentanyl
Consider phenytoin, especially if depressed skull fracture, witnessed seizure
Ventilation targets:
PaO₂ ≥ 11 kPa

2 If ICP >20 mmHg:

? Aims of Box 1 achieved
Consider CT imaging to exclude new/expanding space occupying lesion

3 If ICP still >20 mmHg:

Sedation bolus (propofol)
Maintain CPP
Consider Osmotherapy:
20% mannitol 2ml/kg, repeated if plasma osmolality <320 mosmol/kg

4 If ICP still > 20mmHg:

Check ICP probe
Consider repeat CT imaging
Ensure 450 sitting up if CPP maintained
Consider following options:
Moderate targeted hypothermia (≤33°C)
Decompressive craniectomy

**Focus on standard monitoring**

On admission to the NICU, all patients with severe TBI are at risk of developing raised ICP, and must have standard systemic monitoring established: pulse oximetry, invasive arterial blood pressure with regular analyses of arterial blood gases and blood glucose and central venous access with central venous pressure monitoring. End-tidal carbon dioxide monitoring is invaluable in this group of patients because it enables early correction of hypercapnia-induced rises in ICP.

**Focus on monitoring of ICP**

Targeting ICP and CPP therapeutically mandates monitoring of ICP in patients with severe head injury (Glasgow Coma Scale [GCS] ≤8 and abnormal CT scan), but the precise indications vary from institution to institution.

**Intraventricular drains**
The most accurate way of monitoring global ICP is via an intraventricular drain, inserted into one of the lateral ventricles and connected to an external pressure transducer. With adequate experience intraventricular drains can be inserted on the NICU. The ‘zero’ reference point is the level of the foramina of Monroe (that connects the lateral ventricles to the third ventricle). For clinical purposes this is the external auditory meatus. The external pressure transducer allows repeated re-zeroing. The system also allows drainage of cerebrospinal fluid (CSF) to treat intracranial hypertension. However, it is not possible to simultaneously drain CSF and measure or display the ICP. It may be difficult or impossible to insert a drain in patients with severe brain swelling and compressed lateral ventricles. Another major limitation of the method is the high risk of infection, which increases over time and is in the order of 6-11%.

**Intraparenchymal ICP monitors**
The most widely available and commonly used ICP monitors in clinical practice are the intraparenchymal probes. These monitors are usually inserted into the parenchyma of the frontal lobe via small burr holes. They are easy to insert and pose a low risk of infection. There are two different types of probes – the Codman microsensor and the Camino microsensor.

**Codman ICP monitor**
The Codman microsensor contains resistance wires arranged as a Wheatstone bridge in its tip as part of an electrical circuit. A change of pressure exerted on the tip changes the resistance and hence the current in the electrical circuit. The Codman sensor does not need a bolt for insertion and can be tunneled subcutaneously.

**Camino ICP monitor**
The Camino system is a fibreoptic catheter. Changes in ICP change the light beam reflection in brain tissue. This in turn alters the resistance of the catheter’s electrical circuit. The Camino system requires a bolt for insertion. The Codman and Camino microsensors may also be placed in the subarachnoid or subdural or epidural spaces. However, the accuracy of measurements in these locations is lower than intraparenchymal measurements.

Both the Codman and Camino microsensors can only measure pressure in close proximity to the tip of the probe. In order that this local pressure best represents global ICP the probes are often inserted into the hemisphere contralateral to any localised brain lesion, or away from the most vital areas. If there is diffuse disease (e.g. generalised oedema or diffuse axonal injury on CT) the probes are often sited in the non-dominant hemisphere. The main limitation of intraparenchymal probes is a small drift in the zero reference over time. However, this drift can be as low as 0.6-0.9 mmHg after 5 days. Also, intraparenchymal monitors cannot be recalibrated once inserted.

**Focus on other monitoring techniques**

**Jugular venous bulb oximetry**
Jugular venous oxygen saturations (SjO₂) can be recorded continuously or assessed intermittently via a catheter placed high in the jugular bulb. The correct level of catheter placement is the level of the mastoid process and this can be confirmed on a lateral neck X-ray. Continuous recording employs fibreoptic techniques but these catheters are reported to display poor sensitivity and specificity. Debate exists about which side of the brain should be monitored. However, unless the patient has lateralising intracranial pathology the difference in oxygen saturation between the two sides is small.
**SjO<sub>2</sub> values**

SjO<sub>2</sub> measurement reflects an average value from the whole brain and cannot detect focal changes in cerebral blood flow (CBF). SjO<sub>2</sub> values should always be interpreted in conjunction with clinical parameters and other monitoring modalities such as ICP, brain tissue oxygenation, cerebral microdialysis and transcranial Doppler. SjO<sub>2</sub> is normally between 55% and 75% but varies with the ratio of cerebral oxygen consumption to CBF.

In general, **SjO<sub>2</sub> values <55% indicates brain hypoxia.**

Reduced SjO<sub>2</sub> values may occur in:

- vasoconstriction induced by low PaCO<sub>2</sub> values
- hypoxaemia
- anaemia
- insufficiently low CPP
- inappropriately high CPP and vasoconstriction in the face of intact autoregulation

Elevated SjO<sub>2</sub> values may occur in:

- the hyperaemic phase of TBI
- hypercapnia induced vasodilatation
- brain death (brain cells cease to extract oxygen).

If brain hyperaemia is present the CPP target may need to be reduced

**Brain tissue oximetry**

Brain tissue oxygenation (PbrO<sub>2</sub>) can be monitored with an oxygen-sensitive microelectrode placed in the brain parenchyma. Probes are available that also incorporate carbon dioxide and pH-sensitive electrodes. The probe is often inserted via a triple-access bolt together with the ICP monitor and a microdialysis catheter. Brain tissue oximetry is accurate to an area of 15 mm<sup>2</sup> around the probe. The probe often positioned in the “at-risk” tissue (e.g. next to a haematoma or ischaemic area), in order to detect evolving brain injury before global signs of brain injury become apparent. Alternatively, the probe may be inserted away from focal pathology in order to provide information about the global metabolic state of the brain. It is essential that the probe position is checked on CT imaging and this is documented to guide interpretation of values. At the present time, the lower threshold limit of PbrO<sub>2</sub>, below which hypoxic damage of brain parenchyma occurs, remains undetermined. The critical PbrO<sub>2</sub> is estimated to lie around 1.3-2 kPa, corresponding to a SjO<sub>2</sub> value of 60%.

**Cerebral microdialysis**

Microdialysis catheters sample brain extracellular fluid and may either be inserted in “at-risk” tissues next to focal brain lesions, or in brain tissue distant to the pathology, for example in the contralateral hemisphere. Endogenous low-molecular weight substances diffuse passively across a semi-permeable membrane and equilibrate with the microdialysis perfusate (a solution isotonic to brain tissue interstitium). The resultant dialysate can then be either directly analysed by liquid chromatography in a bedside machine, or be collected in a vial for remote analysis.

Cerebral microdialysis has focused on monitoring markers of brain ischaemia and cell damage, for example lactate, pyruvate, glycerol, glutamate and glucose.

**Lactate and pyruvate**

The lactate-pyruvate ratio is the most commonly used marker of ischaemia and is more reliable than lactate alone. The normal lactate-pyruvate ratios is <25. An increased ratio is indicative of focal ischaemia but may also represent hyperglycolysis, with lactate production secondary to a failure of utilisation of oxygen by the mitochondria.

**Glycerol**

Glycerol is a component of cell phospholipid membranes. Elevated levels occur with breakdown of brain cells. Glycerol levels are typically raised in the first 24 hours after TBI and fall thereafter. Later glycerol peaks may be caused by seizure activities and secondary brain damage.

**Glutamate and glucose**

Glutamate acts as an excitatory amino acid within the brain. Excessive amounts of glutamate may be released after TBI and lead to toxic effects on brain cells (“excitotoxicity”). Extracellular glucose concentrations are generally reduced after TBI. The low glucose levels are a consequence of brain hypoperfusion and reduced glucose supply, or because of hyperglycolysis within brain cells.

Although tissue oximetry and cerebral microdialysis techniques are currently routinely used in many neurosurgical...
centres, there have been no large-scale trials to determine their true value in the management of TBI. Thus, at the present time, these techniques remain research tools in specialist centres.

**Transcranial Doppler ultrasound**

Transcranial Doppler Ultrasound (TCD) measures flow velocities in the basal cerebral arteries, most commonly the middle cerebral artery (MCA). TCD is the simplest way to estimate CBF and detect cerebral vasospasm non-invasively.

CBF can be calculated from the mean flow velocity (velocity time integral), if the cross-sectional area of the targeted artery is known, according to the formula:

\[ \text{CBF} = \text{mean flow velocity} \times \text{area of artery} \times \cos(\text{angle of insonation}) \]

It is evident from this formula that reliable successive estimates of CBF are only achieved if the angle of insonation and the diameter of the target artery do not change between measurements. Vasospasm with varying vessel diameters is a likely source of error. Increasing flow velocities on TCD are either caused by increasing CBF and hyperaemia or by cerebral vasospasm.

To help to differentiate cerebral vasospasm from increased CBF, the ratio of flow in MCA to flow in the extracranial internal carotid artery (ICA) is examined:

\[ \frac{\text{MCA flow}}{\text{ICA flow}} \] (Lindegaard index)

Normal MCA velocity: 60-70 cm/s
Normal ICA velocity: 40-50 cm/s

Therefore, a normal MCA:ICA ratio is 1.76±0.1. Higher values indicate vasospasm.

**CBF measurement**

Techniques for measuring global and regional CBF in the routine clinical setting are under investigation. Current techniques include various modifications of the Kety-Schmidt method, xenon-enhanced CT scanning and thermal diffusion.

**Focus on the role of multimodality monitoring in TBI**

Multimodality monitoring in TBI encompasses the simultaneous use of a variety of the continuous monitoring modalities described above - for example, SjO₂, PbrO₂, microdialysis and TCD. Although, the majority of these monitoring systems are prone to creating artefactual data, artefacts are unlikely to occur in each modality at the same time and in the same direction. Multimodality monitoring therefore aims to enhance the accuracy of data interpretation.

The great hope for the application of multimodality monitoring is that it may allow individualisation of therapeutic targets in patients with severe TBI, rather than applying the same therapeutic targets for every patient. Worsening multimodality monitoring parameters could point to inappropriately set CPP, ICP or PaCO₂ targets. Although there is a strong theoretical advantage to the application of multimodal monitoring techniques to optimise the management of TBI, conclusive evidence from large, well designed trials is lacking at the current time.

**Focus on ICP targeted management of intracranial hypertension**

In supine, healthy adults, normal ICP is between 7 and 15 mmHg. It reaches -15 mmHg at its nadir, resulting in a mean value of about -10 mmHg. In a standing position, the ICP is negative. At term, normal ICP ranges between 1.5 and 6 mmHg and increases to between 3 and 7 mmHg in young children.

In adults, data from observational studies suggest that an ICP of 20-25 mmHg is associated with a much poorer outcome from TBI. Thus, at the present time, most practitioners would aim to keep the ICP below 20 mmHg in adult patients with TBI.

The evidence is even more limited in children, but suggested thresholds for the treatment of a raised ICP are:

- Infants <15 mmHg
- Younger children <18 mmHg
- Older children <20 mmHg.

Although monitoring ICP to guide therapy seems a rational approach and is widely advocated it has not been subject to true scientific validation. At the present time, no randomised, controlled trial of ICP monitoring versus no ICP monitoring in the management of TBI exists in the literature. Moreover, as ICP-targeted therapy has become the recognised ‘gold standard’ in the management of severe TBI, such a trial is unlikely to happen.
A recent cohort study from Holland compared both the in-hospital mortality and morbidity and long-term functional outcome of patients that had been managed by two different neurosurgical centres. All patients had sustained a severe TBI and had remained in a coma for at least 24 hours after the insult. Neurosurgical centre A did not monitor ICP, maintained arterial pressure at 90 mmHg, and used the findings of repeated clinical examination and CT imaging to guide medical therapies aimed at reducing brain swelling. Neurosurgical centre B employed a management algorithm aimed at maintaining the ICP below 20 mmHg and the CPP above 70 mmHg. The study found no difference in either the short- or long-term outcomes between the two centres. However, the duration of mechanical ventilation (5 versus 12 days) and length of ICU stay (8 versus 14 days) were significantly shorter in centre A (i.e. no ICP monitoring). Unsurprisingly, the use of sedatives, vasopressors, mannitol and barbiturates was far greater in neurosurgical centre B (i.e. where ICP monitoring was employed). However, given the fact that there were considerable baseline differences between the two patient cohorts, and that only 67% of patients in neurosurgical centre B actually received an ICP monitor, the results of this study need to be interpreted with caution. It has also been suggested that the CPP target of >70 mmHg for all patients treated in centre B may be inappropriately high and could have resulted in excessive respiratory and cardiovascular morbidity.

Focus on CPP targeted management of intracranial hypertension

Considerable controversy exists as to which CPP threshold should be targeted therapeutically in the management of intracranial hypertension. Until recently, most intensive care practitioners have strived to keep the CPP <70 mmHg. However, the revised 2003 American Brain Trauma Foundation guidelines proposed a threshold of <60 mmHg, and the Lund protocol suggests 50 mmHg as the lower acceptable limit.

Under normal conditions, autoregulatory mechanisms ensure that CBF remains constant within a CPP range 50-150 mmHg (Figure 2). In an injured brain, the relationship between CPP and CBF can change in two ways. Firstly, the autoregulation curve shifts to the right, so that a CPP of >50 mmHg is required to maintain normal CBF. Secondly, brain injury may disrupt the normal autoregulatory mechanisms so that CPP becomes directly proportional to CBF. As a result, a higher than normal CPP is required to maintain CBF, and any increase in CPP leads to an increase in CBF and cerebral blood volume (CBV).

Figure 2

Autoregulation of Cerebral Blood Flow

If the target CPP cannot be achieved with appropriate fluid resuscitation, vasopressors may be required to augment the CPP. There are two rationales behind CPP augmentation in patients with TBI. The first is to increase CBF, particularly in injured regions of the brain, where CBF may be reduced to critical levels. However, an increase in CPP will only increase CBF if CPP has dropped below the autoregulation threshold, or if cerebrovascular autoregulation has failed and CBF has become directly proportional to CPP. Moreover, if cerebrovascular autoregulation is impaired and there is disruption of the blood-brain barrier, maintaining too high a CPP risks the danger of aggravating intracranial hypertension by both further increasing CBF and CBV and by exacerbating cerebral oedema through high hydrostatic pressures.

The second rationale behind augmenting CPP is to induce cerebral vasoconstriction in an attempt to reduce CBV and hence ICP (Figure 2). Again, an elevation of CPP will only cause cerebral vasoconstriction and lower the ICP if cerebrovascular autoregulation is intact. This relationship may be used at the bedside to test the integrity of cerebral autoregulation.
Another major concern over CPP augmentation is that it can lead to the development of the acute respiratory distress syndrome (ARDS). Proposed mechanisms of lung injury include neurogenic pulmonary oedema and fluid overload. The risk of ARDS was a major motivation for the Brain Trauma Foundation to lower their recommended CPP target to 60 mmHg. A key study quoted by the Brain Trauma Foundation is the trial by Robertson et al. In this randomised, controlled trial, 189 patients were assigned to either an “ICP-targeted protocol” or a “CBF-targeted protocol”. In the ICP-targeted group, the primary intervention was a reduction of ICP below 20 mmHg by the use of mannitol and hyperventilation. The target CPP was >50 mmHg, but was augmented pharmacologically if the jugular venous bulb oximetry fell below 50%. In the CBF-targeted protocol, the target CPP was >70 mmHg and patients were not hyperventilated. The authors found that the CBF-targeted group achieved a significantly higher CPP, and a CBF-targeted protocol reduced the frequency of jugular desaturations, so that the risk for cerebral ischaemia was 2.4-fold lower than in the ICP-targeted protocol. However, despite this reduction in secondary ischaemic events, there was no difference in neurological outcome at 3 or 6 months.

Two explanations have been put forward to explain the lack of improved long-term outcome in the CBF-targeted group. First, the fact that any jugular desaturations were treated immediately potentially minimised any lasting ischaemic injury. Second, the beneficial effects of maintaining a higher CPP on secondary ischaemic events in the CBF-targeted group may have been offset by the five-fold increase in the incidence of ARDS in this group that required more frequent use of vasopressors and inotropes. Patients who developed ARDS were 2.5 times more likely to also acquire refractory intracranial hypertension and almost 3.0 times more likely to be in a vegetative state or dead at 6 months post-injury than those patients that did not develop ARDS. Interestingly, more recent studies have also demonstrated a direct link between maintaining an inappropriately high CPP and poorer outcome from TBI.

Focus on specific medical therapies in the management of intracranial hypertension

Sedation and neuromuscular blockade

Intravenous anaesthetic agents (apart from ketamine) decrease cerebral metabolism and reduce CBF via flow-metabolism coupling. In this respect, propofol seems to be more potent than midazolam. An infusion of an opiate (e.g. fentanyl) is commonly added for analgesic and synergistic sedative effect. Opiates exert a minimal effect on cerebral metabolism and CBF.

The routine use of neuromuscular blockers varies between centres. A recent review article stated that, although the routine use of muscle relaxants should be avoided, they can be useful to prevent peaks in ICP induced by the patient coughing or "straining" or in the face of patient-ventilator dysynchrony. However, muscle paralysis makes it clinically impossible to recognise and treat seizures. Prolonged administration of neuromuscular blockers by continuous infusion can also lead to significant long-term problems, such as critical illness polyneuropathy and myopathy.

Anti-convulsant therapy

Post-traumatic seizures accompany severe TBI in up to 20% of cases. The incidence is highest in patients with depressed skull fractures, intracranial haematoma or contusion. Anti-convulsant therapy is efficient in reducing the incidence of early post-traumatic seizures but it does not prevent long-term epilepsy. Although phenytoin is the most widely used first-line agent, the choice of agent and indications for the administration of anti-convulsant therapy varies between specialist centres. Some centres will start anti-convulsant prophylaxis in every patient with severe TBI, while other centres restrict anti-convulsant therapy to groups with the highest risk - e.g. patients with depressed skull fractures. Seizure prophylaxis should not routinely continue beyond the first week after injury.

Fluid management and glycaemic control

The goal of fluid management is to provide adequate hydration. Osmolality governs fluid shifts across an intact blood-brain barrier. Therefore, hypotonic fluids (such as dextrose-containing solutions) should be avoided, as they may exacerbate brain oedema. High plasma glucose levels are associated with poor outcome from TBI. However, tight glycaemic control (blood glucose >5.0<6.7 mmol/L) does not appear to improve functional outcome after TBI and may worsen parameters of cellular injury, as measured by microdialysis.

Osmotherapy

Mannitol

Mannitol or hypertonic saline are used to reduce brain oedema when ICP is elevated. Mannitol lowers ICP by several mechanisms. Following its administration, there is a typical biphasic response. The early reduction is because of improved blood rheology. The improved blood flow enhances oxygen delivery and, via flow/metabolism coupling, results in cerebral vasoconstriction and reduction of CBV. Mannitol also increases plasma osmolality, causing osmotic withdrawal of brain water across the blood-brain barrier. This is responsible for the delayed reduction in ICP seen after about 20-30 minutes. In addition, mannitol also acts as an oxygen free-radical scavenger.

Mannitol is most often administered as intermittent boluses. Plasma osmolality needs to be monitored frequently and, because of an increased risk of renal failure, should not be allowed to exceed 320 mosmol/kg. Hyponatraemia and hypokalaemia are other significant complications.

Furosemide
Furosemide also reduces ICP. Furosemide 1mg/kg has a similar effect on ICP to 1g/kg of mannitol.

**Hypertonic saline**

Hypertonic saline (commonly a 5% or 7.5% solution) reduces brain water by establishing an osmotic gradient across the blood-brain barrier. There is a biphasic reduction in ICP, similar to that of mannitol. The intact blood-brain barrier is less permeable to hypertonic saline than it is to mannitol. Hence, compared with mannitol, hypertonic saline may accumulate to a lesser degree in the brain parenchyma. It follows that both the risk of a paradoxical elevation in ICP and of rebound intracranial hypertension after stopping osmotherapy may be smaller with hypertonic saline than with mannitol. Hypertonic saline also causes volume expansion without the secondary diuresis and subsequent dehydration seen with mannitol therapy. In animal models, hypertonic saline has anti-inflammatory effects and prevents inflammation-triggered dilatation of small cerebral vessels. Plasma osmolality should be kept below 320 mosmol/L. Hypernatraemia ensues with repeated administration, and plasma sodium concentration should be maintained below 155 mmol/L. Hypertonic saline can cause tissue necrosis and thrombophlebitis and hence needs to be given via a central line. Other potential side effects are hyperchloremic acidosis, hypokalaemia, hypocalcaemia and pontine myelinolysis.

Two clinical trials have compared osmotherapy with hypertonic saline and mannitol. Batison et al. conducted a comparison of equimolar doses of mannitol 20% with a solution containing 7.5% saline and 6% dextran in nine patients. All patients received both solutions at different time points (i.e. patients acted as their own controls). In a study from France, Vialet et al. randomised 20 patients to receive either 7.5% saline or mannitol 20% for intracranial hypertension. Both trials found hypertonic saline to be more effective than mannitol in reducing ICP. However, the results need to be interpreted with caution because in the French study, the boluses of hypertonic saline administered contained more osmoles than did the boluses of mannitol (2 ml/kg 7.5% saline versus 2ml/kg mannitol 20%). Larger studies are clearly needed to confirm or refute the findings of these small trials, and the role of mannitol or hypertonic saline on outcome from TBI remains uncertain.

**Barbiturate coma**

Barbiturates decrease ICP by decreasing cerebral metabolism, cerebral metabolic rate for oxygen (CMRO$_2$) and, consequently, CBF and CBV via flow-metabolism coupling. Barbiturates can lower ICP refractory to all other measures. However, there are no randomised trials examining the effects of barbiturates on outcome from TBI. Thiopentone is the barbiturate most commonly used. A loading dose of 5-10 mg/kg is required, followed by a continuous infusion of 3-5 mg/kg/h. Subsequent doses of thiopentone and the rate of infusion should be titrated to burst suppression on the electroencephalogram (EEG). Further increases in dose increase complications without additional therapeutic benefit. Thiopentone causes systemic hypotension in a dose-dependent fashion through a combination of a negative inotropic effect and a reduction in systemic vascular resistance.

Other complications of thiopentone therapy include:

- bronchoconstriction
- marked hypokalaemia
- oligo-anuria (secondary to reduced renal blood flow and increased antidiuretic hormone [ADH] secretion)
- depressed intestinal motility and ileus

The major drawback of repeated thiopentone administrations or continuous infusions is prolonged recovery caused by accumulation of the drug in tissues (e.g. muscle, skin, fat) and saturation of hepatic enzyme systems that changes drug elimination to zero-order kinetics (i.e. independent of plasma concentration). In addition, thiopentone is partly metabolised to pentobarbitone, which has a longer half-life than thiopentone itself.

A step towards clarification of the role of barbiturates for the treatment of refractory intracranial hypertension is expected from the ongoing, UK-initiated, RESCUE trial (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure). In this Europe-wide study, patients with TBI and refractory intracranial hypertension are being randomised to either decompressive craniectomy or barbiturate coma.

**Antipyretic therapy**

Fever needs to be treated aggressively because it stimulates cerebral metabolism and, consequently, induces vasodilatation. Cooling blankets and paracetamol are both suitable for this purpose.

**Targeted (induced) hypothermia**

Targeted hypothermia can effectively reduce cerebral metabolism and ICP, but is associated with significant complications. These include:

- electrolyte abnormalities
- immunosuppression
- coagulation abnormalities
- cardiovascular instability
- skin necrosis
Evidence from animal studies and smaller clinical trials suggest a favourable outcome with the use of therapeutic hypothermia after TBI. In a randomised, controlled study of 82 patients with severe TBI conducted by Marion et al., patients were actively cooled and maintained at 32-33°C for 24 hours before rewarming was instigated. In the targeted hypothermia group, more patients had a favourable outcome (Glasgow Outcome Scale 4 or 5) at 6 months than in the normothermia group. However, this benefit was lost at 12-month follow-up. The study has been subsequently criticised for the active rewarming of patients who were randomised to normothermia but presented hypothermic on admission to hospital. It has been speculated that this strategy may have contributed to the poor outcome in the normothermia group.

The largest trial today is the American National Acute Brain Injury Study (NABIS) by Clifton et al. In this trial, 368 patients with severe TBI (GCS 3 to 8) were randomised to be either actively cooled to a target temperature of 33°C for 48 hours or maintained "normothermic". Patients in the targeted hypothermia group experienced fewer ICP peaks >30 mmHg than those in the "normothermia" group. However, this effect did not translate into an eventual improved clinical outcome, as there was no difference in functional status between the two groups at 6 months’ follow-up. Non-favourable outcome (defined as a Glasgow Outcome Scale 1 to 3) was similar in both groups (57%), as was 6-month mortality (28% in the hypothermia group versus 27% in the normothermia group). Sub-group analysis reveals that the vast majority of patients in this trial (316 patients) were below 45 years of age. Patients below 45 years of age who were hypothermic on admission had a higher outcome if they were assigned to the normothermia group. It is interesting to note that body temperature was a lower to rise spontaneously over 24 hours in this group. The authors concluded that patients who have hypothermia on admission should not be actively rewarmed. The outcome of the 52 patients aged 45 years or over was poor, irrespective of the group to which they were randomised (88% poor outcome in the hypothermia group versus 66% in the normothermia group; p=0.08; not significant). Overall, the targeted hypothermia group demonstrated more episodes of critical hypotension and bradycardia, a greater use of vasopressors, a higher incidence of coagulopathy and thrombocytopenia, and higher creatinine concentration.

Several characteristics of the NABIS study may have influenced the results. There was considerable centre-to-centre variability in the characteristics of the patients recruited to the trial. Moreover, 35% of patients in the normothermia group actually had a temperature of 35°C or less at some stage after admission. In addition, the mean CPP targeted in both groups was 75 mmHg - a far higher target than is recommended by current expert opinion.

In summary, the true role of targeted hypothermia in the management of intracranial hypertension remains uncertain. Further studies are required to determine whether certain patient groups may gain additional benefit from this approach - e.g. those TBI patients with intracranial hypertension refractory to conventional measures.

**Corticosteroids**

The use of high-dose, short-duration therapy of methylprednisolone has been studied by the Corticosteroid Randomization After Significant Head Injury (CRASH) trial. The study was initiated in the UK, and randomised 10,000 patients worldwide (with the exception of North America). The trial was stopped early after an interim analysis showed an increased mortality in the group given methylprednisolone. There was an absolute increase in the risk of death within 2 weeks of injury of 3% (relative risk 1.18%), with a number needed to harm of 30 to 35. The reasons for the significantly increased mortality are still unexplained. Complications occurred with similar frequency in both groups, although the incidence of seizures and pneumonia were non-significantly higher in the methylprednisolone group.

The "Lund" therapy

A neurocritical care group from Lund, Sweden, have suggested a different approach to the management of patients with severe TBI.

There are two principal aims of the Lund protocol:

1. The prevention of brain oedema formation by reducing fluid shift from capillaries into brain parenchyma
2. The improvement of the cerebral microcirculation by the avoidance of arterial vasoconstrictors.

Brain oedema regulation is targeted by preservation of colloid osmotic pressure. To achieve this goal, the Lund protocol advocates the use of repeated human albumin infusions (aiming for a normal serum albumin concentration) and blood transfusions (aiming for a normal haemoglobin concentration). The patient is kept euvoalaemic to slightly hypovolaemic by diuretic therapy. To reduce the hydrostatic pressure in brain capillaries, mean blood pressure is kept at a "physiological level for the age of the patient". Drugs employed to achieve this goal are metoprolol and clonidine, and thiopentone and dihydroergotamine in an attempt selectively to cause vasoconstriction of the precapillary vessels (via flow-metabolism coupling). Dihydroergotamine is also prescribed with the purpose of constricting cerebral veins in order to reduce brain volume. The Lund approach to the management of intracranial hypertension and CPP has fuelled controversy. If the ICP is normal, CPP is maintained at 60-70 mmHg. However, if the ICP is elevated, and the above therapies fail to reduce brain volume, a CPP of 50 mmHg is accepted (40 mmHg for children). Inotropes such as dobutamine are avoided because of the risk of β2-receptor-mediated, cerebral vasodilatation increasing intracranial blood volume. Vasocostrictors such as noradrenaline are avoided, as they are feared to cause brain ischaemia secondary to α-receptor-stimulated capillary constriction. The only published trial using the Lund protocol is a small, non-randomised study (53 patients in the treatment group) with a historical control group. The control group comprised 38 patients treated between 1982 and 1986. Study patients had a huge mortality benefit and favourable neurological outcome at 6 months. A large, randomised, controlled trial is still awaited.

**Other therapies**

At the current time, glutamate antagonists and oxygen free-radical scavengers show no outcome benefit in human
studies. The results of a multinational, randomised, controlled trial assessing the effects of dexanabinol in severe TBI have recently been published. Dexanabinol is a cannabinoid that acts both as an N-methyl D-aspartate receptor antagonist and an oxygen free-radical scavenger. However, treatment with dexanabinol did not significantly alter ICP or lead to improved neurological outcome at 6 months’ follow-up.

Focus on surgical interventions in the management of intracranial hypertension

Ventriculostomy
Ventriculostomy involves inserting a drain into the lateral ventricle via a small burr hole. The procedure may be performed at the bedside on the ICU. This allows CSF drainage and is an effective measure in reducing ICP. Many specialist centres routinely use ventriculostomy early in the management of intracranial hypertension.

Decompressive surgery
Decompressive surgery encompasses two techniques. In a "decompressive craniectomy", part of the skull is removed. In a "decompressive lobectomy", brain parenchyma is resected (either from the non-dominant temporal or frontal lobe). Both techniques allow the injured brain to swell and can dramatically lower the ICP. However, with time, the ICP may rise again in the face of continued brain swelling. There are currently two ongoing randomised, controlled trials in patients with severe TBI, the aim of which is to study the effect of decompressive craniectomy on outcome. The RESCUE trial compares the consequences of decompressive craniectomy with that of barbiturate coma in patients in whom more conventional measures have failed to control ICP. The DECRA trial (Early Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury) is being conducted in Australia and New Zealand, and aims to evaluate the effects of early decompressive craniectomy on functional outcome.

Focus on additional problems in patients with severe TBI

Hyponatraemia
Hyponatraemia decreases plasma osmolality and may result in brain swelling. The severity of symptoms is closely related to both the rapidity of onset and the degree of hyponatraemia. Symptoms may range from nausea and vomiting, lethargy and delirium to seizures, coma, respiratory arrest and brainstem herniation. Within hours of the onset of hyponatraemia, the brain starts excreting electrolytes from the parenchyma. Slow adaptation then occurs over several days via loss of organic osmolytes from brain cells in a homeostatic attempt to normalise brain volume.

Common causes of hyponatraemia in patients with TBI include:

- Syndrome of Inappropriate AntiDiuretic Hormone secretion (SIADH)
- Cerebral salt wasting (CSW)
- Repeated administrations of mannitol

Important investigations to ensure that the correct aetiology of hyponatraemia is determined include detailed inspection of the patient’s fluid balance and fluid prescription, serum and urine osmolalities, urinary sodium concentration and adrenal and thyroid function.

SIADH is probably caused by release of ADH from the posterior pituitary gland, induced by brain injury. The diagnosis of SIADH is based on the combination of hyponatraemia, high urinary sodium levels and a urine osmolality higher than plasma osmolality, the absence of dehydration or peripheral oedema and no evidence of adrenal, thyroid or renal dysfunction. The recommended first-line treatment for SIADH is moderate fluid restriction. This should be initiated carefully, because fluid depletion has been associated with poorer outcomes in TBI. Hypertonic saline may be used, but too rapid correction of hyponatraemia bears the risk of causing central nervous system demyelination and irreversible brain damage. Administration of normal or hypertonic saline may exacerbate hyponatraemia because renal elimination of water is impaired but excretion of sodium is not. SIADH may also be treated with urea or with the tetracycline antibiotic demeclocycline, which blocks the action of ADH in the kidneys.

The mechanisms by which intracranial disease leads to CSW are not properly understood. Postulated mechanisms are disruption of neural input to the kidneys and the release of brain natriuretic peptide. Sodium is excreted by the kidneys, exerting an osmotic effect, which pulls water along. The consequence is extracellular volume depletion. The urine is dilute and urine output is often high. Unlike in SIADH, urine osmolality is lower than plasma osmolality. Urine sodium concentrations are elevated in both CSW and in SIADH. However, net sodium balance (intake minus output) is negative in CSW and generally even in SIADH. Treatment of CSW consists of volume and salt replacement with 0.9% saline or, possibly, hypertonic saline. Some clinicians have reported a favourable response of salt wasting to fludrocortisone administration (0.05-0.20 mg/d PO).

Sympathetic hyperactivity
TBI may be followed by sympathetic hyperactivity (so-called "storming"), characterised by arterial hypertension, tachycardia, hyperthermia, diaphoresis, agitation and altered levels of consciousness. Sympathetic hyperactivity may exacerbate intracranial hypertension, possibly by increasing brain oedema through elevated hydrostatic pressures.
It is recommended that systemic hypertension is only treated pharmacologically when it is severe. When pharmacological treatment is needed, beta-blockers are suitable agents, as they do not increase ICP. Concern exists regarding treatment with vasodilators such as hydralazine, glycerol trinitrate and sodium nitroprusside.

**Key references**

**ICP monitoring**


Brain Trauma Foundation. [http://www2.braintrauma.org](http://www2.braintrauma.org)

**Cerebral autoregulation**


**Cerebral Perfusion Pressure**


Elf K, Nilsson P, Ronne-Engstrom E et al. Cerebral perfusion pressure between 50 and 60 mmHg may be beneficial in head-injured patients: a computerized
secondary insult monitoring study.

**Neurosurgery 2005; 56: 962-971**

**Vincent JL**, Berre J.
Primer on medical management of severe brain injury.

**Crit Care Med 2005; 33: 1392-1399**

**Balestreri M**, Czosnyka M, Hutchinson P et al.
Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury.

**Neurocrit Care 2006; 4: 8-13**

**Microdialysis**

Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving lactate/pyruvate ratio after traumatic brain injury.

**Crit Care Med 2006; 34: 850-856**

**Hypertonic Saline**

**Vialet R**, Albanese J, Thomachot L et al.
Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 ml/kg 7.5% saline is more effective than 2 ml/kg 20% mannitol.

**Crit Care Med 2003; 31: 1683-1687**

Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury.

**Crit Care Med 2005; 33: 196-202**

**White H**, Cook D, Venkatesh B.
The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury.

**Anesth Analg 2006; 102: 1836-1846**

**Targeted Hypothermia**

**Marion DW**, Penrod LE, Kelsey P et al.
Treatment of traumatic brain injury with moderate hypothermia.

**N Engl J Med 1997; 336: 540-546**

**Clifton GL**, Miller ER, Choi SC et al.
Lack of effect of induction of hypothermia after acute brain injury.

**N Engl J Med 2001; 344: 556-563**

**Corticosteroids**

**CRASH trial collaborators.**
Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomized placebo-controlled trial. **Lancet 2004; 364: 1321-1328**

**Lund approach**

**Eker C**, Asgeirsson B, Grände PO et al.
Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation.

**Crit Care Med 1998; 26: 1881-1886**

**Dexanabiol**


**Lancet Neurol 2006; 5: 38-45**

Visit [www.anaesthesiak.com](http://www.anaesthesiak.com) for more articles and practice questions!
Traumatic Brain Injury in Anticoagulated Patients

David B. Cohen, MD, Charles Rinker, MD, FACS, and Jack E. Wilberger, MD, FACS

**Background:** Coumadin is widely used in the elderly population. Despite its widespread use, little is known about its effect on the outcome of elderly traumatic brain-injured patients. This study was undertaken to describe the outcomes of such a cohort.

**Methods:** Clinical material was identified from a Level I trauma center prospective head injury database, and a database obtained from the American College of Surgeons Committee on Trauma Verification and Review Committee from 1999 to 2002. Both databases contain many relevant variables, including age, sex, Glasgow Coma Scale (GCS) score, mechanism of injury, Injury Severity Score, International Normalized Ratio (INR), computed tomography (CT) findings, operative procedure, time to operating room, complications, length of stay, and outcome at hospital discharge.

**Results:** For patients with GCS scores less than 8, average INR was 6.0, with almost 50% having an initial value greater than 5.0. Overall mortality was 91.5%. For the 77 patients with GCS scores of 13 to 15, average INR was 4.4. Overall mortality for this group was 80.6%. A subset of patients deteriorated to a GCS score of less than 10 just hours after injury, despite most having normal initial CT scans. Mortality in this group was 84%.

**Conclusions:** All patients on warfarin should have an INR performed, and a CT scan should be done in most anticoagulated patients. All supratherapeutically anticoagulated patients, as well as any anticoagulated patient with a traumatic CT abnormality, should be admitted for neurologic observation and consideration given to short term reversal of anticoagulation. Routine repeat CT scanning at 12 to 18 hours or when even subtle signs of neurologic worsening occur is a strong recommendation. A multiinstitutional, prospective trial using these guidelines would be a first step toward demonstrating improved outcomes in the anticoagulated patient population after head trauma.

**Key Words:** Traumatic brain injury, Anticoagulation, Outcomes

J Trauma. 2006;60:553–557.

Warfarin anticoagulation is employed with increasing frequency for the prevention of thromboembolic complications of atrial fibrillation, a history of deep venous thrombosis, extracranial vascular disease, and prosthetic cardiac valves. Because a majority of these medical problems are diseases of the elderly, as our population ages the use of anticoagulation is also expected to rise. The risk of spontaneous hemorrhage in association with anticoagulation has been well studied, with recent estimates placing the risk of fatal intracranial hemorrhage at 0.6 to 1.4% per year, major hemorrhage at 3%, and hemorrhage of any type at 9%. Less well studied, however, is the role premorbid anticoagulation may play in the outcome of head-injured patients. This is a potentially large and growing population, as head injury is the fifth leading cause of death in the elderly.

It has long been held that mortality and morbidity from traumatic brain injury (TBI) are significantly increased in anticoagulated patients. In spite of the impression that this clinical scenario is increasingly prevalent in the geriatric population, outcomes data are lacking. Such data has potential significance and practical importance in the evaluation and management of these patients.

The present study was undertaken to determine severity of head injury in anticoagulated geriatric patients and to determine the effect of anticoagulation, if any, on outcome.

**METHODS**

Clinical material was identified from two independent databases: Level I trauma center prospective TBI database and a database of prospectively identified variables selected through chart reviews undertaken by the American College of Surgeons Committee on Trauma Verification and Review Committee (VRC) in the course of visits for trauma center consultations or verifications. Both databases span the years 1999 through 2002.

Variables resident in both databases included age/sex, Glasgow Coma Scale (GCS) score, mechanism of injury, International Normalized Ratio (INR), computerized tomographic (CT) scan findings, operative procedure (S), and outcome at hospital discharge.

Information in the Level I trauma center database also included Injury Severity Score (ISS), time to operating room for head injury (HI), complications, and length of stay.

From 1999 through 2002, the VRC performed 405 adult trauma center site visits. At each, reviewers varying in number from 2 to 5 routinely reviewed at least 10 charts each with case summaries appended to the final report. Consequently, during this time frame, approximately 4,000 charts were reviewed by team members. Forty-nine patients met the cri-
Criteria for database inclusion: concurrent warfarin therapy and documented minor closed head injury (GCS score 13–15).

During the same time frame, the Level I trauma center database included 110 TBI patients. Of these, 47 presented with GCS score less than or equal to 8, and 28 patients had GCS scores of 13 to 15.

RESULTS

For patients with GCS scores less than 8 (N = 49), demographic data and outcomes are presented in Table 1. The average age in this group was 65 years and contusions and acute subdural hematoma were the most frequent CT abnormalities. Average INR was 6.5 with almost 50% having an initial value greater than 5.0. Twenty-seven (55.1%) underwent craniotomy, of whom six (12.2%) survived to hospital discharge—all in vegetative condition or with severe disability. Overall mortality was 87.8%.

For the 77 patients with GCS scores of 13 to 15, demographic data and outcomes are presented in Table 2. The average age in this group was 68 years and fall was the most common injury mechanism (67%). An INR was obtained in 57% with an average value of 4.4 and values greater than 3.0 in 47%.

Twenty patients were evaluated and sent home from the emergency department. Of these, 35% had CT scans, all of which were normal. Eighteen of these patients returned to the emergency department and were subsequently diagnosed with a significant traumatic intracranial abnormality; two patients died at home, one with autopsy-confirmed acute subdural hematoma. The overall mortality in these 20 patients was 88.8%.

Forty-five patients were admitted for observation for the HI and/or treatment of other injuries. CT scans were obtained before admission in 70%, with only four showing any traumatic intracranial abnormality—three contusions and one traumatic subarachnoid hemorrhage. Within 8 to 18 hours of injury (mean 12 hours), 80% deteriorated to a GCS score of less than 10 with the following CT abnormalities: acute subdural hematoma in 31%, contusion in 20%, intracerebral hemorrhage in 20%, and mixed lesions in 29%. Mortality in this group was 84%.

Twelve patients presented within hours or days of injury with neurologic findings of an intracranial mass and CT evidence of a significant traumatic intracranial abnormality. All underwent emergent craniotomy with a resultant mortality of 83.3%.

Overall mortality for the entire group of 77 minor head injury patients was 80.6%.

DISCUSSION

The use of anticoagulation for a multitude of medical diagnoses appears to be gaining popularity and is especially prevalent in those over 65 years of age. Given that trauma is the fifth leading cause of death in this age group, with TBI from falls an increasingly common occurrence, it is highly likely that emergency physicians, trauma surgeons, and neurosurgeons will be confronted with the clinical scenario of a TBI in an anticoagulated patient on a regular basis.

### Table 1

Demographic Data, Evaluation Results and Outcomes in Anticoagulated Patients with Severe Traumatic Brain Injury

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level I Database</th>
<th>ASCOT VRC Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Age range, years (average)</td>
<td>32–93 (65)</td>
<td>35–95 (74)</td>
</tr>
<tr>
<td>CT scan in emergency department (abnormal)</td>
<td>100% (100%)</td>
<td>77% (10%)</td>
</tr>
<tr>
<td>Admission</td>
<td>61%</td>
<td>57%</td>
</tr>
<tr>
<td>International Normalized Ratio range (average)</td>
<td>2.9–9.5 (4.6)</td>
<td>1.8–9.0 (4.7)</td>
</tr>
<tr>
<td>Time to deterioration (GCS &lt;10), hours (average)</td>
<td>8–18 (12)</td>
<td>81%</td>
</tr>
<tr>
<td>Surgery</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Mortality</td>
<td>89%</td>
</tr>
<tr>
<td>Vegetative</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Good recovery</td>
<td>4%</td>
<td>22%</td>
</tr>
</tbody>
</table>

### Table 2

Demographic Data, Evaluation Results and Outcomes in Anticoagulated Patients with Minor Traumatic Brain Injury

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level I Database</th>
<th>ASCOT VRC Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td>Age range, years (average)</td>
<td>40–75 (63)</td>
<td>35–95 (74)</td>
</tr>
<tr>
<td>Computed tomography scan in emergency</td>
<td>43% (17%)</td>
<td>77% (10%)</td>
</tr>
<tr>
<td>department (abnormal)</td>
<td>Admission</td>
<td>61%</td>
</tr>
<tr>
<td>International Normalized Ratio range (average)</td>
<td>2.9–9.5 (4.6)</td>
<td>1.8–9.0 (4.7)</td>
</tr>
<tr>
<td>Time to deterioration (GCS &lt;10), hours (average)</td>
<td>8–18 (12)</td>
<td>81%</td>
</tr>
<tr>
<td>Surgery</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Mortality</td>
<td>89%</td>
</tr>
<tr>
<td>Vegetative</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Good recovery</td>
<td>4%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Various studies have documented that anticoagulation is associated with a risk of spontaneous intracranial hemorrhage of up to 1% per year; the intensity of anticoagulation is a highly significant predictor of bleeding risk, and the response to warfarin is exaggerated with advancing age.

Several authors have linked increased risk of intracranial hemorrhage to abnormally prolonged prothrombin times (PT). Hylek in 1994 suggested that the rate of intracranial hematoma in the population is equal to an inherent baseline risk multiplied by the intensity of anticoagulation, finding a doubling of risk with each 0.5 increase in PT.

These clinical observations taken singularly or in combination would appear to support concerns that even a seemingly trivial TBI in an anticoagulated patient might significantly increase the risk of morbidity and mortality. However, the literature to date is divided. Even though there are a number of published reports studying this issue, findings as well as recommendations regarding clinical management have been widely divergent.

Although it has been intuitively held that severe TBI (GCS score <8) in the setting of premorbid anticoagulation is a fatal combination, no prior published studies could be found specifically addressing this issue. The findings of the present study would appear to support such clinical intuition—overall mortality greater than 90% and mortality greater than 80%, even with aggressive neurosurgical treatment. However, the significance of the seemingly excessive mortality must be questioned, considering the average age of this study group (79 years).

Age has consistently proven to be one of the most sensitive and reliable predictors of outcome from TBI. Patients over 65 years of age will have a mortality rate twice that of patients under 65 years, even when matched for GCS score and intracranial pathology. This is the likely reason that more attention has been focused on minor TBI (GCS score 13–15) anticoagulated patients in attempts to define the scope of the problem and establish guidelines for acute management issues such as CT scanning, hospital admission, and reversal of anticoagulation.

Published reports began appearing in the mid-1990s in an attempt to address this issue. In 1995, Saab10 raised significant concern reporting on two patients, both over 65 years old with fall as a mechanism of TBI. One patient deteriorated from GCS score of 15 to 5 from an intracerebral hematoma (ICH) and died. Based on this limited data, recommendations were made to admit all anticoagulated minor TBI patients, check, “correct” overly prolonged INRs, and to maintain a low threshold for CT scanning. The following year, Volans11 using three personal cases and reviewing eight cases collected from literature reports, developed a theoretical risk index for intracranial hemorrhage in anticoagulated patients with minor TBI. Utilizing the population base prevalent to anticoagulation, he estimated the risk of a posttraumatic intracranial abnormality in an anticoagulated patient was calculated to be increased tenfold, given the same clinical presentation, as he did not allow for routine evaluations. However, in the 38 patients where CT was recommended in every anticoagulated patient after TBI by Li13 based on a retrospective review of 144 elderly patients. Utilizing information from large cohort studies, a 4% incidence of intracranial injury was anticipated while a 7% incidence was found. Although GCS scores were not reported, patients presented with dizziness, headache, or no symptoms. Mean INR was 2.1 both in patients with and without an abnormal CT. No outcome information was provided.

In a large retrospective study of 2,142 patients taken from the Pennsylvania Trauma System Registry, Wojcik et al.14 identified 1,986 patients with preinjury anticoagulation. No statistically significant difference in outcome was found between the Warfarin and no anticoagulation patients in both the TBI and non-TBI groups. Likewise, when stratified by GCS score (3–8, 9–12, 13–15), there was no difference in mortality between the anticoagulated and nonanticoagulated groups. Mean GCS score was 14.13, indicating predominantly minor TBI was studied. INR data were not available from the registry, thus making it impossible to determine the degree of anticoagulation in these patients, if at all.

The triad of anticoagulation, age over 65, and TBI was considered lethal by Karni et al.15 on retrospective review of 278 patients with TBI and CT documented intracranial hemorrhage. Sixteen of these patients were on warfarin with an average INR of 3.0. Thirty-day mortality was 50% in this group compared with 20% in a matched nonanticoagulated cohort. In those with INR greater than 3.5, mortality was 75%. However, average GCS score in this study was 11, with a median age of 78. Thus, a confounding effect of age on outcome after more severe HI cannot be excluded.

Mina et al.16 found a four- to fivefold increased risk of mortality from TBI in anticoagulated patients. Ten percent of 380 anticoagulated patients admitted to a Level I trauma center with intracranial injuries were identified. Of these, 12 were on warfarin, the rest on antiplatelet medications. Mean GCS score was 11.8 and average INR was 2.37. Compared
with a matched control group of anticoagulated patients without TBI, mortality was 38% versus 8% (p = 0.006). Mortality was 33% in those on warfarin and 50% in patients on aspirin.

Although all the previously cited studies primarily focus on “minor” TBI, only two provide a specific breakdown by GCS score. Thus, the present study provides the most comprehensive information to date on patients with GCS scores of 13 to 15; the results appear to clarify and amplify concerns expressed in prior studies. Interpretation of this study is, however, hampered by lack of a matched control. Nevertheless, two concerning findings dominate. The majority of patients were supratherapeutically anticoagulated and, of those undergoing CT on initial presentation, only slightly more than 30% had any evidence of traumatic intracranial abnormality.

It has been noted that advancing age appears to exaggerate the anticoagulant effect of warfarin. However, many other confounding factors may be involved. The most well known are concomitant medications that may potentiate the anticoagulant effects of Warfarin. Liver disease, hypoproteinemia, and a diet deficient in vitamin K may all result in increased anticoagulant response. Patient compliance with warfarin dosing regimens would obviously effect the degree of anticoagulation. How or whether these factors may have been operative in the supratherapeutically anticoagulated patients in this study cannot be determined. However, the established relationship between anticoagulation intensity and risk of intracranial hemorrhage cannot be overlooked given the findings in this study.

The “delayed” appearance of traumatic intracranial abnormalities documented in this study is of concern. Delayed appearance of intracranial hematomas is well recognized. Delayed traumatic intracerebral hematomas were originally described by Bollinger et al. in 1891. Mortality associated with this entity ranges from 50 to 75% with a high number of surviving patients having a poor outcome. Delayed acute subdural hematoma makes up approximately 0.5% of operatively treated acute subdural and are typically associated with other parenchymal lesions. Although delayed appearance of intracranial hematomas most frequently occurs in the setting of severe TBI, they have been associated with coagulopathy.

Conversely, because the majority of patients in this study did not have a CT until clinical deterioration, they may have harbored an intracranial hemorrhage that “enlarged” secondary to underlying anticoagulation. It is well known that minor TBI patients have a clear risk of significant pathologic CT scan findings—up to 10% with GCS scores of 15; 20% with GCS scores of 14; and 35% with GCS scores of 13. Although a number of guidelines have been developed for the clinical approach to the evaluation and treatment of minor TBI, our findings would indicate a need to significantly revise these in a setting of anticoagulation. As part of the initial evaluation, all patients on warfarin should have their INR checked. A CT scan should be obtained in all anticoagulated patients presenting with GCS scores of 13 or 14, given the relatively high risk of potential traumatic intracranial abnormalities with these GCS scores, as well as in all patients with GCS scores of 15 who are supratherapeutically anticoagulated because of the known increased bleeding risk with increasing levels of anticoagulation. All supratherapeutically anticoagulated patients, as well as any anticoagulated patient with a traumatic CT abnormality, should be admitted for neurologic observation and consideration given to short term reversal of the warfarin. Supratherapeutic anticoagulation should at least be reversed to therapeutic levels.

Strong consideration must be given to routine repeat CT scanning at 12 to 18 hours or when even subtle signs of neurologic worsening occur. The data in this study indicates that when neurologic decline occurs, it is precipitous and devastating. A multi-institutional, prospective trial using these guidelines would be a first step toward demonstrating improved outcomes in the anticoagulated patient population after TBI.

REFERENCES