

# Neuroanesthesiology Update 2010

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**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

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## 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.<sup>1</sup> In this context, accreditation and standardization of neuroanesthesiology fellowship training programs have again

come under discussion.<sup>2–5</sup> Mashour et al<sup>6</sup> 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 al<sup>6</sup> report.

### Clinical Trends

Understanding the trends in neurosurgical procedures and utilization is critical to both the training and allocation of anesthesia providers. Hughey et al<sup>7</sup> analyzed neurosurgical utilization data from the Nationwide Inpatient Sample<sup>8</sup> (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

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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.<sup>9</sup> 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 of 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 neurosurgical (or neurosurgical-like) cases performed in 2007.

Although implantation of DBSs represent a small fraction of neurosurgical 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 al<sup>10</sup> 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.<sup>11–13</sup> 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  $37.5 \pm 14.6$  and  $38.7 \pm 13.7$  (mean  $\pm$  SD) in the surgery and medical management groups, respectively. At 1 year, scores were  $32.5 \pm 15.8$  and  $38.1 \pm 13.5$ , 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), post-operative 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 al<sup>14</sup> 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, prognathism, 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,<sup>15</sup> 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 acromegalics.<sup>16</sup> 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.<sup>17</sup> 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

difficulty, although this technique has not been validated in acromegalic patients. Sharma et al<sup>18</sup> prospectively assessed both Mallampati score and ULBT in 127 patients undergoing pituitary surgery, of which 64 patients had acromegaly. Two patients in the acromegaly group underwent elective awake fiberoptic intubation and were excluded from data analysis. In the remaining patients, the Cormack and Lehane grade, at the time of laryngoscopy, was used to define difficulty with laryngoscopy. There are 4 Cormack and Lehane grades: grade 1, most of glottis visualized; grade 2, only posterior portion of the glottis is visualized; grade 3, only epiglottis but no glottic structures are visualized; and grade 4, neither epiglottis nor the glottis is visualized. Patients with a Cormack and Lehane grade 3 or 4 were considered to pose difficulty with laryngoscopy. Tracheal intubation was considered difficult if more than 2 attempts were required involving use of other equipment (eg, laryngoscope blade change, bougie, fiberoptic bronchoscope). Airway assessment and management data from the Sharma et al research are given in Table 1. Thirty-eight (61%) and 9 (14%) acromegalics had an airway assessment predicting airway management difficulty based on the Mallampati score (III or IV = difficult) or ULBT (grade 3 = difficult), respectively. Twenty-three (37%) and 12 (19%) non-acromegalics had an airway assessment predicting airway management difficulty based on the Mallampati score or ULBT, respectively. However, upon direct laryngoscopy, significantly more patients in the acromegaly group [15 (24%)] had a Cormack and Lehane grade view of  $\geq 3$  versus the non-acromegaly group [6 (10%);  $P = 0.01$ ]. Difficulty with tracheal tube placement was encountered in 7 (11%) and in 2 (3%) acromegalics and non-acromegalics, respectively ( $P = 0.10$ ). For the Mallampati system, the sensitivity and specificity for predicting a difficult airway was 67% and 40% in acromegalics and 83% and 68% in non-acromegalics. The sensitivity and specificity of the ULBT at predicting airway management difficulty was 27% and 89% in acromegalics and 67% and 86% in non-acromegalics. The area under the receiver operating characteristic curve

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).<sup>19</sup> 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.<sup>20</sup> 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.<sup>21,22</sup> To confirm that the pressure recorded by the neuroendoscope correlates with ICP, Salvador et al<sup>23</sup> 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

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

	Acromegaly Group (n = 62)		Non-acromegaly Group (n = 63)	
	CL 1 or 2	CL 3 or 4	CL 1 or 2	CL 3 or 4
Mallampati class				
I or II	19	5	39	1
III or IV	28	10	18	5
Upper lip bite test grade				
1 or 2	42	11	49	2
3	5	4	8	4
Difficult airway management		7		2

Data represents the number of patients in each group.

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.

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CL indicates Cormack and Lehane grade.

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 CPP may not be the only driving force of cerebral blood flow (CBF).<sup>24–28</sup> Currently, it is unclear whether changes in posture influence cerebral perfusion enough to lead to a stroke. Murphy et al<sup>29</sup> studied changes in regional cerebral oxygen saturation (rSO<sub>2</sub>) [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 rSO<sub>2</sub> values (only directly observed by a research assistant), if a cerebral desaturation event (defined as a decrease in rSO<sub>2</sub> by >20% of baseline value or a decrease to <55% for >15s) 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 CO<sub>2</sub> 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 suggests 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 rSO<sub>2</sub> 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. Sloan<sup>30</sup> 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 cm<sup>3</sup>. 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<sup>31,32</sup>). Specifically, the incidence and volume of air was 42% and 87 ± 91 cm<sup>3</sup> in patients with either a shunt or a drain and 42% and 71 ± 79 cm<sup>3</sup> 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 cm<sup>3</sup> 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 (PaCO<sub>2</sub>) are important homeostatic mechanisms for the regulation of CBF. Induced changes in blood pressure and PaCO<sub>2</sub> 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 PaCO<sub>2</sub> can be attenuated by the presence of a brain tumors<sup>33,34</sup>; however, whether the integrity of these systems is restored after tumor resection remains to be elucidated. Accordingly, Sharma et al<sup>35</sup> evaluated the effect of tumor resection on parameters thought to be reflective of autoregulation of CBF and responsiveness to PaCO<sub>2</sub> in 35 patients having supratentorial tumor resection. Cerebrovascular responsiveness to blood pressure changes was assessed by the transient hyperemic response when the ipsilateral common carotid artery is compressed for 10s 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  $V_{mca}$  after the release of compression divided by the  $V_{mca}$  before compression. Under normal conditions (ie, intact autoregulation), the THRR has the value  $1.35 \pm 0.09$  as one would expect an increase in  $V_{mca}$  after the release of compression due to the presence of compression-induced cerebral vasodilation.<sup>36</sup> To assess reactivity to changes in  $PaCO_2$ , patients were asked to spontaneously hyperventilate to achieve a 10 mm Hg decrease in  $PaCO_2$  and  $CO_2$  reactivity was estimated by:

$$100 - (100 \times V_{mcaf} / V_{mcai}) / (PaCO_{2i} - PaCO_{2f})$$

where  $V_{mcai}$  and  $V_{mcaf}$  are the  $V_{mca}$  values obtained before and after hyperventilation, respectively, and  $PaCO_{2i}$  and  $PaCO_{2f}$  are values of  $PaCO_2$  obtained before and after hyperventilation, respectively. A normal value for  $CO_2$  reactivity assessed by this method is  $2.74 \pm 1.0\%/mmHg$ .<sup>37</sup> The investigators found no difference between preoperative and postoperative (obtained 6 to 24 h after resection) THRR ( $1.27 \pm 0.10$  vs.  $1.30 \pm 0.12$  for preoperative and postoperative values, respectively;  $P = 0.11$ ) or the calculated reactivity of the cerebral vasculature to changes in  $CO_2$  ( $3.41 \pm 0.46\%/mmHg$  vs.  $3.60 \pm 0.63\%/mmHg$  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 THRR cutoff criteria to define impairment, these 7 patient all had impairment of blood pressure reactivity postoperatively (THRR preoperative and postoperative were  $1.07 \pm 0.02$  vs.  $1.06 \pm 0.01$ , respectively;  $P = 0.18$ ) but intact reactivity to  $CO_2$  ( $3.39 \pm 0.49\%/mmHg$  vs.  $3.67 \pm 0.24\%/mmHg$  for preoperative and postoperative values, respectively;  $P = 0.17$ ). Although the investigators also did not report the criteria used to define impairment of  $CO_2$  reactivity, when comparing patients with and without impairment of blood pressure reactivity, the only 2 factors associated with impairment were a larger tumor size ( $100 \pm 32\text{ cm}^3$  vs.  $40 \pm 8\text{ cm}^3$ ;  $P = 0.002$ ) 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 al<sup>38</sup> that showed the utility of a novel device for intraoperative monitoring of the cerebral microcirculation. The  $O_2C$  device (oxygen-to-see device, LEA Medizintechnik, Giesen, Germany) allows for the simultaneous assessment of surrogate parameters of the cerebral microcirculation such as regional capillary venous blood flow,  $rSO_2$ , and regional hemoglobin concentration (based on photospectrometry and laser Doppler flowmetry measurements).

Although  $PaCO_2$  is an important factor modulating cerebral vascular resistance, monitoring of end-expired (tidal) carbon dioxide ( $ETCO_2$ ) is often used intraoperatively as a surrogate marker of  $PaCO_2$ . Although changes in minute ventilation are used to control  $ETCO_2$ , and thus

$PaCO_2$ , cardiac output variations can impact the relationship between  $ETCO_2$  and  $PaCO_2$ . 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  $PaCO_2$  and  $ETCO_2$  is not well understood. Luostarinen et al<sup>39</sup> reported a prospective analysis of the relation between blood pressure and  $PaCO_2$  to  $ETCO_2$  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  $PaCO_2$  and  $ETCO_2$  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  $ETCO_2$  among groups ( $31.6 \pm 3.7$  mm Hg,  $31.2 \pm 2.9$  mm Hg,  $31.7 \pm 3.7$  mm Hg, and  $32.3 \pm 2.9$  mm Hg, respectively;  $P = 0.811$ ) during the conduct of the study,  $PaCO_2$  was significantly higher with greater decreases in blood pressure from baseline awake values ( $35.7 \pm 4.5$  mm Hg,  $36.3 \pm 3.8$  mm Hg,  $38.0 \pm 4.4$  mm Hg, and  $39.3 \pm 2.8$  mm Hg, respectively;  $P = 0.036$ ) despite no differences in other perioperative 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  $ETCO_2$  as a surrogate marker for  $PaCO_2$ .

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.<sup>40-42</sup> Qiao et al<sup>43</sup> 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:

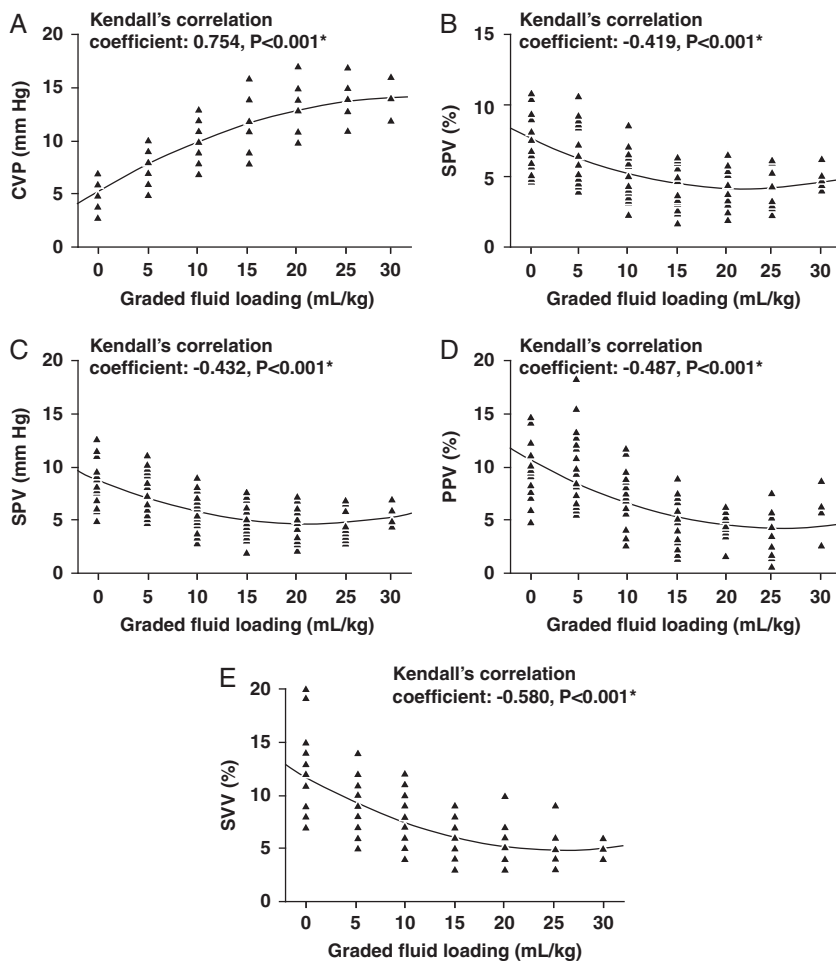
1.  $SPV$  (mm Hg) =  $SBP_{max} - SBP_{min}$ , where  $SBP_{max}$  indicates maximum systolic blood pressure and  $SBP_{min}$  indicates minimum systolic blood pressure associated with the respiratory cycle.
2.  $SPV$  (%) =  $200 \times (SBP_{max} - SBP_{min}) / (SBP_{max} + SBP_{min})$ ,
3.  $PPV$  (%) =  $200 \times (PP_{max} - PP_{min}) / (PP_{max} + PP_{min})$  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,



**FIGURE 1.** The correlation between graded fluid loading and hemodynamic variables. A, CVP (mm Hg); (B) SPV (%); (C) SPV (mm Hg); (D) PPV (%); and (E) SVV (%). During surgery, increasing amounts of fluid were infused, shown on the x axis, with simultaneous measurement of the variables, which are shown on the y axis of separate panels. CVP indicates central venous pressure; PPV, pulse pressure variation; SPV, systolic pressure variation; SVV, stroke volume variation. Adapted with permission from *J Neurosurg Anesthesiol.* 2010;22:316–322.

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).<sup>44-47</sup> 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<sup>48</sup> 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.<sup>49</sup> Repetitive tetanic stimuli can lead to fatigue of muscles and a decrease in motor responses,<sup>50</sup> although the duration of potentiation was previously unknown. Yamamoto et al<sup>51</sup> evaluated posttetanic motor-evoked potential recording in patients having spine surgery to determine the impact of fatigue and the duration of potentiation. Posttetanic motor-evoked potentials were elicited by applying a 50 mA tetanic stimulus for 5 s to the posterior tibial nerve immediately after which a transcranial electric stimulation was performed and responses were recorded in the contralateral abductor hallucis muscle during a standardized anesthetic consisting of infused propofol and fentanyl. To determine whether

there was a degradation of responses with multiple stimuli, posttetanic motor-evoked responses were elicited 10 times with an interval of 10 s or 60 s between each stimulation. Although no suppression of subsequent waveforms was found with a 60 s delay between stimuli, when a delay of only 10 s was allowed, a significant decrease in recorded waveform intensity was noted after 8 stimulation cycles, with a maximum decrease to about 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.<sup>52</sup> 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<sup>53</sup> 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-remifentanyl anesthetic and without neuromuscular blocking drugs. For awake craniotomies, the mean propofol and remifentanyl doses were  $125 \pm 35 \mu\text{g}/\text{kg}/\text{min}$  and  $0.11 \pm 0.03 \mu\text{g}/\text{kg}/\text{min}$  during surgical opening; however, only remifentanyl was administered during mapping and closure at doses of  $0.05 \pm 0.03 \mu\text{g}/\text{kg}/\text{min}$  and  $0.07 \pm 0.06 \mu\text{g}/\text{kg}/\text{min}$ , respectively. For asleep mapping, propofol and remifentanyl doses were  $107 \pm 30 \mu\text{g}/\text{kg}/\text{min}$  and  $0.11 \pm 0.08 \mu\text{g}/\text{kg}/\text{min}$  during opening,  $63 \pm 28 \mu\text{g}/\text{kg}/\text{min}$  and  $0.11 \pm 0.05 \mu\text{g}/\text{kg}/\text{min}$  during mapping, and  $93 \pm 30 \mu\text{g}/\text{kg}/\text{min}$  and  $0.11 \pm 0.09 \mu\text{g}/\text{kg}/\text{min}$  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 intraoperative complication rate in patients who underwent asleep mapping (41%) versus those having awake mapping (57%) ( $P < 0.01$ ), although many intraoperative 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/remifentanyl-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.<sup>54</sup> 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.<sup>55,56</sup> As in animal models, dexmedetomidine reduces CBF in humans<sup>57,58</sup>; however, data from one investigation showed that in humans, dexmedetomidine produces a parallel decrease in cerebral metabolism.<sup>59</sup> Drummond and Sturaitis<sup>60</sup> 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  $\mu\text{g}/\text{kg}/\text{h}$ ). After attaining stable blood pressure and heart rate with constant anesthetic concentrations, dexmedetomidine was administered as a 1  $\mu\text{g}/\text{kg}$  bolus over 5 to 10 minutes followed by an infusion at 0.5 to 0.7  $\mu\text{g}/\text{kg}/\text{h}$  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  $\alpha$ 1-adrenergic receptor agonist, is a commonly used pressor in the perioperative period. Some data suggest that acidosis may attenuate the vasoconstrictive response of phenylephrine.<sup>61</sup> To determine whether the pressor response to phenylephrine is affected by the alkalosis associated with hypocapnia, Schwartz and Adams<sup>62</sup> measured the amount of phenylephrine required to increase systemic blood pressure by 33% and 66% in 6 monkeys receiving isoflurane anesthesia during both normocapnia ( $\text{PaCO}_2$ , 35 to 44 mm Hg) or hypocapnia ( $\text{PaCO}_2$ , 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%,  $2.4 \pm 0.9 \mu\text{g}/\text{kg}/\text{min}$  and  $1.7 \pm 0.9 \mu\text{g}/\text{kg}/\text{min}$  phenylephrine were required in the normocapnia and hypocapnia groups, respectively ( $P < 0.05$ ). To increase systemic blood pressure by 66%,  $4.9 \pm 2.4 \mu\text{g}/\text{kg}/\text{min}$  and  $3.1 \pm 1.7 \mu\text{g}/\text{kg}/\text{min}$  phenylephrine were required in the normocapnia and hypocapnia groups, respectively ( $P < 0.05$ ). The investigators hypothesize that either an alkalosis-induced increase in  $\text{Ca}^{+2}$  currents in vascular smooth muscle, or an increase in the ionized fraction of phenylephrine leading to an increased proportion of molecules interacting with the  $\alpha$ 1-adrenergic receptors, may account for these effects.<sup>63</sup> 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.<sup>64-66</sup> Currently available intravenous antihypertensive medications are limited by either a long half-life (eg, labetalol), 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<sup>67</sup> 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 phenylephrine). 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 al<sup>68</sup> 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  $\mu$ -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 to 10). 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 Sebeo<sup>69</sup> 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,<sup>70</sup> nitrous oxide use,<sup>71</sup> postcraniotomy pain,<sup>72</sup> thromboprophylaxis in neurosurgical patients,<sup>73</sup> antiepileptic drug use,<sup>74</sup> neuroendoscopic procedures,<sup>75</sup> cerebral oximetry,<sup>76</sup> and ischemic optic neuropathy.<sup>77</sup>

## INTRACRANIAL HEMORRHAGE

### General Management Issues

In 2005, the results of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) were published.<sup>78,79</sup> 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.<sup>80-82</sup> Cerebroprotective drugs, such as thiopental, may attenuate the adverse effect of temporary clipping.<sup>83</sup> Hindman et al<sup>84</sup> 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,  $\leq 10$  min, 11 to 19 min,  $\geq 20$  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  $\leq 10$  minutes, 11 to 19 minutes, and  $\geq 20$  minutes, respectively ( $P < 0.001$ ). Despite the greater use of neuroprotective drugs in

patients with longer temporary clip durations (33%, 53%, and 52% for durations of  $\leq 10$  min, 11 to 19 min, and  $\geq 20$  min, respectively;  $P < 0.001$ ), postoperative cerebral infarction was more common in patients with an occlusion duration of  $\geq 20$  minutes (45%) versus  $\leq 10$  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  $\leq 10$  minutes, those with a duration of  $\geq 20$  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 coiling involves less external manipulation of the major cerebral arteries, thus coiling may reduce the risk of vasospasm relative to clipping. Current data either support no difference in the incidence of vasospasm between techniques<sup>85,86</sup> or a greater risk in patients who have undergone surgical clipping.<sup>87,88</sup> Dumont et al<sup>89</sup> performed a post hoc analysis of data from the Clazosentan to Overcome Neurologic Ischemia and Infarction After SAH trial<sup>90</sup> 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 on 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.<sup>91,92</sup> 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.<sup>93</sup> 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<sup>94</sup> reviewed the records of 34 consecutive patients with SAH who underwent simultaneous monitoring of ICP, brain tissue oxygen partial pressure (PbrO<sub>2</sub>), 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  $\leq 10$  g/dL in 54% of samples. Values for PbrO<sub>2</sub> indicating cerebral hypoxia (PbrO<sub>2</sub>  $< 15$  mm Hg) were more common in patients with a hemoglobin  $\leq 9$  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  $\leq 9$  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  $\leq 9$  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,<sup>95</sup> 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,<sup>96</sup> patients with SAH were randomized to a target hemoglobin of either 10.0 to 11.5 g/dL or  $> 11.5$  g/dL. Their data suggested a trend toward reduced cerebral infarctions and improved functional neurological status in patients in the higher hemoglobin group.

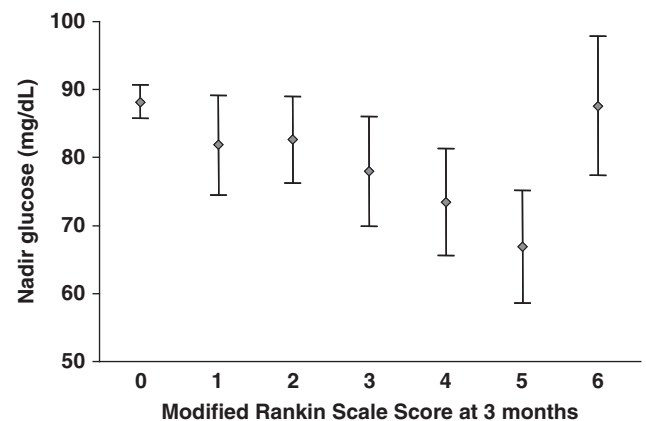
Aberrations in serum glucose concentration in the setting of neuronal insult can have a profound impact on overall outcome. Studies in both animal models and humans have shown that elevated serum glucose concentration is associated with poor outcome after ischemic brain injury.<sup>97-100</sup> However, attempts to strictly control glycemia increase the risk of hypoglycemic episodes.<sup>101,102</sup> 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.<sup>103</sup> Helbok et al<sup>104</sup> 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  $< 0.7$  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  $148 \pm 32$  mg/dL (obtained 2 h before onset of metabolic crisis) to  $124 \pm 34$  mg/dL at the onset of metabolic crisis ( $P < 0.001$ ). Similarly, the lactate-to-pyruvate ratio increased from  $45 \pm 16$  (obtained 2 h before onset of metabolic crisis) to  $54 \pm 17$  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 (OR = 2.8; CI, 1.7-4.5;  $P < 0.001$ ) and a  $> 25\%$  increase in lactate-to-pyruvate ratio (OR = 1.6; 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<sup>105</sup> 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  $< 40$  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 ( $78 \pm 12$  mg/dL vs.  $84 \pm 16$  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 ( $81 \pm 15$  mg/dL vs.  $87 \pm 16$  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.

definitive effect of magnesium sulfate in this setting.<sup>106–110</sup> In addition, magnesium may reduce headache and subsequent analgesic requirements associated with SAH.<sup>111</sup> 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.<sup>112,113</sup> Unlike many earlier investigations in which magnesium sulfate was administered by a set dose, Westermaier et al<sup>114</sup> 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  $140 \pm 51$  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 delayed ischemic neurological deficits (ie, new focal deficits or neurological deterioration without other identifiable causes such as rebleeding, seizures, electrolyte disturbances, or hydrocephalus) was similar between groups (17% vs. 28% for the magnesium and placebo groups, respectively;  $P = 0.150$ ). 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<sup>115</sup> 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,<sup>114</sup> 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<sup>116</sup> performed a meta-analysis of those prospective studies. The investigators identified 6 investigations<sup>108–110,117–119</sup>; however, the data of Wong et al<sup>115</sup> and Westermaier et al<sup>114</sup> were not included in this analysis due to the later dates of publication. There was some variability among the investigations with respect to primary endpoints and magnesium administration protocols. 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<sup>120</sup> 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 neurological 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 currently few data describing the systemic hemodynamic consequences of this intervention.<sup>121</sup> Schmidt et al<sup>122</sup> retrospectively reviewed hemodynamic data, vasopressor requirements, and systemic complications (which may be attributed to systemic hypotension or vasopressors) 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 intra-arterial 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.<sup>123,124</sup> The trace element selenium is a cofactor for antioxidant enzymes responsible for reducing peroxides (eg, glutathione peroxidase).<sup>125</sup> In

a rabbit model of SAH and vasospasm, Kocaogullar et al<sup>126</sup> 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<sup>127</sup>) 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  $\mu\text{g}/\text{kg}/\text{d}$ . This dose, if given for many days, can become toxic, and a single dose of 5 mg can be lethal.<sup>128</sup> As such, if this therapy is ever applied to humans, a much lower dose than that used in the Kocaogullar et al<sup>126</sup> 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.<sup>129-133</sup> 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<sup>134</sup> 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<sup>135</sup> 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 1s of expected asystole, 1 mg of adenosine should be administered. For example, to attain 30s 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.<sup>136</sup> However, these data, reported in 1998, preceded the current advances in medical therapy.<sup>137,138</sup> As such, the medical versus invasive treatment debate must continue

to take into account evolving treatment options.<sup>139,140</sup> 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.<sup>141–146</sup> 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).

CREST<sup>147,148</sup> 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 between groups; however, patients having stenting were more likely to suffer a stroke, and those having endarterectomy were more likely to experience myocardial infarction or cranial nerve injury (Table 2). At 4 years, there was no difference in the combined endpoint between groups. Although the incidence of stroke was initially more common after stenting (hazard ratio = 1.89; 95% CI,

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

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

Data reported as number within group (percentage).

Adapted with permission from *N Eng J Med*. 2010;363:11–23 and *Lancet*. 2010;375:985–997.

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.<sup>149</sup> 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 or restenosis were not reported in this study.

The ICSS<sup>150</sup> 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.<sup>151</sup> 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<sup>152</sup> 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 was \$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 anal-

ysis 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<sup>139</sup> (with an accompanying editorial by Adams<sup>140</sup>) in the December issue of the *Mayo Clinic Proceeding*. 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<sup>139</sup> and Adams<sup>140</sup> also emphasize the role that evolving medical treatment and reimbursement mechanisms will have on future choices in treating carotid artery atherosclerosis.

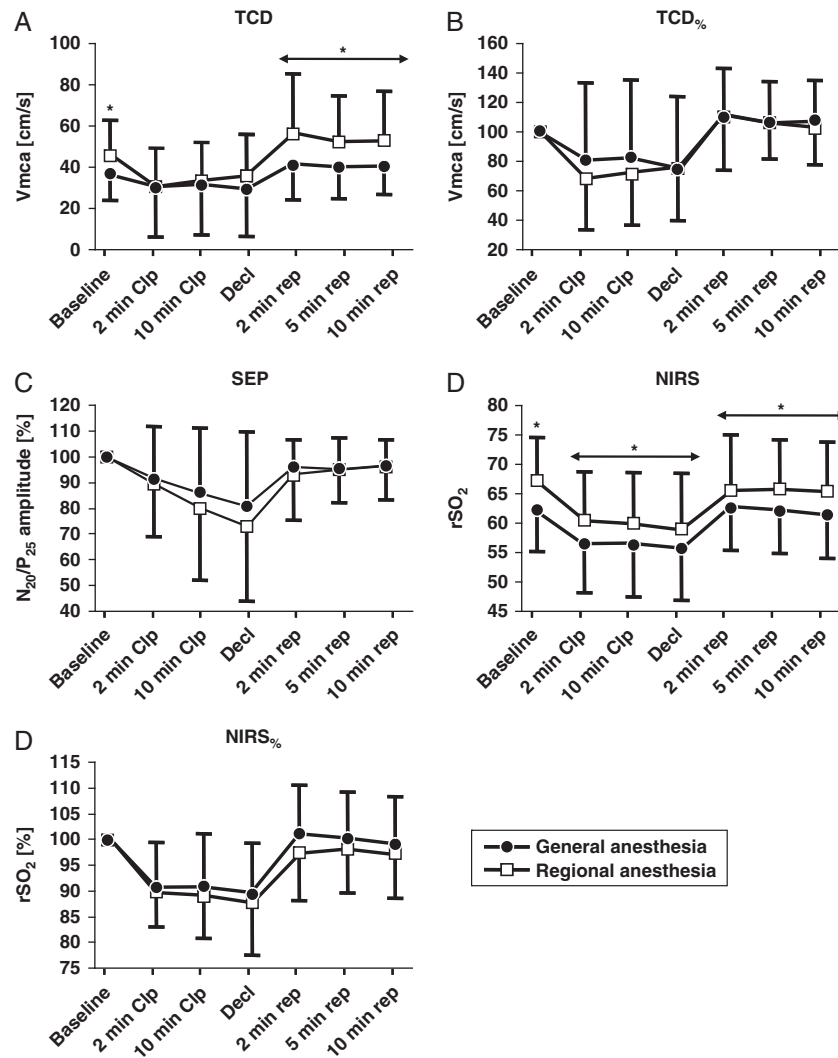
The application and design of distal protection devices, and their efficacy in preventing intraprocedural embolization of plaque, will likely have an important role in the future success and desirability of carotid stenting procedures. There currently exists no good-quality evidence to support the use of distal protection devices, and using stroke as an endpoint would require a large study population to identify benefit. Macdonald et al<sup>153</sup> 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 emboligenic 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<sup>154,155</sup>). 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.<sup>156–158</sup> 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<sup>159</sup> 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<sub>2</sub> 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<sub>MCA</sub>, 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 [ $52 \pm 20$  mm Hg and  $50 \pm 21$  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<sub>MCA</sub> from baseline ( $P = 0.795$ ,  $P = 0.885$ ), N20/P25 amplitude ( $P = 0.294$ ,  $P = 0.317$ ), or percentage change in rSO<sub>2</sub> ( $P = 0.177$ ,  $P = 0.166$ ) ( $P$  values given for unadjusted and after adjustment for MAP, respectively for linear regression analysis of data over the entire study period). Absolute V<sub>MCA</sub> 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. rSO<sub>2</sub> 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<sup>160</sup> 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



**FIGURE 3.** Course of neuro-monitoring parameters in awake patients (regional anesthesia) and in patients under sevoflurane/fentanyl anesthesia (general anesthesia). Values are given as mean  $\pm$  SD. TCD indicates transcranial Doppler sonography absolute blood flow velocity in the middle cerebral artery ( $V_{mca}$ ); TCD%, % change in  $V_{mca}$  compared with baseline (ie, preclamp value); SEP, % change in somatosensory evoked potential N20/P25 wave derived from the contralateral median nerve compared with baseline; NIRS, ipsilateral near-infrared spectroscopy-derived regional cerebral oxygen saturation ( $rSO_2$ ); NIRS%, % change in  $rSO_2$  versus baseline. \* $P < 0.05$  for values obtained in general versus regional groups at that time point. Baseline indicates before carotid clamp placement; 2 minutes Clp, 2 minutes after carotid clamp placement; 10 minutes Clp, 10 minutes after carotid clamp placement; Decl, carotid declamping; 2 minutes Rep, 2 minutes after restoration of perfusion (reperfusion); 5 minutes Rep, 5 minutes after restoration of perfusion; 10 minutes Rep, 10 minutes after restoration of perfusion. Adapted with permission from *J Neurosurg Anesthesiol.* 2010;22:288–295.

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<sup>161</sup> 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 al<sup>162</sup> 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 Schramm<sup>163</sup> 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.<sup>164</sup> 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 re-enforce 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

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

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).

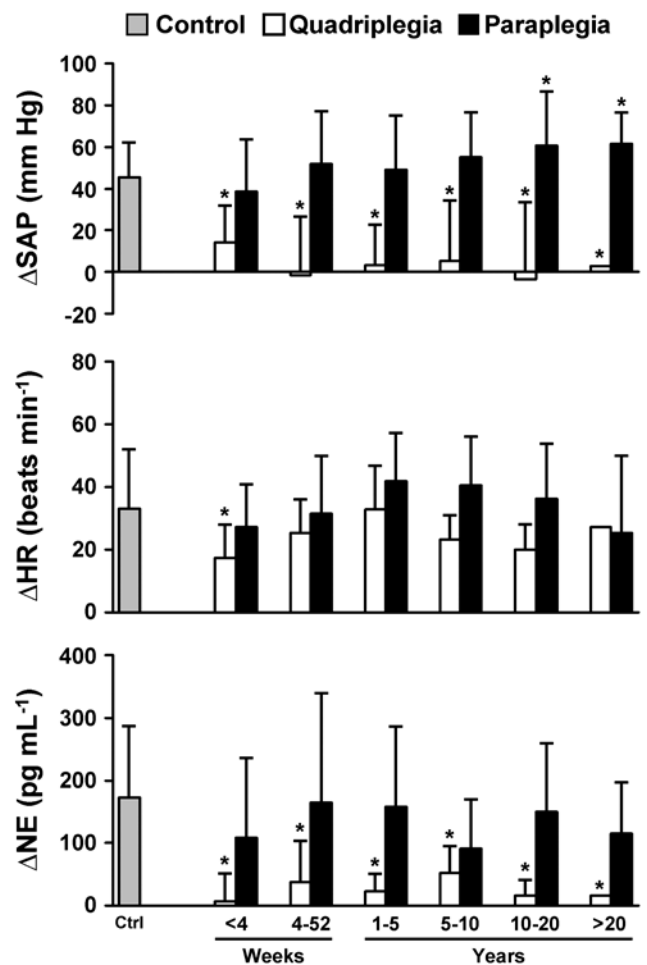
their data, but it was not clear whether any of the data in this investigation were subject to statistical analysis (we performed the statistical analysis of the categorical data shown in Table 3). Noting that this is an “observational study” does not obviate the need for formal statistical analysis, 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.<sup>165</sup> 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<sup>166</sup> prospectively assessed the impact of the level of spinal cord injury (ie, 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.<sup>167</sup> 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.<sup>168,169</sup> Hu et al<sup>170</sup> 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



**FIGURE 4.** Maximum increase from baseline of SAP ( $\Delta$ SAP), HR ( $\Delta$ HR), and plasma norepinephrine concentrations ( $\Delta$ NE) after tracheal intubation according to the time since spinal cord injury. Values are means with 1 standard deviation designated by error bars. Controls (Ctrl) are without spinal cord injury. Patients with quadriplegia all have complete lesions above C7. Patients with paraplegia all have complete lesions below T5. Time values represented on the x axis refer to time since spinal cord injury. \* $P < 0.05$  versus controls. Adapted with permission from *Br J Anaesth.* 2010;105:753–759.

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 occupation 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.<sup>171-174</sup> In addition, the preoperative administration of gabapentin to patients who are to undergo lumbar spine surgery reduces acute postoperative narcotic requirements<sup>175</sup>; however, these data are obtained from adult patients. Rusy et al<sup>176</sup> 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 ( $0.044 \pm 0.17$  vs.  $0.064 \pm 0.031$  mg/kg/h;  $P = 0.003$ ), and on postoperative day 2 ( $0.036 \pm 0.016$  vs.  $0.047 \pm 0.019$  mg/kg/h;  $P = 0.018$ ) with a trend toward reduced morphine requirement on postoperative day 1 ( $0.046 \pm 0.0160$  vs.  $0.055 \pm 0.017$  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 ( $2.5 \pm 2.8$  vs.  $6.0 \pm 2.4$ ;  $P < 0.001$ ) and on the morning after surgery ( $3.2 \pm 2.6$  vs.  $5.0 \pm 2.2$ ;

$P < 0.001$ ) 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 day 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.<sup>177,178</sup> 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<sup>179</sup> 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 mcg/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 ( $51 \pm 27$  mg morphine equivalents vs.  $67 \pm 44$  mg for placebo;  $P = 0.034$ ). Total narcotic consumption was reduced 48 hours after surgery in patients receiving ketamine ( $195 \pm 111$  mg morphine equivalents vs.  $309 \pm 341$  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;  $3.1 \pm 2.4$  vs.  $4.2 \pm 2.4$  for placebo;  $P = 0.026$ ) and lower daily opioid consumption (converted to mg/h of a continuous intravenous morphine infusion;  $0.8 \pm 1.1$  mg/h vs.  $2.8 \pm 2.4$  mg/h;  $P = 0.041$ ). Similarly, Amr<sup>180</sup> 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 et al<sup>181</sup> 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.<sup>182</sup> TENS also reduces postoperative narcotic requirements after abdominal and shoulder, but not knee, surgery<sup>183-185</sup>; 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<sup>184</sup> has utility after lumbar spine fusion, Unterrainer et al<sup>186</sup> 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 piritramid, 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 piritramid consumption ( $0.158 \pm 0.051$  mg/kg for 24 h) compared with those in whom the stimulation was initiated after surgery ( $0.221 \pm 0.066$  mg/kg;  $P = 0.011$ ). Those in whom the TENS unit was never

activated had the highest 24 hours piritramid consumption ( $0.583 \pm 0.167$  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.<sup>187,188</sup> There are sparse data describing the time course of the development of elevated ICP and how these changes are associated with outcome. Bremner et al<sup>189</sup> 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

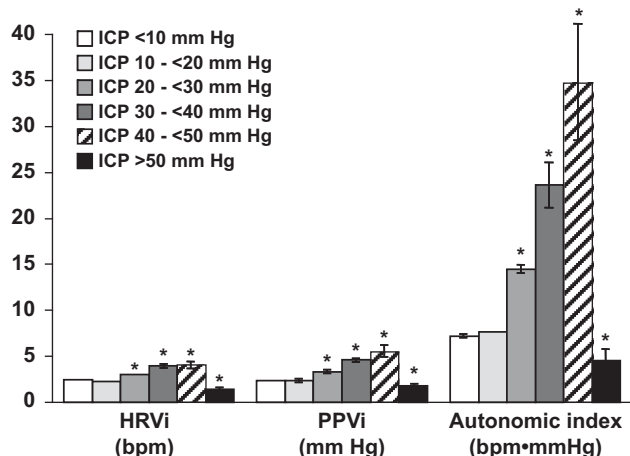
cannot be extrapolated to those patients with a mild initial injury at the time of admission or those who deteriorate later in their clinical course.

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.<sup>190–193</sup> Traditionally, assessing heart rate variability involved complex mathematical modeling; however, Mowery et al<sup>194</sup> 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<sup>195</sup> 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-minute 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 × 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.<sup>196–198</sup> One major limitation is the development of hyperchloremic metabolic acidosis and associated renal impairment.<sup>199–202</sup> In 10 patients with severe TBI, Bourdeaux and Brown<sup>203</sup> 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 *Brain Injury* recently published a series of 3 review articles by Meyer et al<sup>204–206</sup> that address TBI topics in an evidence-based manner. In the first article,<sup>204</sup> the usefulness of individual nonpharmacologic interventions, such as hypothermia, hyperbaric oxygen, cerebrospinal fluid drainage, and decompressive craniectomy are addressed. In the second article,<sup>205</sup> 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,<sup>206</sup> 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



**FIGURE 5.** Distribution of the mean ± standard error of integer heart rate variability (HRVi), integer pulse pressure variability (PPVi), and autonomic index (HRVi times PPVi) across 6 groupings of intracranial pressure (ICP). \**P* < 0.05 versus group with ICP < 10 mm Hg. Adapted with permission from *J Neurosurg Anesthesiol.* 2010;22:296–302.

optimal environment for caring for TBI patients. Teig and Smith<sup>207</sup> argue that patients should be managed in a specialty neurocritical care unit, whereas Petsas and Waldmann<sup>208</sup> 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<sup>209</sup> and the effect of anesthetics on apoptosis,<sup>210–212</sup> and neuroprotective strategies in neonates experiencing hypoxic or ischemic brain insults.<sup>213</sup> 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.<sup>214–217</sup> 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 anesthetic-induced neurotoxicity.<sup>218–220</sup> 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.<sup>221</sup> 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<sup>222</sup> 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 S100 $\beta$  protein, an intracellular neuronal protein that enters the systemic circulation after neuronal injury and disruption of the blood-brain barrier.<sup>223</sup> In contrast, sevoflurane did not produce a significant increase in serum S100 $\beta$ . Isoflurane also caused a 4-fold and 6-fold increase in cleaved caspase-3, a biomarker of apoptosis,<sup>214</sup> 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,<sup>222</sup> 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<sup>224</sup> 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), iontophoretic 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  $\gamma$ -aminobutyric acid (GABA) to the GABA<sub>A</sub> receptor induces the opening of a chloride channel where chloride ions flow along their concentration gradient. The GABA<sub>A</sub> receptor is also a primary site of action of volatile anesthetics and may indirectly modulate volatile anesthetic-associated neuronal apoptosis. The  $\alpha$ -subunit of the GABA<sub>A</sub> receptor has 2 isoforms:  $\alpha 1$  and  $\alpha 2$ .<sup>225</sup> Initially, the  $\alpha 2$  isoform is present but, at some point during development, there is a transition such that GABA<sub>A</sub> receptors containing primarily the  $\alpha 1$  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.<sup>226</sup> In younger animals, opening of the GABA<sub>A</sub> chloride channel results in an efflux of chloride from neurons, thus causing neuronal depolarization. In adult animals, opening the GABA<sub>A</sub> chloride channel results in chloride influx and thus neuronal hyperpolarization. This change in GABA<sub>A</sub> 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.<sup>226,227</sup> Piehl et al<sup>228</sup> exposed hippocampal slices obtained from 4, 7, and 14 postnatal rats (these dates corresponding to pre- GABA<sub>A</sub>, during, and post-GABA<sub>A</sub>  $\alpha$ -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 GABA<sub>A</sub> 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 GABA<sub>A</sub> 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 GABA<sub>A</sub> 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 GABA<sub>A</sub> receptor, there is a change in expression of an ion transporter which may impact the function of the GABA<sub>A</sub> receptor. Chloride currents in immature neurons are in part governed by an isoform of the Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter (NKCC1), which is considered the driving force for neuronal depolarization after GABA<sub>A</sub> stimulation. Peak expression of NKCC1 occurs around postnatal days 5 to 7 in rats.<sup>229</sup> In older animals, a different chloride transporter isoform—K<sup>+</sup>-Cl<sup>-</sup> 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 GABA<sub>A</sub> receptors. Data from Edwards et al<sup>230</sup> 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

**TABLE 4.** Effect of Sevoflurane on Cell Death, Activated Caspase-3 Staining, and the Nature of the GABA<sub>A</sub> Receptor  $\alpha$  Subunit in Rat Hippocampal Slices

	Postnatal Day Number		
	4	7	14
Cell death			
Immediate	0	0	+
After 24 h	0	0	0
After 72 h	+	+	0
Activated caspase-3			
Immediate	+	+	Not assessed
After 24 h	0	0	Not assessed
After 72 h	0	0	Not assessed
GABA <sub>A</sub> $\alpha$ 1 subunit			
Immediate	0	–	0
After 24 h	–	0	+
After 72 h	0	+	+
GABA <sub>A</sub> $\alpha$ 2 subunit			
Immediate	0	0	0
After 24 h	+	+	0
After 72 h	0	0	0

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; GABA<sub>A</sub>, type A  $\gamma$ -aminobutyric acid.

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 GABA<sub>A</sub> 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<sup>231</sup> 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).

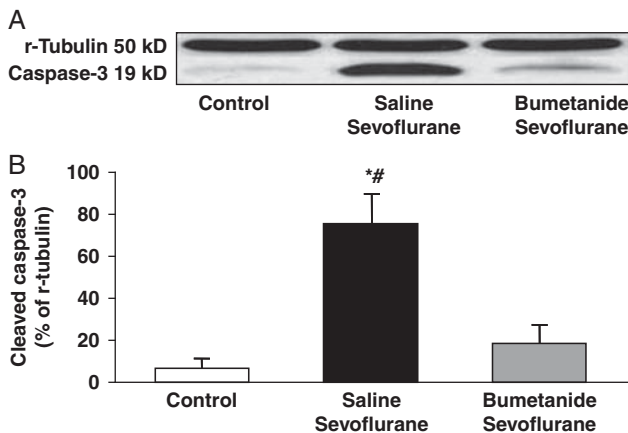
We refer readers with further interest in the topic of anesthetic-induced neurotoxicity to a review article by Stratmann et al.<sup>232</sup> This brief but focused study addresses topics such as the relationship between cell death and subsequent development of cognitive dysfunction, specific effects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

### 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.<sup>233</sup> 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.<sup>234</sup> This may account for the observation that statins have a protective role in stroke<sup>235–237</sup>; however, their effect on outcome after peripheral nerve injury is unknown. Pan et al<sup>238</sup> 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-1 $\beta$  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  $\beta$ -adrenoreceptor antagonist, propranolol, provides neuronal protection from focal ischemic injury.<sup>239–241</sup> Further, there exists limited data describing the outcome after cerebral ischemia associated with selective  $\beta_1$ -adrenoreceptor antagonists.<sup>242</sup> Iwata et al<sup>243</sup> administered either propranolol, esmolol, landiolol (esmolol and landiolol are selective antagonists for the  $\beta_1$ -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  $\beta_1$ -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<sup>244</sup> 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.



**FIGURE 6.** Bumetanide attenuates sevoflurane-induced increase in cleaved caspase-3 in postnatal day 4 rats. Rats in the control group (control, n=5) did not undergo anesthesia. Brains were isolated after exposure for cleaved caspase-3 evaluation. A, Representative Western blot images of cleaved caspase-3 in the brain of all 3 groups of rats to illustrate band intensities. B, Histogram showing results of the densitometric analysis of Western blot images of cleaved caspase-3. Densities of r-tubulin blots from the same tissue sample were taken as 100%. \* $P < 0.05$  versus control group. # $P < 0.05$  versus bumetanide/sevoflurane group. Adapted with permission from *Anesthesiol.* 2010;112:567–575.

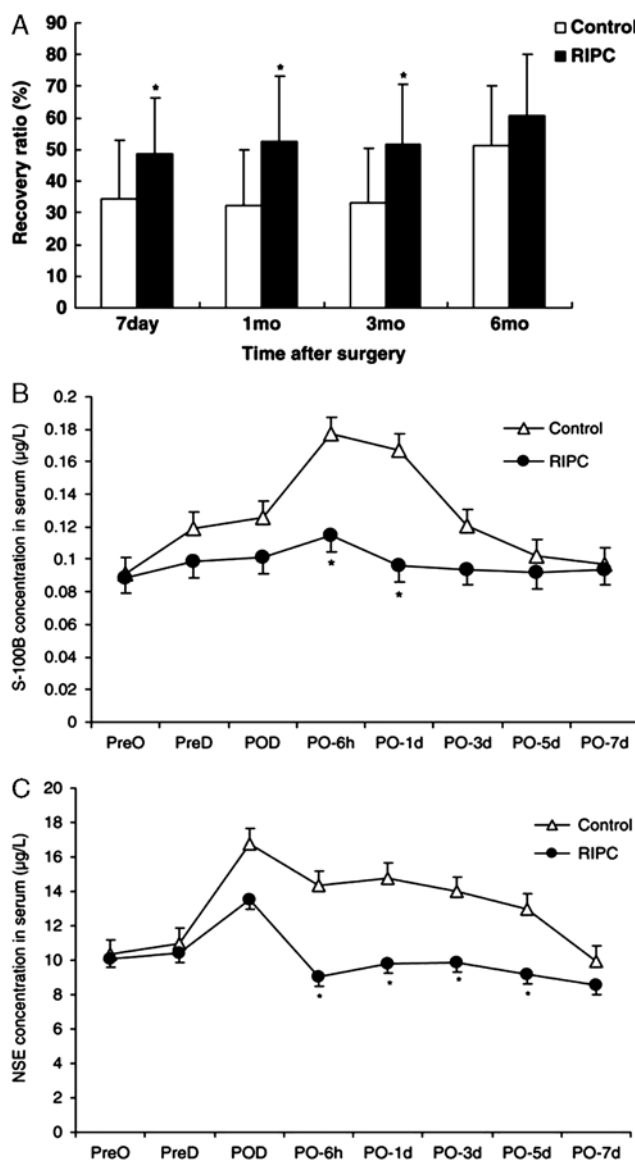
### Nonpharmacologic Protection

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.<sup>245</sup> 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.<sup>246–248</sup> Rutherford et al<sup>249</sup> performed a post hoc analysis of patients included in the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial<sup>250</sup> 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.<sup>251,252</sup> Later, ischemic preconditioning was found to protect against injury to neural tissues.<sup>253–255</sup> 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).<sup>256</sup> Hu et al<sup>257</sup> 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. Fourty 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-minute 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 remifentanyl; 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,<sup>223,258</sup> 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,<sup>259</sup> 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.

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<sup>260</sup> and p38 mitogen-activated protein kinase-induced upregulation of heat-shock protein 70<sup>261</sup> may play a role.

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