Acute management of vascular air embolism
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Abstract

Vascular air embolism (VAE) is known since early nineteenth century. It is the entrainment of air or gas from operative field or other communications into the venous or arterial vasculature. Exact incidence of VAE is difficult to estimate. High risk surgeries for VAE are sitting position and posterior fossa neurosurgery, cesarean section, laparoscopic, orthopedic surgeries invasive procedures, pulmonary embolism syndrome, and decompression syndrome. Risk factors for VAE are operative site 5 cm above the heart, creation of pressure gradient which will facilitate entry of air into the circulation, and accidental interruption of venous or arterial communication. Large volumes of air can lead to right ventricular outflow and immediate fatality. In up to 35% patients, the forearm isleve is patent which can cause paradoxical arterial air embolism. VAE affects cardiovascular, pulmonary and central nervous system. High index of clinical suspicion is essential to diagnose VAE. The transesophageal echo and most sensitive device will be used initially. Treatment of VAE is to prevent further entrainment of air, reduce the volume of air entrained and tamponade of the stream of air. Emergency interventions are needed to remove or arrest further embolization, and optimal hydration. Avoiding the use of nitrous oxide, meticulous care during operation, removal of central venous catheter, good guidance, and training of scuba divers.

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Introduction

Vascular air embolism (VAE) is known since early 19th Century but the interest and reporting of VAE significantly increased in last three decade. Most of the episodes of VAE are preventable if meticulous precaution taken or airway detected early and managed properly. It is important that all acute care physicians should be aware of this medical emergency. VAE can be venous or arterial, both condition can be differentiated by mechanism of air entry as well as site of embolization. The venous or pulmonary air embolism is air entry in systemic venous circulation reaching the right atrium while arterial air embolism occurs due to entry of air in to the arterial circulation and potentially lethal threatening as it can lead to circulatory death by blocking the body organs with poor collateral circulation. Here we will review the VAE in the following sub-headings.

Definition

VAE is the entrainment of air (or exogenous/collected gas) from open operative field or communication with entrance into the venous or arterial vasculature, producing systemic effects.

Epidemiology

Exact incidence of VAE is difficult to know as the sub clinical cases will be unnoticed. VAE probably most common embolic event to occur during the intra-operative period. In neurosurgical patients the incidence of VAE varies from 10 to 60%.[2] While in obstetric-gynaecological surgeons VAE can occur from 11 to 97% of patients.[3] In laparoscopic surgical patients it is reported to occur in up to 69% of the patients.[4] In orthopedic surgeries the incidence of VAE can be 67%.[5] During invasive monitoring catheter insertion the incidence of VAE are less than 2%.[6] Approximately, 7% of penetrating chest trauma patient will have VAE.[7] Few case reports of VAE after barotrauma.[8] and use of pressure infusor bag.[9] In scuba (self contained underwater breathing apparatus) divers air embolism is second common fatal cause, the incidence are 1/100,000 dives.[10]

Etiology

As mentioned VAE is probably most common embolic event to occur during surgical procedure.[11] The primary etiology of VAE is surgical procedure where the operative site is above the level of the heart, such as sitting neurosurgical procedure, posterior fossa surgery,[12] obstetric procedure,[13] and orthopedic surgeries.[14] Second etiological reason is ischemic creation of pressure gradient which facilitate entry of air into the circulation such as during insertion of central venous catheter.[15] Third etiological cause is mechanical instillation or pressure infusion such as laparoscopic surgeries [16] and gastroenteral endoscopy.[17] Fourth reason for VAE is scuba divers, aviators, astronauts (due to dysbaric or changes in the ambient barometric pressure) and positive pressure ventilation.[18] The other etiological factors are blunt and penetrating trauma to chest[19] and head.[20]

Risk Factors

In most of VAE episodes there are clear risk factors.
Pathophysiology

Smaller amount of air in the circulation does not cause any clinical manifestations as it is broken and absorbed from circulation.

Moderate amount of air causes pulmonary vascular injury leading to pulmonary hypertension and permeability pulmonary edema. [25]

Large bulges of air in venous system can cause an air lock in right side of the heart leading to right ventricular flow obstruction and death. [26]

In up to 30% of patients due to presence of patent foramen ovale, the air passes from right side to the left side of the heart and leading to systemic air embolization is termed as paradoxical embolism. [27] In such cases cerebral (Figure 2) and myocardial embolism (Figure 3) can result from embolization of arterial or coronary circulation. [28]

The total amount of air in human is reported to be either 200 and 300 ml bulus or 3-6 ml/kg. [29]

The pathophysiology of decompression sickness in scuba divers is different from other iatrogenic air embolisms. These dyspneic changes affecting in divers than high altitude climbers or astronauts as the density of water is 1000 times more at the sea level and the ambient pressure is linear to the depth of submersion, to understand the pulmonary overpressure syndrome and decompression sickness pathology we must know the law of physics concern with the partial pressure of gases in relation to the ambient pressure and gas solubility. The ambient pressure changes or dyabatization causes remarkable changes in the physiology of the breathing gases; [1) according to Daniel's law, the partial pressure of the diver's breathing gases increases proportionally to the increase in ambient pressure as the depth increases; [2] these exposure to the supernormal pressures of breathing gases will lead to progressively supranormal amount of these gases dissolved into the diver's body tissues and this may lead to nitrogen narcosis or oxygen toxicity. [30]

The third type of changes in the body of the divers which can be explained by Boyle's law, that is the amount of gas compressed in the body cavities inversely related to the increased ambient pressure. These gases will expand due to assist and demand in ambient pressure leading to barotrauma in non-dissolvable body tissues (in middle ear and sinuses) and dissolvable body tissues (bosophy and lung) leading to pulmonary over compression and barotrauma which ultimately causes rupture of skull, pneumothorax, pneumomediastinum, arterial embolism and decompression syndrome. [31]

The gas bubbles at the capillary level causes direct endothelial injury leading to post capillary congestion, platelet aggregation around the air bubbles with neutrophilic sequestration and inflammatory changes.

Clinical Manifestations

Presentation of VAE varies according to the nature, volume and speed of an air entrainment into the circulation. The main affected systems in VAE are cardiovascular, respiratory, and central nervous system.

The cardiac manifestations are chest pain, bradycardia or tachycardia, increased filling pressures due to right sided heart failure and in late stage typical mill-wheel murmur. Electrocardiogram may show a segment changes or right ventricular strain pattern. [32]

The pulmonary changes include dyspnea, hypoxemia and 'gasp reflex' as a result of acute hypoxemia or even pulmonary edema. Patient may have reduced lung compliance, increased dead space and acute shunting leading to hypoxemia and hypercapnia. [33]

Neurological manifestations are due to two reasons: first the cardiovascular collapse causing reduced cerebral output leading to cerebral hypo-perfusion, secondly direct cerebral and peripheral cerebral embolism in [28] may occur through patent foramen ovale.

In divers there will be two types of injuries. First one is due to chest pressure, which leads to expansion of the breathing gases causing pulmonary over inflation syndrome: second type of injuries occur due to changes in ambient pressure leading to bubble formation initally in the body tissue then entering in to the circulation causing to decompression syndrome (DCS) or decompression sickness.

The pulmonary over inflation syndrome ranges from minor pulmonary lung injury causing local bleed, pneumothorax and less commonly but potentially dangerous, over expansion of alveoli leading to ruptures and empty air into the pulmonary venousules and arterioles causing systemic air embolism, death by these can present as cardiovascular accidents, paralysis, convulsion, coma, and may also be associated with cardiovascular instability. [31]

DCS is the clinical manifestation associated with liberation of gas originally held in the solution into a free gas phase within the tissues as a result of decrease in the barometric pressures; these bubbles finally reaches venules.

The DCS manifests as bends shakes and skinny bends (Figure 4). The bends is boring pain in major joints (hip, elbow, and knee) of the divers mostly due to increase in intradural pressure at the ends of long bones and gas phase separation along ligaments and tendon sheath causing severe pain. Chokes is subatmospheric burning, cough and shortness of breath with or without neuromechanical instability. The main explanation for chokes is that the exhaled high load of venous gas embolized in the pulmonary artery leading to increased pressure on right side of the heart. Slimmy bends are the costocervical manifestation of DCS. The dangerous form of DCS is affection of spinal cord leading to ascending paralysis and associated bowel and urinary bladder dysfunction. [34]

Detection of Vascular Air Embolism

High index of suspicion in high risk cases is the cornerstone for diagnosis of VAE.

VAE should be considered when unexplained hypotension or sudden decrease in end-tidal CO2 level occurs, inspissatively in high risk cases. If patient complains of short of breath during or immediately after insertion or removal of central venous catheter in conscious patient who suddenly develops hypotension and hypoxia after delivery of the fetus.

Various monitoring devices can help in early detection of air in the vascular system.

The transesophageal echocardiography is the most sensitive monitoring, it can detect 0.02 ml/kg of air injected by bolus administration or air bubbles as small as 5-10 microns. [35]

Precordial Doppler ultrasound is the most sensitive non-invasive monitoring which can detect as little as 0.05 ml/kg of air. [36]

End tidal nitrogen (ETN2) can show the changes 30-90 seconds earlier than end tidal carbon dioxide (ETCO2) changes. [37]

End tidal carbon dioxide (ETCO2) is the most common and easily available monitoring, which will reveal sudden decrease in level in event of VAE. [38]
Transcranial doppler (TCD) and ECG (Electrocardiogram) changes are also used to guide the diagnosis of VAE. Pulmonary artery catheter will show rise in pulmonary artery pressure, its sensitivity is only 15%. Ventilation-perfusion scan findings are similar to those found in pulmonary thromboembolism, however, air embolism causes perfusion defect which get resolved rapidly usually within 24 hours. Computed Tomography (CT) chest will show air in central venous system, ventricles, pulmonary artery or pleura/thorax. Figure 1. CT brain may show intraventricular air or without infection (Figure 2). [40]

Differential Diagnosis

VAE should be differentiated from acute coronary syndrome, cardiogenic shock, cerebrovascular accidents, and pulmonary embolism.

Treatment

The goal of treatment in VAE is to prevent further air entry, reduction in volume of air entrained, and hemodynamic support immediately causing the surgical field with saline soaked dressing and if possible tilting the Tubb's may help in preventing further air entrainment. In sitting position surgery, by-pass venous compression, it is documented that it limits or restricts the air entry into chest circulation. [41]

Administration of 100% oxygen will maximize the patient's egestion as well as reduces embolic volume by eliminating nitrogen. [42]

By maintaining the systemic arterial pressure with optimal fluid status and isotropic support to the heart will help by keeping the patient stable [43] Air look in right side of heart may be relieved by partial lateral decubitus position. [44]

Trendelenburg position as a favorable position to operate the heart in the chest is now controversial. [45]

Aspiration of air from right atrium is possibly the best treatment to improve the hemodynamic parameters immediately and this can be done, with use of Bunge-Allen multilumen catheter up to 60%, success rate. [44]

Rapid cardopulmonary resuscitation with chest compression demonstrated to be effective in mass VAE which results in cardiac standstill. [47]

Hyperbaric oxygen therapy in cases of VAE is beneficial as it causes compression of existing air bubbles, by establishing a high diffusion gradient to speed dissolution of bubbles and by improving oxygenation in the ischemic tissues. [48] In hyperbaric therapy, patient inspires 100% oxygen at pressure above that of atmospheres at sea level with achieving an arterial partial pressure of oxygen greater than 2900 mm Hg. In decompression syndrome, patients should be transferred in supine position to minimize risk of cerebral embolization. The early compression therapy has better results, as per Boff's law, the compression by hyperbaric oxygen therapy will decrease the bubble size. Most commonly initial schedule of recompression is for 1 hour with intermittent air breaks. If symptoms are not relieved, therapy can be repeated once or twice daily and most of the patients require one to three therapeutic sessions. [49]

Anticoagulation therapy with heparin in patients with air embolism decreases the severity of the disease, if treated with heparin before air embolization. [50] As steroids do not have any effect on cerebral brain edema which occurs in the patients with air embolism, the use of steroids is controversial. [51] Interestingly, prophylactic lidocaine is effective in reducing the gas embolism effect on brain, it decreases brain edema in experimental animals. Various case reports suggesting that the lidocaine has beneficial effect in patient with decompression syndrome. [52]

Morbidity and Mortality

Morbidity and mortality in VAE is directly related to volume of air entrainment, rate of accumulation of air, and position of the patient at the time of VAE. Mortality of VAE ranges from 40% to 60%. [53]

Prevention

Instead of sitting position for surgeries the alternative 'lay bench' position provides adequate surgical conditions and to take extra precautions and meticulous monitoring in patients with documented right to left shunt [54] During caesarean section, 15 degree left tilting position facilitates entry of air into the circulation; hence institution of 50 degree reverse Trendelenburg position decreases the chances of VAE from 44 to 1%. [55] During insertion and removal of central venous catheter one has to take care of all these risk factors for VAE to prevent its occurrence. [56] Optimizing the volume values will prevent the wide gradient between right atrium and ventricle and hence decreasing the risk of VAE. [57]

Avoidance of use of intravenous cable will help in preventing VAE. [43] The use of positive end expiratory pressure (PEEP) in preventing VAE is controversial. [58]

The use of dual monitors, published Tables and personal software algorithm recommended limiting the dive duration, at green depth and pressuring maximum ascent and decompression stops for various combinations of depth, dive time, and breathing gases which will be helpful in preventing decompression sickness in divers.

Conclusion

Vascular air embolism (VAE) is preventable critical medical emergency. Apart from sitting position neurosurgical procedures, VAE is common in obstetric and laparoscopic surgeries. It is the most feared complication in scuba divers. Small amount of air in the circulation get absorbed but large bulks of air can cause air lock in the heart causing sudden death. Clinical manifestation of VAE is mainly due to the involvement of respiratory, cardiovascular, and central nervous system. In scuba divers, the barometric pressure changes lead to changes in breathing gas solubility and expansion causing bubble formation in body tissue and circulation.

Pneumothoracic air embolism occurs through patent foramen ovale causing significant and organ damage. Pneumocutaneous ultrasound is the most sensitive method in detection of air embolism, but high index of suspicion in the high-risk patients and knowledge about VAE are the corner stone for diagnosis of vascular air embolism. The goal of treatment of VAE is to prevent further air entry in the circulation, reduction in volume of air entrained and hemodynamic support. Aspiration of air from heart will immediately improve the hemodynamic parameters, but use of Trendelenburg position is controversial. The early use of hyperbaric oxygen therapy will in the treatment of VAE. To prevent occurrence of VAE the proper positioning during surgery, optimal hydration, and indwelling catheters during insertion and removal of central venous catheter is of vital importance. Use of diving computers, proper training and will prevent the decompression syndrome in the scuba divers.

References

General Page 4
Cerebral Monitoring

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The assessment of central nervous system function includes cerebral function, cerebral blood flow, intracranial pressure, oxygen uptake and spinal cord monitoring.

**Cerebral Function Monitoring**
- Awake patient
- Isolated forearm technique
- Lower oesophageal contractility
- Frontalis muscle electromyogram
- Unprocessed electroencephalogram
- Processed electroencephalogram
  - BIS®
  - ENTROPY®
- Evoked potentials
  - ALARIS AEP®
- Heart rate variability
- Ocular microtremor

**Cerebral Oxygenation Monitoring**
- Near-infrared spectroscopy
  - INVOS®
- Intracerebral PO₂ electrode
- Intracerebral microdialysis catheter
- Jugular venous bulb O₂ saturation
- Conjunctival PO₂

**Cerebral Blood Flow Monitoring**
- Transcranial doppler
- Positron emission tomography
- Internal carotid artery stump pressure
- Arterial plethysmography
- Radioactive Krypton 85 / Xenon 133
- Kety-Schmidt technique

**Spinal Cord Monitoring**
- Wake-up test
- Somatosensory evoked potentials
- Motor evoked potentials
**Cerebral function monitoring**

**Awake patient**

“The best monitor of cerebral function is cerebral function”. Direct communication with a patient as to whether they are awake, asleep, or feeling pain, still remains the best way of testing cerebral function.

**Isolated forearm technique**

An arm isolated with a tourniquet before induction of anaesthesia prevents anaesthetic drugs from reaching the hand. Hand and finger movement can then be assessed as a crude guide to depth of anaesthesia.

**Lower oesophageal contractility**

The oesophagus demonstrates three kinds of muscular activity:

- **Primary peristalsis** is initiated in the striated muscle of the upper oesophagus, and produces the propulsive activity of swallowing.
- **Secondary peristalsis** arises spontaneously and is probably triggered to remove food particles.
- **Tertiary peristalsis** is non-propulsive, under control from higher centres, and can be provoked by stress and pain.

The frequencies with which these tertiary lower oesophageal contractions occur are related to the depth of anaesthesia. A balloon is placed in the lower oesophagus and inflated; subsequent pressures are recorded. Both spontaneous and provoked lower oesophageal contractility can be used to detect depth of anaesthesia and awareness.

**Frontalis muscle electromyogram**

When placing electrodes on the scalp, at least four physiological waveform signals can be elicited: the electroencephalogram (EEG) which represents the electrical activity of the brain, the electrocardiogram (ECG) from the R-wave vector sweeping through the neck, the electro-oculogram (EOG) caused by electrical activity within the globe as the eye moves, and the electromyogram (EMG) which results from the electromechanical activity of scalp muscle. Biopotentials obtained from voluntary muscles are generally of higher frequency (70 – 3000 Hz) than the EEG (0 – 40 Hz). Selective filtering of signals can separate EMG from EEG and other potentials.

The amplitude of the biopotential is representative of muscle activity during isometric contraction and the amount and intensity of activity is thought to be related to the depth of anaesthesia. The frontalis muscle is particularly useful because:

- It is relatively resistant to muscle relaxants and therefore easier to monitor.
- It has a dual nerve supply in the form of voluntary cholinergic motor fibres and efferent sympathetic fibres from *nervus facialis* that participate in reflex responses to pain, stress and sounds.

**Unprocessed electroencephalogram**

The electroencephalogram (EEG) is the most easily accessible non-invasive measure of brain activity, recorded from the scalp. The "raw" EEG (21 scalp electrodes) reflects the algebraic summation of inhibitory (IPSP) and excitatory post-synaptic potentials (EPSP) of the nearby underlying neurones. Alternating currents with frequencies of 0.5 to 30 Hz and amplitudes of 10 to 100 microvolts are usually registered. These are small voltages, and so require high amplification.

The electrical potentials in the EEG bear a general relationship to the level of cerebral blood flow and to oxygen consumption. The EEG signal can be divided into specific frequency bands:

- Very low frequencies (Delta) 0 – 4 Hz
- Low frequencies (Theta) 4 - 8 Hz
- Medium frequencies (Alpha) 8 - 14 Hz
- High frequencies (Beta) 14 - 30 Hz
Unlike the electrocardiogram (ECG), the EEG has no obvious repetitive patterns, nor does the shape of the EEG waveform correlate with specific underlying events. On the contrary, the EEG is a randomly occurring signal.

Decades of study and observation have shown that there are some characteristics of the EEG that may be measured to provide a quantitative, if indirect, monitor of some aspect of brain function. If the IPSP’s and EPSP’s occur synchronously they summate to produce rhythmic oscillations of high amplitude, the so-called hypersynchronous and synchronous patterns, e.g. deep sleep, resting states, anaesthesia or mild hypoxia. Asynchronous neuronal activity summates to form an EEG of high frequency and low amplitude, e.g. awake and excited states.

Effects of anaesthesia

These are very variable, ranging from electrical excitation (asynchronous) to electrical silence (isoelectricity). The usual progression is asynchronous → synchronous → hypersynchronous → burst suppression → isoelectricity.

Processed electroencephalogram

Conventional unprocessed EEG utilises multiple (21) electrodes on the scalp, but is cumbersome and bulky with multiple tracings and an overwhelming amount of paper is utilised (over 100 metres of paper per hour at normal speeds). The unprocessed EEG also requires skilled, trained personnel for its interpretation. Diagnosis is effected by visual inspection of the tracing. The processed EEG on the other hand, uses fewer electrodes (2 - 4), utilises a compact, lightweight machine, displays its information on a screen, and does not use paper. It is also much easier to interpret by a non-“EEG expert”. The processed EEG is a computerised quantitative EEG analysis employing the Fourier principle. The analogue signal is converted to a digital format. There are 3 basic techniques used to process the EEG signal; Time Domain Analysis, Frequency Domain Analysis and the new Bispectral Index Analysis System.

Time domain analysis (amplitude/volt vs time)

The most frequently used technique using this principle is burst suppression. Burst suppression is a term implying periods of electrical silence interspersed with bursts of electrical activity. Normal corticothalamic connections are necessary for rhythmic cortical potentials. Disruptions of these connections lead to burst suppression (e.g. hypoxia and deep anaesthesia). It is customary to quantify burst suppression by presenting the relative amount of suppression, called the burst suppression ratio (BSR), within a one minute timescale. This is then given as a percentage to quantify the amount of suppression during a burst suppression ratio.
Frequency domain analysis (amplitude/volt vs frequency)
Spectral edge frequency  The frequency below which 95% of the power of the frequencies is located
Median frequency      The 50th percentile frequency of the total power
Peak power frequency  The single frequency of the spectrum that contains the highest amplitude
Time compressed formats Compressed spectral array and density spectral array

In general terms, spectral displays merely demonstrate the phenomenon of a shift of power to low frequencies with increasing depth of anaesthesia, as previously mentioned. They are especially useful when the adequacy of the blood supply to the brain is being assessed.

There have been several commercial monitors that have been used in the past, using the processed EEG techniques described, with variable results. Some have been validated clinical use, but the majority have not. No single monitor could or has shown itself able to accurately predict the depth of anaesthesia of a patient and prevent awareness. A combination of existing techniques and some new technological advances were required to bring us the current clinically validated monitors such as the Bispectral Index Monitor® Entropy® and Alaris Auditory Evoked PotentialMonitor®.

An example of an EEG compressed spectral array during anaesthesia with N₂O/O₂ and Enflurane. Natural sleep and anaesthesia show similar power spectra.
(1) Awake, (2) Asleep, (3) Anaesthetised, (4) Return to consciousness (From Sykes and Vickers, 1991)
Bispectral index monitor (BIS)
Aspect Medical Systems was founded in 1987 with the goal of developing a “depth of anaesthesia” monitoring system based upon more advanced processing of the EEG signal. After several studies evaluating the correlation of EEG changes with a variety of clinical endpoints such as movement, cardiovascular responses and consciousness, it became clear that the assessment of “depth of anaesthesia” represents a process of integrating multiple endpoints to predict the likelihood of awareness during a particular procedure.

This work resulted in a focus on the relationship between changes in the EEG signal and consciousness – a key component for managing depth of anaesthesia. During the 12-year development, more than 5,000 patients at a total of 30 institutions were studied, resulting in more than 250 peer reviewed abstracts and articles on the technology and clinical outcomes. In 1996, the Food and Drug Administration (FDA) of the United States cleared the BIS as the first commercially available measure of anaesthetic effects on the brain.

The BIS is a single number that is patient- and drug independent. It requires no calibration for either the patient or the drugs that are being used. The BIS is statistically and empirically derived from the EEG. It is a combination of several signal-processing parameters including the power spectrum, bispectrum and time domain variables. These parameters were combined to provide a linear transition across a variety of EEG patterns representing the awake, sedated, unconscious and isoelectric states.

The Bispectral Index is a number between 100 and 0. 100 represents the awake state and 0 denotes a flat line EEG, or complete EEG suppression. Below 70 the risk of recall decreases dramatically. Below 60 the patient has a low probability of consciousness. The lower the number is below 60, the deeper the level of anaesthesia. As the number goes above 60, the patient is increasingly at risk for recall.

The BIS is now widely used in the United States and other countries around the world, including South Africa. In published studies and day to day clinical use, BIS monitoring has been shown to reduce anaesthetic requirement, improve the quality of patient recovery and act as a cost-effective tool for improving the administration of anaesthetic agents. A recent study has shown that in a group of individuals at high risk of awareness undergoing general anaesthesia, BIS use reduced the incidence of subsequent awareness.

<table>
<thead>
<tr>
<th>Bispectral index</th>
<th>Description</th>
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<tbody>
<tr>
<td>100</td>
<td>Awake</td>
</tr>
<tr>
<td>70</td>
<td>Light hypnotic effects</td>
</tr>
<tr>
<td>60</td>
<td>Moderate hypnotic effects</td>
</tr>
<tr>
<td>40</td>
<td>Deep hypnotic effects</td>
</tr>
<tr>
<td>0</td>
<td>EEG suppression</td>
</tr>
</tbody>
</table>

Bispectral index monitor (From www.aspectms.com)
The BIS uses a set of three disposable electrodes that are attached to the patient's forehead and temple. A lightweight signal processor that clips onto the patient's clothes or bed converts the data from analogue to digital form. The information is processed and then displayed on the screen as a numerical number between 0 and 100. The trend of this number against time can be seen in this example. Different displays can be used, e.g. Compressed Spectral Array and EMG display. The monitor fits easily on an anaesthetic machine.
Entropy

The regularity of the EEG signal alters with changing levels of consciousness. By applying a variety of algorithms to analyse the EEG, investigators have found a way to describe the amount of order in the EEG signal. They have also managed to apply their techniques to show the effect of anaesthesia on the changing EEG signal. The most recent addition to the "depth of anaesthesia" monitors to be validated is the Entropy™ monitor. Entropy is a term borrowed from the description of thermodynamic systems and relates to the amount of "disorder" in the system.

Different entropy concepts have been applied to describe the amount of order in the EEG. One of these is Shannon entropy which has been shown to be a useful measure of anaesthetic drug effect. Shannon entropy measures the predictability of the future amplitude values of the EEG based on the probability of amplitudes already analysed in the signal. Unfortunately, Shannon entropy values' absolute value may vary between individuals because of inter-individual differences in signal strength, which precludes its use clinically.

To overcome these shortcomings, spectral entropy was developed. This is obtained by applying the Shannon entropy concept to the power distribution of the digitalised EEG signal that has been Fourier transformed. The separate contributions from different frequency ranges are then individually analysed. This means that the high EEG frequencies (>32 Hz) can be dealt with in a smaller time window or epoch than the lower EEG frequencies (<32 Hz). The separation of the two frequencies also gives an indication of whether the contribution comes primarily from the EEG or the EMG.

This technology is now commercially available in South Africa in the form of an Entropy™ module on Datex-Ohmeda anaesthetic delivery units. In this device, two spectral entropy indicators are used, one over the EEG dominant frequency (0.8 – 32 Hz) called state entropy (SE) and another over the complete range of frequencies (0.8 – 47 Hz) called response entropy (RE), which includes both EEG and EMG components. SE always has a number less than or equal to RE. Estimation of the hypnotic effects on the brain may be assessed by the SE number. RE has a response time of less than two seconds. Activation of RE to painful stimuli may be interpreted as a sign of inadequate analgesia. As SE will be the same as RE when EMG power becomes zero, SE ranges from 0 to 91, and RE from 0 to 100. Lower values indicate deeper levels of the hypnotic component of anaesthesia. The number to target during general anaesthesia to prevent recall is suggested to be between 40 and 60.

<table>
<thead>
<tr>
<th>State entropy</th>
<th>Response entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG frequency</td>
<td>EEG + EMG</td>
</tr>
<tr>
<td>0.8 – 32 Hz</td>
<td>0.8 – 47 Hz</td>
</tr>
<tr>
<td>Range 0 - 91</td>
<td>Range 0 - 100</td>
</tr>
</tbody>
</table>

Adequate anaesthesia: 40 - 60
Evoked potentials

Evoked potentials (EP) are electrical responses in the nervous system, which are linked in time with a stimulus. Various peripheral stimuli (somatosensory, brainstem auditory, motor, cranial nerve or visual) reach a certain measuring point after a specific time (latency), at a specific intensity (amplitude). The latencies of the response increase in time, and the amplitudes of the response decrease with increasing anaesthetic depth. These responses are very drug-specific and require expert interpretation. There are many different types of evoked potentials used for depth of anaesthesia monitoring, the more common being brainstem auditory and visual evoked potentials. Somatosensory and motor evoked potentials monitor not only cerebral function but also spinal cord pathways.

Auditory evoked response with increasing end-tidal concentrations of enflurane. The compressed brainstem response (BS) remains unchanged whilst the latencies of the early cortical responses (Pa, Nb) increase and the amplitudes decrease with increasing enflurane concentrations. (From Sykes and Vickers, 1991)

Auditory evoked potentials (AEP)

Loud repetitive clicks are delivered to the patient by small ear inserts placed in the external auditory canal. This monitors the integrity of the auditory pathways, which begins at the eighth cranial nerve and extends through the medulla and pons to the temporal lobe. This technique is also used during procedures like acoustic nerve- and posterior fossa surgery.

The evoked potential always appears at the same time after the stimulus, and is thus recorded in the same part of the memory. These potentials are therefore summated; whereas all the random activity unrelated to the stimulus is averaged, and approaches zero. This process is called “signal averaging”. The auditory evoked response is referred to in three sections:

- Brainstem response
- Middle latency (early cortical) response
- Late cortical response

The middle latency auditory evoked potential (MLAEP) waves occur 10 – 80ms after the click stimulus as the activity arrives at the primary auditory cortex. These are the waves that show graded changes with a variety of anaesthetic agents.

South Africa now has a commercially available AEP monitor available in the form of the “Alaris AEP - AAI”. This is the second commercially available “Depth of anaesthesia” monitor to be registered, and has a similar index system to the BIS monitor to quantify the level of anaesthesia. The ARX-index varies between 0 and 100, with surgical anaesthesia being below 30. 2-6 seconds of signal are analysed and displayed at a time, giving a continuous display of depth of anaesthesia.

High levels of muscular or EMG activity can interfere with the “Alaris AEP” under certain circumstances. This is because the frequency of the MLAEP is at a similar frequency to the EMG. The monitor therefore incorporates an EMG filter that removes most of the interfering EMG activity. An EMG bar is displayed on
the monitor and should be checked frequently. If the ARX-index has a sudden increase and muscular activity is also increased, then there is a risk that EMG is causing interference.

Visual evoked potentials (VEP)
Light stimulation of the eyes is recorded with electrodes over the occipital cortex. This method is potentially useful for procedures near the anterior visual pathways, e.g. optic chiasm and pituitary. Associated problems include the application of large, bulky, light-emitting diode goggles for neurosurgical procedures, which proved to be impractical, and in some series, the monitoring did not consistently correlate with visual outcome. These problems limited their use in practice.

Heart rate variability
Heart rate variability (HRV) is the basis of a new monitor. “Fathom” uses a high-resolution electrocardiogram, along with an indication of respiratory cycle provided by either an encoding Wright’s spirometer or a chest belt, to discriminate respiratory sinus arrhythmias (RSA) from other arrhythmias on a breath-by-breath basis. This indicates the level of vagal outflow from the medulla oblongata, which correlates with the activity in the solitary nucleus, and has been demonstrated to indicate the fall in brain metabolism associated with volatile anaesthesia.

Ocular microtremor
Ocular microtremor (OMT) is a fine physiologic tremor of the eye related to neuronal activity in the reticular formation of the brainstem. The frequency of OMT is suppressed by propofol and sevoflurane and predicts the response to command at the emergence from anaesthesia. This means that it could serve as a marker of the unconscious state. Recent studies have shown that it can be measured using an automated analysis module even in the presence of muscle relaxants and altered patient position.
Intracranial pressure monitoring

The indications for intracranial pressure (ICP) monitoring are not generally agreed. There are technical difficulties in making the measurement, its use is not without risk and there are no conclusive studies which demonstrate a significant increase in survival in patients where the technique has been used. Indications for ICP devices:

- Management of the head injury patient – measuring ICP & response to treatment
- If clinical signs are masked by the use of sedation or muscle relaxants
- Measuring changes in ICP in hydrocephalus & monitoring performance of shunts
- Post aneurysm surgery when arterial spasm may give rise to cerebral oedema

Intraventricular catheter

The gold standard and the most widely used ICP monitoring devices. A catheter is inserted into the lateral ventricles via a burrhole, filled with saline, transduced and zeroed against a fixed point (eg: external auditory meatus). Cerebrospinal fluid (CSF) can be withdrawn through the catheter in case of a raised ICP. Intracranial compliance may also be measured. The disadvantages include an increased risk of intracerebral bleeding or oedema along the cannula track, high risk for infection, and transducer repositioning is required with head movement.

Subarachnoid Bolt/Screw

A hollow bolt is screwed through a Burr-hole made through the fronto-parietal suture line. The tip of the bolt is passed through the dura and the interior is filled with saline so that there is a liquid bridge between the CSF and the pressure transducer. The most common device used is the Becker bolt. These devices have the advantages of being easy to install, no penetration of the brain is required, direct pressure measurement takes place, and there is a decreased risk of infection. Disadvantages are that they require an intact skull, CSF cannot be withdrawn and a high ICP may cause herniation of brain tissue into the bolt.

Epidural monitors

Pressure is measured via an intact dura by placing a catheter in the epidural space on the inner surface of the skull. No fluid bridges are used, there is less risk of infection and no transducer adjustment with head movement is required. Disadvantages are that one is unable to recalibrate or zero after placement, there is decreased accuracy in sensing through the dura and CSF cannot be drained.

Fiberoptic monitors

A fibre-optic catheter tip is covered with an elastic membrane and the distortion of the membrane is sensed by the intensity of light reflected from the back of the membrane. These are versatile monitors and may be placed in the ventricle or subarachnoid space. The disadvantages are that a separate monitoring system is required, the catheters are relatively fragile and recalibration or rezero after placement can’t be done.
Cerebral oxygenation monitoring

Near-infrared spectroscopy

The fundamental principle in near-infrared spectroscopy (NIRS) is straightforward: For a fixed distance the absorption of near-infrared (NIR) light is proportional to the concentration of the chromophobe (HbO₂) according to the Beer-Lambert law. This technique is used for studying cerebral oxygenation and haemodynamics. Transmission spectroscopy is used in neonates where light is shone across the skull between two optodes. Reflectance spectroscopy is used in adults (because of the large head/thick skull) where optodes are placed on the same side of the head a few centimetres apart. NIRS technology has also been used to monitor oxygenation in the muscle, liver and kidney.

The current bedside implementation of NIRS technology is the INVOS®. This has been made practical because of advances in microprocessor function and validation in a cerebral model. NIRS devices rely on the different light signal based on the changing absorption spectrum of haemoglobin depending on its oxygen saturation. The INVOS® uses a dual-detector system to subtract a shallow light path from a deep light path. This theoretically allows the monitor to derive the average oxyhaemoglobin saturation in a volume of tissue about 2.5 to 3.0 cm deep to the skin. The device displays an approximation of the venous-weighted haemoglobin saturation in tissue deep to the sensor. The parameter is displayed as a relative number from 0% to 100% using an algorithm calibrated from in vivo and in vitro cerebral models and is termed rSO₂. INVOS provides a window on the oxygen economy in the monitored tissue bed.

Clinical data in children and adults support the hypothesis that cerebral rSO₂ less than 40% to 50%, or a change in baseline of more than 20%, is associated with hypoxic-ischemic neural injury. Many centres have adopted rSO₂ as a clinical parameter to target in their anaesthetic management (particularly in cardiac surgery), and the impact of these strategies on organ injury awaits long term follow-up.

Intracerebral PO₂ electrode

Direct monitoring of brain tissue partial pressure of O₂ (PtiO₂) is a promising new technique that allows early detection of impeding cerebral ischemia in brain injured patients and patients undergoing neurosurgery. For PtiO₂ monitoring, a microcatheter is inserted in the frontal cerebral white matter. Threshold for treatment would be a PO₂ of less than 8.5 mmHg.

Intracerebral microdialysis catheter

The composition of the interstitial fluid reflects the biochemistry of neurons and cells in the brain. Microdialysis is used to evaluate how seriously ischemia, trauma, haemorrhage and various physiological, pharmacological and surgical interventions affect the brain. Experience shows that the lactate/pyruvate ratio and the level of glycerol are excellent markers of ischemic and cell membrane damage in the brain.
A microdialysis catheter monitors the chemistry of the interstitial fluid by mimicking the function of a blood capillary. Substances measured are either from the blood or they are released from the cells. Changes in the blood flow or uptake into the cells change the concentration of the dialysate.

Chemical substances in the interstitial fluid diffuse across the dialysis membrane and into the perfusion fluid inside the catheter. Samples are collected in microvials and brought to a bedside analyser as often as necessary – usually every hour. The concentration of chemical substances in the dialysate depends on the flow of perfusion fluid, the length and properties of the dialysis membrane and the diffusion coefficient in the tissue. If the membrane is long enough and the flow is slow enough then recovery of a particular substance from the interstitial fluid approaches 100%.

**Jugular venous bulb O₂ saturation**

Jugular venous Oxygen saturation (SjvO₂) monitoring is the assessment of the amount of O₂ dissolved in the internal jugular vein. This is the amount of dissolved O₂ in the blood returning from the brain, which was not used by the brain. SjvO₂ monitoring records the balance of the supply of O₂ available to the brain and the brain’s demand for O₂. The knowledge of such a balance (sometimes referred to as the cerebral oxygen balance) is important as it indicates the brain’s O₂ consumption. For example, a low SjvO₂ value indicates that the brain needs more O₂. SjvO₂ is measured via a catheter, which is advanced, retrograde under fluoroscopic guidance in the jugular vein until its tip lies in the jugular bulb from where blood can be aspirated and PO₂/Sats can be measured. Measurement can also be done continuously using a small fibreoptic catheter.

- SjvO₂ < 55% - Inadequate cerebral O₂ flux
- SjvO₂ > 75% - Excessive cerebral O₂ flux

Problems associated with this technique are:
- Evaluates only the global O₂ balance. Blood sampled from the jugular bulb is 70% from the ipsilateral side and 30% from the contralateral side
- A high SjvO₂ can be falsely reassuring if there is decreased bloodflow to a small area of cortex
- A jugular catheter may block jugular outflow or cause thrombosis after prolonged use

**Conjunctival PO₂**

Partial pressure of O₂ of the conjunctiva is used to correlate with cerebral O₂ flux. Experimental use only.
Cerebral blood flow monitoring

Transcranial doppler

This is a non-invasive technique using major intracranial vessels via “acoustic windows” in the skull (transstemporal, transorbital and transforaminal). In about 20% of patients it is impossible to find such a bone window. Usually the middle cerebral artery or the internal carotid artery is used. The technique is painless, can be performed at the bedside and it gives immediate results. In order for transcranial doppler measured blood velocity to have a direct relationship to cerebral blood flow three assumptions have to be made; (1) The vessel diameter has to be known and remain constant (2) The angle of insonation has to remain constant (3) That bloodflow in a measured artery represents cortical bloodflow.

Positron emission tomography

Positron emission tomography (PET) is the study and visualisation of human physiology by electronic detection of short-lived positron emitting radiopharmaceuticals. It is the only non-invasive technology that can routinely and quantitatively measure metabolic, biochemical and functional activity in living tissue. It is a functional, not an anatomical imaging technique. The accompanying picture illustrates different areas of the brain that are identified when certain functions are performed.

It is a nuclear medicine imaging technique where hundreds of radiation detectors and sophisticated computers technologies are used to identify the biochemistry of internal organs, using labelled oxygen and glucose molecules. Its greatest clinical utility lies in the field of epilepsy where it is used to localise epileptogenic foci for surgical resection. The technology continues to progress rapidly through improvements in imaging and radiopharmacology with potential applications in neurooncology, cerebral vascular disease, coronary disease and metabolic diseases. Implications for anaesthesia are mainly research related.
Internal carotid artery stump pressure

Used principally in carotid endarterectomy surgery to decide whether to use a shunt intraoperatively or not. The common carotid and the external carotid are clamped and the pressure in the internal carotid artery is taken with a needle inserted distal to the common carotid clamp. The assumption is made that the internal carotid stump pressure reflects pressure (and therefore flow) via the circle of Willis from the contralateral hemisphere's blood supply and the ipsilateral vertebral artery.

Uncertainty exists about the validity of the readings, and there is insufficient evidence to support the notion that measuring and acting on internal carotid artery stump pressures alters outcome, so the practice is fading. A shunt may be indicated if:
- MAP < 40 mmHg
- Non-pulsatile waveform is seen

Arterial plethysmography

Ocular and supraorbital techniques are used. Experimental use only.

Radioactive Krypton 85 / Xenon 133

A bolus of radioactive Krypton 85 or Xenon 133 dissolved in saline is injected into the internal carotid artery. The radioactivity is detected with scintillation counters or gamma cameras and plotted on a semi-logarithmic scale.

Kety-Schmidt technique

This method utilises the Fick principle. The subject inhales 10% N₂O in air for 10 min. During this period samples are taken at fixed intervals from an artery and the jugular bulb, analysed for N₂O and plotted on a graph. The rise in venous concentration lags behind the arterial concentration whilst N₂O is taken in by the brain. By the end of the period of breathing, the venous and arterial concentrations are almost the same, indicating that the brain is fully saturated.

\[
\begin{align*}
\text{If:} \\
\text{Mass of the brain} = M \\
\text{Final concentration of N}_2\text{O in the brain} = C \\
\text{Blood: Brain partition coefficient for N}_2\text{O} = \lambda \\
\text{Then the quantity of N}_2\text{O in the brain is} MC\lambda. \\
\text{This quantity equals the total bloodflow during the period Q,} \\
\text{multiplied by the integral of the arterial – venous difference, A}
\end{align*}
\]

\[
\begin{align*}
\therefore QA &= MC\lambda \\
\therefore Q &= \frac{MC\lambda}{A}
\end{align*}
\]

Kety-Schmidt technique

\[
\begin{align*}
\text{[N}_2\text{O]} \\
\text{(min)}
\end{align*}
\]
**Spinal cord monitoring**

**Wake-up test**

This has been considered for many years to be the gold standard of spinal cord function during scoliosis surgery. However, its sensitivity is open to question as the test is only applied intermittently, and during most of the operation spinal cord function is unknown. Ideally the test should be applied in conjunction with other less dangerous and more continuous forms of neurological function monitoring. The significant problems associated with this test include the fact that the patient has to be very co-operative, as there is the very real risk of endotracheal tube dislodgement. The patients are usually prone which makes monitoring that much harder, there is intermittent monitoring only (once or twice during the course of the operation), there is the added risk of increased blood pressure & pulse-rate when waking up, and of course the test in contra-indicated in deaf patients.

**Somatosensory evoked potentials (SSEP)**

A peripheral nerve (e.g.: posterior tibial, common peroneal, ulnar, median) is stimulated supramaximally and the response measured centrally with scalp or epidural electrodes. These techniques are commonly used in the US and the UK but one has to bear in mind that volatile anaesthetic agents, N₂O and the opioids can all suppress these recordings. There is also a significant amount of operator experience needed to make any sense of the readings, which accounts for their unpopularity outside of centres of excellence.

The problem here is that this technique only evaluates the function of the posterior and lateral columns of the spinal cord. The paired posterior spinal arteries supply the posterior and lateral columns, which continue to be supplied by multiple collateral sources during aortic occlusion. Since paraplegia results from ischemia of the anterior spinal cord motor tracts, which are supplied by the anterior spinal artery, SSEP fails to monitor the function of the anterior spinal cord.

**Motor evoked potentials (MEP)**

This evaluates the function of the anterior spinal cord, which is supplied by radicular arteries, the largest of these being the so-called *arteria radicularis magna*. This blood supply renders the anterior spinal cord (motor) much more vulnerable to ischemic damage during aortic cross clamping. The motor cortex can be stimulated in two ways:

- **Magnetically**: Non invasive, painless, easier to obtain in awake patients
- **Electrically**: not painless

When a magnetic or electrical impulse is applied over the motor cortex, a muscle twitch may be observed in the arm or leg, depending on which area of the cortex is stimulated. Recordings can be done at the spinal cord level, peripheral mixed nerve or directly from the muscle with EMG.

Problems with this method are that recordings of MEP are difficult below the thoracic regions and this limits its usefulness in scoliosis surgery and that concern has been expressed about the safety of repeated transcranial electrical stimuli. MEP’s are also even more affected by anaesthetic agents, and a total intravenous anaesthetic is suggested when using these monitors.
College questions

1. Write short notes on measuring the depth of Anaesthesia
2. Discuss the assessment of Cortical function during Anaesthesia
3. Describe monitoring of the electrical activity of the brain during Anaesthesia
4. Discuss the measurement of depth of anaesthesia
5. Discuss monitoring of the central nervous system during anaesthesia
6. Discuss the methods, advantages, disadvantages and limitations of the different ways of using the EEG for the determination of the level of consciousness
7. What are the problems associated with spinal cord monitoring
8. Describe how a biological electrical signal is detected and quantified. Illustrate your answer using Auditory Evoked Potential Monitoring
9. Give a brief description of how increases in depth of Anaesthesia change the latency and the amplitude of the biological electrical signals in Auditory Evoked Potential Monitoring.
10. Describe the physical principles and limitations of a near infrared spectroscopy monitor used for the measurement of cerebral oxygenation
11. Describe how a dynamic biological pressure is transduced into an electrical signal suitable for quantification and display. Use an intraventricular catheter, used for the measurement of intracranial pressure, to illustrate your answer.

Further reading

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Neuroanesthesiology Review-2006
Jeffrey J. Pasternak, MD, and William L. Lanier, MD

Abstract: In this article, we will provide a review of the 2006 literature of interest to those readers who provide perioperative care to patients with neurologic disease. This evaluation of the literature is not intended to be comprehensive, nor were systematic criteria used to include or exclude articles. Instead, the authors attempted to highlight those articles of greatest clinical relevance or those that provided unique insights into the physiology, pharmacology, and pathomechanisms of neurologic function for practicing clinicians and clinician-investigators. This article focuses on intracranial hemorrhage, anesthetic considerations in neurosurgical patients, cerebral hemodynamics, electrophysiologic monitoring, neuroprotection, and traumatic brain injury.

Key Words: intracranial hemorrhage, cerebral hemodynamics, neuroprotection, electrophysiologic monitoring, traumatic brain injury

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This article focuses on intracranial hemorrhage, anesthetic considerations in neurosurgical patients, cerebral hemodynamics, electrophysiologic monitoring, neuroprotection, and traumatic brain injury.

INTRACRANIAL HEMORRHAGE
Aneurysm Clipping Versus Endovascular Coiling

The Cerebral Aneurysm Rerupture After Treatment (CARAT) trial was designed to compare rates of rebleeding following either endovascular coiling or surgical clipping for the primary treatment of their cerebral aneurysms. In this prospective multicenter cohort trial involving 1010 patients, overall, nonprocedural-associated rerupture (3.3%) and retreatment (11.0%) of the primary aneurysm was more common after coil embolization in 299 patients compared with 1.1% and 1.7%, respectively, in 711 patients after surgical clipping (P = 0.02 and < 0.0001 for rerupture and retreatment, respectively). The mean and maximum duration of follow-up was 4.4 and 9.6 years for those who underwent clipping and 3.7 and 8.9 years for those who had endovascular treatment. Similarly, long-term (ie, after 12 mo) risk of both rerupture and retreatment was still lower after the clipping compared with coiling (Figs. 1, 2). The results of this study are consistent with that of the Intraoperative Subarachnoid Aneurysm Trial (ISAT), which also demonstrated an increased rate of rebleeding after endovascular treatment, most commonly occurring within 30 days of the procedure. Specifically, 1.9% and 0.7% patients had a subsequent episode of rebleeding within 30 days after the endovascular and surgical treatment, respectively (P < 0.05).

Grunwald et al prospectively evaluated the incidence of new thromboembolic events, which followed endovascular coiling. In 50 patients who had diffusion-weighted magnetic resonance imaging, a technique with high sensitivity for detecting ischemic stroke, both before and after endovascular coiling, the appearance of new postprocedural hyperintense lesions was present in 42% of patients. Further, there seemed to be no correlation with regard to aneurysm location, size, number of coils used, patient age, or embolization procedure duration versus the development of new lesions on imaging. The functional correlates of these observations were not reported.

Of note, Brisman et al reviewed the current epidemiology, diagnosis, and treatment options available for cerebral aneurysms. In addition, Suarez et al reviewed the current epidemiology, diagnosis, and treatment of subarachnoid hemorrhage. Although the articles appear similar, the Brisman et al article focused on invasive treatment options (ie, surgical clipping and endovascular coiling), whereas the Suarez et al article focused on noninvasive management and complications.

Glucose Management in Patients With Aneurysmal Subarachnoid Hemorrhage

Hyperglycemia is known to exacerbate ischemic neurologic injury, and contribute to poor outcome in
critically ill patients. More recently, it was found that in patients with poor-grade subarachnoid hemorrhage, those having lesser blood glucose concentrations experienced better neurologic recovery. Frontera et al prospectively evaluated the extent to which hyperglycemia contributed to in-hospital complications and poor outcome in 281 patients who suffered subarachnoid hemorrhage. By calculating a glucose burden (defined as the difference between each patient’s daily peak blood glucose concentration and 105 mg/dL), the authors found that elevated blood glucose was associated with an increased risk of: (1) congestive heart and respiratory failure, (2) pneumonia, and (3) brainstem herniation, but not: (1) fever, (2) bacteremia, (3) presence of stroke, (4) vasospasm, or (5) aneurysmal rebleeding. Further, increased glucose burden was associated with an increased risk of death [odds ratio = 1.10 (95% confidence interval (CI) = 1.01-1.21), \( P = 0.027 \)] and death or disability [odds ratio = 1.17 (CI = 1.07-1.28), \( P < 0.001 \)] after 90 days. In this study, only those with blood glucose concentrations >180 mg/dL were treated with insulin, and 74% of patients received postsurgical edema prophylaxis with corticosteroids. The latter factor is of interest in that, although corticosteroids continue to be

\[ \text{FIGURE 1. Survival analysis of nonprocedural rerupture after surgical clipping (dashed line, } n = 711 \text{) and endovascular coil embolization (solid line, } n = 299\). Overall, rerupture was more frequent in those treated with coil embolization (\( P = 0.02 \) by log-rank test). The difference was present in the first year after the treatment (\( P = 0.04 \)) but not afterward (\( P = 0.11 \)). With permission from Stroke. 2006;37:1437–1442. \]

\[ \text{FIGURE 2. Survival analysis of index aneurysm retreatment after surgical clipping (dashed line, } n = 711 \text{) and endovascular coil embolization (solid line, } n = 299\). Retreatment was more frequent after coil embolization (\( P < 0.0001 \) by log-rank test). The difference was present in the first year (\( P < 0.0001 \)), the second year (\( P < 0.0001 \)), and thereafter (\( P < 0.0001 \)). With permission from Stroke. 2006;37:1437–1442. \]
used in acute brain injury, they have been reported to worsen outcome after stroke\textsuperscript{13} and closed-head injury\textsuperscript{14} in humans.

**Intravenous Magnesium After Subarachnoid Hemorrhage**

Despite the negative results of the IMAGES trial,\textsuperscript{15} where intravenous (IV) magnesium was no better than placebo in influencing gross neurologic outcome in acute stroke patients, little is known about the effectiveness of magnesium as a neuroprotectant in other clinical settings.\textsuperscript{16} Specifically, magnesium is a known cerebral vasodilator,\textsuperscript{17,18} and therefore, may be effective for the prevention or treatment of cerebral vasospasm after subarachnoid hemorrhage.\textsuperscript{19,20} In a small-scale randomized, partially blinded, prospective study by Schmidt-Elaesser et al,\textsuperscript{21} 104 patients who suffered acute aneurysmal subarachnoid hemorrhage received either IV nimodipine (48 mg/d) or IV magnesium sulfate (10 mg/kg bolus followed by an infusion of 30 mg/kg/d) in addition to routine care consisting of early aneurysm obliteration either by clipping or coiling, hemodynamic monitoring, and treatment of vasospasm if it developed. The authors compared the incidence of clinical vasospasm and infarction between groups. Treatment groups were well matched for demographics, severity of subarachnoid hemorrhage on admission (as measured by the Fisher grade and World Federation of Neurological Surgeons grade), and treatment (ie, clipping or coiling). Despite this, there was no difference in the incidence of vasospasm, cerebral infarction, or outcome at 1 year (Table 1). The authors concluded that, on the basis of these preliminary data, magnesium seemed to be as effective as nimodipine for the prevention of vasospasm and its consequences.

It is currently unknown if the combination of IV magnesium and nimodipine is superior to nimodipine alone for the prevention of vasospasm. In a small-scale prospective trial in 60 patients with subarachnoid hemorrhage, Wong et al.\textsuperscript{22} randomized patients to receive IV nimodipine (0.5 to 2 mg/h) with saline placebo or in combination with IV magnesium sulfate (500 mg over 30 min followed by an infusion of 2000 mg/d) for up to 14 days following ictus. Patients underwent routine care consisting of early aneurysm obliteration either by clipping or coiling, hemodynamic monitoring, and treatment of vasospasm (eg, with hypertension, hypervolemia, and hemodilution), if it developed. There was no difference between groups with regard to demographics, severity of subarachnoid hemorrhage upon hospital admission, aneurysm location, or treatment (ie, clipping or coiling). The study demonstrated no difference between groups with respect to the incidence of vasospasm (37% for magnesium and nimodipine vs. 57% for nimodipine alone; $P = 0.06$), or neurologic outcome (as measured by Glasgow Outcome Score, modified National Institutes of Health Stroke Scale, or Barthel’s index); however, there was significantly longer duration of transcranial Doppler sonographically apparent vasospasm in the group which received nimodipine alone [median (range) was 4 d (2 to 6 d) vs. 2 d (2 to 3 d) for the magnesium/nimodipine group; $P < 0.01$]. The authors concluded that a larger-scale trial is feasible and necessary to further evaluate the efficacy of magnesium sulfate in combination with nimodipine on the incidence, severity, and duration of vasospasm, and also on outcome, in patients with aneurysmal subarachnoid hemorrhage.

**S100B Proteins**

S100B proteins belong to a class of low molecular-weight calcium binding proteins abundant in glial cells, particularly astrocytes, in the central nervous system.\textsuperscript{23} Spillage of this intracellular protein into the extracellular space is reported to correlate with acute brain injury\textsuperscript{24}, however, one must keep in mind that S100B is rapidly cleared from serum (ie, half-life = 97 min).\textsuperscript{25} For a more recent review of the role of S100B protein, we refer the reader to an article by Kleindienst et al.\textsuperscript{26}

Weiss et al\textsuperscript{27} evaluated the prognostic role of blood S100B concentrations in the setting aneurysmal subarachnoid hemorrhage. The study was conducted in 74 patients (mean age 48 ± 11 y, 43% men) with

### TABLE 1. Incidence of Vasospasm and Outcome in Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine</th>
<th>Magnesium</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Incidence of clinical vasospasm</td>
<td>27%</td>
<td>15%</td>
<td>0.193</td>
</tr>
<tr>
<td>Incidence of vasospasm via Doppler sonography</td>
<td>33%</td>
<td>38%</td>
<td>0.792</td>
</tr>
<tr>
<td>Incidence of cerebral infarction</td>
<td>27%</td>
<td>25%</td>
<td>0.908</td>
</tr>
<tr>
<td>Incidence of good outcome</td>
<td>66%</td>
<td>54%</td>
<td>0.373</td>
</tr>
</tbody>
</table>

Clinical vasospasm was defined as a delayed ischemic neurologic deficit that could not be accounted for by other causes such as hydrocephalus, hematoma, seizure, or electrolyte abnormality, combined with ultrasonographic or angiographic evidence of vasospasm. A mean velocity of more than 140 cm/s or Lindegaard Index of more than 4 or an increase in the flow velocity by more than 40 cm/s within 24 h was regarded as pathologic. Angiographic evidence of vasospasm was defined as any moderate-to-severe (ie, > 30%) narrowing of the diameter of the arterial vessel lumen on high-resolution images using a digital subtraction method. The diagnosis of clinical vasospasm was made only in patients who could be assessed neurologically, because in comatose patients with or without analgesia or sedation, the criteria of secondary deterioration or new focal neurologic deficit could not be met.

Infarction attributable to vasospasm was defined as the occurrence of a new spontaneous hypodense lesion as revealed by a CT scan (or infarction according to diffusion-weighted or perfusion-weighted magnetic resonance imaging scan) that was not associated with the initial hemorrhage or was caused by operation or endovascular procedure.

A good outcome was defined as a Glasgow Outcome Score of 5. Adapted with permission from *Neurosurgery.* 2006;58:1054-1065.
subarachnoid hemorrhage of less than 48 hours of duration, and in whom intervention [ie, clipping (28%) or coiling (72%)] was planned within 48 hours of admission. Blood concentrations of S100B continued to increase in patients who eventually died before postictal day 8 compared with those who were discharged from the intensive care unit before day 8 (Fig. 3). The threshold concentration of S100B for predicting a poor outcome at 6 months in this subarachnoid hemorrhage study was 0.4 µg/L (sensitivity = 0.50, specificity = 0.67). After multivariate analysis, only surgery [odds ratio = 6.1 (CI = 1.7-21.9)] remained independently associated with mean S100B values greater than 0.4 µg/L. Finally, mean daily S100B concentrations greater than 0.4 µg/L was independently associated with poor outcome at 6 months [odds ratio = 7.3 (CI = 2.3-23.6)]. It is unknown if this latter finding is due to treatment (ie, clipping or coiling) or the severity of disease given the high likelihood of selection bias.

Oertel et al28 prospectively investigated the utility of S100B in subarachnoid hemorrhage as an early marker of vasospasm. In 51 patients who suffered subarachnoid hemorrhage (mean age = 51 ± 11 y, 38% men), blood S100B concentrations were determined for the first 3 days after the initial hemorrhage. Most patients underwent early clipping (n = 38) compared with coiling (n = 10) or conservative management (n = 3). Unlike the prior investigation by Weiss et al,27 there was no difference in S100B concentrations between groups with respect to treatment (average S100B = 0.75 ± 1.8 µg/L for coiling and 0.7 ± 0.9 µg/L for clipping, P = 0.17; those patients who underwent conservative management were not considered in this analysis). Patients with worse disease as evident by World Federation of Neurological Surgeons score and Fisher grade had significantly higher mean S100B concentrations. Vasospasm was recorded in 51% of patients and mortality was 52% in those who experienced vasospasm. Within the first 3 days, average S100B concentration was significantly less in those who later experienced vasospasm (0.3 ± 0.3 µg/L) compared with those who did not (1.4 ± 1.6 µg/L) (P = 0.0008). A reason for this paradoxical result is not clear although the authors speculated on several possibilities. Although this is an interesting and potentially clinically relevant finding, given the small size of the study and the lack of a reliable mechanistic explanation, further studies will be needed to both validate and define the cause of this unique phenomenon. Finally, no patient with an average S100B concentration greater than 1 µg/L, obtained during the first 3 days after the subarachnoid hemorrhage, had a good outcome, with or without vasospasm.

Intracerebral Hemorrhage

Although intracerebral hemorrhage accounts for a small fraction of strokes, mortality is high.29 Other than hypertension,30,31 other risk factors have not been consistently recognized. In 33,346 persons registered in the Malmo Preventive Project Database32,33 in Sweden between 1974 and 1994, 147 patients with verified primary intracerebral hemorrhage were identified by Zia et al.34 For their study, each of these 147 patients were matched with 7 control subjects having similar age, sex, and screening year. Average age at the time of hemorrhage was 61.7 ± 7 years. On multivariate regression analysis, the authors discovered that elevated systolic blood pressure [odds ratio = 1.2 (CI = 1.2-1.5)], presence of diabetes [odds ratio = 2.4 (CI = 1.1-5.5)], elevated triglycerides [odds ratio = 1.5 (CI = 1.04-2.1)], short stature [odds ratio = 1.03 (CI = 1.002-1.05)], and history of psychiatric disease [odds ratio = 1.6 (CI = 1.002-2.7)] were associated with the development of intracerebral hemorrhage. Further, regarding the subtypes of intracerebral hemorrhage, risk factors for lobar hemorrhage, which occurs in subcortical white matter, were systolic blood pressure [odds ratio per 10 mm Hg = 1.3 (CI = 1.1-1.5)] and smoking [odds ratio = 2.0 (CI = 1.1-3.9)]. For nonlobar hemorrhage, systolic blood pressure [odds ratio per 10 mm Hg = 1.5 (CI = 1.3-1.7)], diabetes

FIGURE 3. S100B individual data for the 14 patients who stayed less than 8 days in the intensive care unit because of an early discharge to the ward (n = 9, empty circles) or death (n = 5, filled circles). This prospective study was conducted in 74 patients with subarachnoid hemorrhage. Blood concentrations of protein S100B were obtained at admission and then daily for up to 8 days post subarachnoid hemorrhage. With permission from Anesthesiology. 2006;104:658–6566.
Pasternak and Lanier

Predictors of increased mortality

Predictors of poor outcome (based on modified Rankin Score = 4-6)

Significant predictors of intraventricular hemorrhage (at baseline or 24 h)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>O.R.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5y)</td>
<td>1.19</td>
<td>1.06-1.34</td>
<td>0.0043</td>
</tr>
<tr>
<td>Intracerebral hemorrhage volume at baseline (per mL)</td>
<td>1.04</td>
<td>1.03-1.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (mean arterial pressure &gt; 120 mm Hg)</td>
<td>2.11</td>
<td>1.21-3.66</td>
<td>0.008</td>
</tr>
<tr>
<td>Thalamic location</td>
<td>2.64</td>
<td>1.39-5.03</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

Significant predictors of intraventricular hemorrhage growth

<table>
<thead>
<tr>
<th>Predictor</th>
<th>O.R.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage volume at baseline (per mL)</td>
<td>1.04</td>
<td>1.03-1.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (mean arterial pressure &gt; 120 mm Hg)</td>
<td>3.09</td>
<td>1.35-7.09</td>
<td>0.0078</td>
</tr>
<tr>
<td>Presence of intraventricular hemorrhage at admission</td>
<td>4.32</td>
<td>1.99-9.38</td>
<td>0.0002</td>
</tr>
<tr>
<td>Use of recombinant activated factor VIIa</td>
<td>0.44</td>
<td>0.20-0.95</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Predictors of poor outcome (based on modified Rankin Score = 4-6)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>O.R.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5y)</td>
<td>1.59</td>
<td>1.39-1.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline Glasgow Coma Score</td>
<td>0.71</td>
<td>0.60-0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intracerebral hemorrhage volume at baseline (per mL)</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.0007</td>
</tr>
<tr>
<td>Increase in intraventricular hemorrhage volume by &gt; 2 mL</td>
<td>4.21</td>
<td>1.06-16.63</td>
<td>0.041</td>
</tr>
<tr>
<td>Intraventricular hemorrhage present within 24h</td>
<td>2.53</td>
<td>1.43-4.47</td>
<td>0.0014</td>
</tr>
<tr>
<td>Use of recombinant activated factor VIIa</td>
<td>0.5</td>
<td>0.26-0.94</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Predictors of increased mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>O.R.</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5y)</td>
<td>1.18</td>
<td>1.03-1.37</td>
<td>0.019</td>
</tr>
<tr>
<td>Baseline Glasgow Coma Score</td>
<td>0.71</td>
<td>0.62-0.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>3.61</td>
<td>1.77-7.35</td>
<td>0.0004</td>
</tr>
<tr>
<td>Intracerebral hemorrhage volume at baseline (per mL)</td>
<td>1.02</td>
<td>1.01-1.04</td>
<td>0.0003</td>
</tr>
<tr>
<td>Increase in intraventricular hemorrhage volume by &gt; 2 mL</td>
<td>6.09</td>
<td>2.68-13.86</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

This study was conducted in 374 adult patients who had spontaneous intracerebral hemorrhage documented by computerized tomographic scan within 1h of onset of symptoms. Exclusion criteria were: a Glasgow Coma Score of 5 or less; planned surgical hematoma evacuation; secondary intracerebral hemorrhage related to aneurysm, arteriovenous malformation, trauma, or other causes; known use of oral anticoagulant; known thrombocytopenia; history of coagulopathy, acute sepsis, crush injury, or disseminated intravascular coagulation; pregnancy; preexisting disability modified Rankin Scale Score greater than 2; and symptomatic thrombotic or vaso-occlusive disease (ie, angina, claudication, deep vein thrombosis, or cerebral or myocardial infarction) within 30d before the onset ICH.

Adapted with permission from Neurosurgery. 2006;59:767–774.
Visual Loss After Spine Surgery

Visual changes are common in the perioperative period and can occur secondary to a variety of disorders such as corneal exposure (dehydration), corneal abrasions, glaucoma, retinal artery occlusion or venous obstruction, optic nerve ischemia, and strokes. An uncommon but devastating complication after the spine surgery, and other forms of major surgery (e.g., cardiac) is postoperative visual loss due to optic nerve ischemia or central retinal artery occlusion. Given that the incidence of this complication is low (i.e., less than 0.2%),40 risk factors have been difficult to study. In 1999, the American Society of Anesthesiologists (ASA) Professional Liability Committee established a postoperative visual loss registry to collect information on patients experiencing visual loss after the nonocular surgery.

Lee et al41 reported on the initial 93 cases associated with spine surgery in the ASA registry. Ischemic optic neuropathy was the cause in 89% of cases. Of these cases, 67% were due to posterior ischemic optic neuropathy, 23% were due to anterior ischemic optic neuropathy, and the rest were unspecified as to whether the anterior or posterior portion of the optic nerve was affected. In those with either anterior or posterior ischemic optic neuropathy: (1) there were significantly more males (72% vs. 28% females, \( P < 0.05 \)), (2) most patients were healthy (64% were either ASA physical status classification I or II), (3) 96% were undergoing elective surgery, (4) 89% were undergoing instrumented fusion, (5) 66% had bilateral loss of vision, and (6) only 42% had some recovery. Various characteristics of patients with ischemic optic neuropathy can be found in the Table 3. The authors recommend that in any patient undergoing spine surgery in the prone position, the risk of visual loss should be included in the preoperative discussion.

The ASA Task Force on Perioperative Blindness published a practice advisory dealing with visual loss associated with spine surgery.42 The article provides a consensus view of current data and practice recommendations specifically regarding blood pressure control, fluid and hemoglobin management, use of vasoressors, patient positioning, and the use of staged surgical procedures. The last item is an attempt to lessen the duration of surgery in the prone position plus the administration of IV fluids, blood replacement, and vasopressors, all factors thought to be associated with perioperative visual loss.

<table>
<thead>
<tr>
<th>TABLE 3. Characteristics of Patients With Ischemic Optic Neuropathy Following Spine Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
</tr>
<tr>
<td>Ischemic optic neuropathy</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>n</td>
</tr>
</tbody>
</table>

Demographics

- Age (y) (mean ± SD) | 50 ± 14 |
- Male sex | 60 (72%) |
- ASA I or II | 53 (64%) |
- Elective procedure | 80 (97%) |
- Coexisting diseases |
  - Hypertension | 34 (41%) |
  - Diabetes | 13 (16%) |
  - Smoking | 38 (46%) |
  - Obesity | 44 (53%) |

Surgical characteristics

- Fusion/instrumentation | 74 (89%) |
- Previous spine surgery | 32 (39%) |
- Location |
  - Cervical or cervicothoracic | 4 (5%) |
  - Lumbar or lumbosacral | 57 (69%) |
- No. vertebral levels |
  - 1 | 9 (11%) |
  - 2 | 19 (23%) |
  - 3 | 15 (18%) |
  - ≥ 4 | 30 (36%) |
- Operative table |
  - Wilson | 25 (30%) |
  - Jackson | 22 (27%) |
  - Soft chest rolls | 17 (20%) |
- Headrest |
  - Foam pads | 47 (57%) |
  - Mayfield | 16 (19%) |
- Anesthetic characteristics |
  - Volatile plus narcotic | 74 (89%) |
  - Mean anesthetic duration (h) (mean ± SD) | 9.8 ± 3.1 |
  - Estimated blood loss (L) (mean/range) | 2.0–10.125 |
  - % of cases with >1L estimated blood loss | 82% |
  - Crystalloid replacement (L) (mean ± SD) | 9.7 ± 4.7 |
  - Lowest reported hematocrit (%) (mean ± SD) | 26 ± 5 |
  - Use of deliberate hypotension | 22 (27%) |
- Outcome |
  - Documented bilateral involvement | 55 (66%) |
  - Complete blindness with loss of light perception | 47 (57%) |
  - Any visual recovery | 35 (42%) |

Adapted with permission from Anesthesiology. 2006;105:652–659.

Postoperative Nausea and Vomiting After the Neurosurgical Procedures

Postoperative nausea and vomiting (PONV) continues to be a major cause of patient discomfort and morbidity. In 1 report, Meng and Quinlan43 reviewed factors associated with PONV after retromastoid craniectomy for microvascular decompression of cranial nerves. One hundred eighty-five ASA physical class I-III patients in the age range of 18 to 65 years were included in the study. Despite the use of prophylactic ondansetron in 99% and preoperative transdermal scopolamine patch in 11% of patients, the overall incidence of PONV within 24 hours postoperatively was 60%. Upon multivariate logistic regression analysis, the only factors associated with the increased risk of PONV in this patient population were: (1) female sex, (2) cranial nerve V decompression (as compared with cranial nerve VII, IX, or X), (3) use of desflurane (as compared with isoflurane or sevoflurane), and (4) lack of use of transdermal scopolamine \( P < 0.005 \) for all comparisons). The authors concluded that multiple prophylactic interventions against PONV should be considered in this high-risk population.
Pasternak and Lanier

Flynn and Nemergut evaluated the incidence of and risk factors for PONV after transsphenoidal surgery in 877 patients. They report an overall 7.5% incidence of PONV in the operating room or postanesthesia recovery unit. Significant risk factors for PONV included: (1) placement of a fat graft for cerebrospinal fluid (CSF) leak (11.7% vs. 5.4%, *P* < 0.001), (2) requirement of a lumbar drainage catheter (17.1% vs. 6.6%, *P* < 0.001), and (3) craniopharyngioma [18% vs. 6% to 10% for all other surgical indications (ie, Cushing disease, acromegaly, prolactinoma, nonsecreting tumors), *P* = 0.007]. It is likely that reduced CSF pressure, either from a dural leak requiring a fat graft or during placement and aspiration from the lumbar drainage catheter, might be a major contributor to the increased incidence of PONV observed in this investigation.

Airway Management in Neurosurgical Patients

Vocal cord dysfunction is an uncommon but potentially devastating complication after anterior-approach cervical spine surgery. Nerve insult or injury is thought to occur during airway traction such that pressure is placed on branches of the recurrent laryngeal nerve. Deflation and subsequent re-inflation of the endotracheal tube cuff has been suggested as a means to allow the endotracheal tube the ability to move away from the tracheal wall, where the injury is thought to occur. In a prospective, randomized fashion, Audu et al evaluated the efficacy of this maneuver toward the prevention of vocal cord injury in 100 patients undergoing cervical spine surgery via the anterior approach. Vocal fold motion was assessed pre- and post-operative by an otolaryngologist via fiberoptic examination. Patients were randomized to receive either standard management (ie, cuff inflated without preset guidelines following tracheal intubation and deflated prior to extubation; cuff pressure was measured only after the anesthesia provider was satisfied with the degree of cuff inflation) or inflation of the cuff until no leak was ascultated when 20 to 25 cmH2O pressure was applied to the circuit following intubation. In this latter group, the cuff was deflated for 5 s following retraction of the airway by the surgeon and subsequently re-inflated in a similar manner to that following tracheal intubation. Despite greater pressures within the cuff in the control group (50 ± 49 mmHg vs. 18 ± 14 mmHg, respectively; *P* < 0.001), there was no difference between groups with regard to the development of new vocal cord paresis or paralysis post-operatively (15.4% vs. 14.5% for control versus intervention groups, respectively; *P* > 0.05). There was no difference between those who did and those who did not develop a new vocal cord injury (ie, paresis and paralysis) with regard to demographics, side of surgery, duration of surgery, retractor time, or pressure within the cuff of the endotracheal tube. With respect to vocal cord paralysis, three of eleven patients with a new paralysis underwent surgery via a right-sided approach versus zero of 83 patients who developed a new paralysis following a left-sided approach. This may be due to anatomic differences in the course of the recurrent laryngeal nerve in the neck. Unlike the left nerve which is usually located in the tracheo-esophageal groove, the right recurrent laryngeal nerve usually lies unprotected outside the groove. This latter finding suggests that surgical, and not anesthetic, factors may be the cause of vocal cord paralysis.

The safest means to provide airway management in patients with cervical spine trauma has often been debated. Crosby et al published a near-comprehensive review of the literature dealing with this issue. This article describes the epidemiology, anatomy, and pathophysiologic mechanisms of cervical spine injury, as well as discusses the data regarding recommendations for safe airway management in this group of patients. The authors conclude that a variety of airway management options are safe and acceptable. Further, there are insufficient data to support a particular practice option. The key principal to consider when intubating patients with acute cervical spinal cord trauma is to minimize neck movement and maintain hemodynamic stability. All factors considered, airway management during induction of anesthesia in the presence of cervical spine injury should be dictated by common sense, not by dogmatic approaches.

Patients with acromegaly may present for neurosurgical resection of their hormone-secreting tumor, most commonly via a transsphenoidal approach. This disease state can predispose to difficulty in securing an airway by standard (ie, direct laryngoscopic) means due to factors such as an enlarged tongue and hypertrophy of laryngeal and pharyngeal tissue. Nemergut et al retrospectively reviewed the records of 746 patients who underwent transsphenoidal pituitary surgery at a single institution and discovered overall 3.8% incidence of unanticipated difficult intubation. Acromegaly was the only factor associated with increased unanticipated difficulty (9.1% vs. 2.6% in patients with non-functioning tumors, *P* = 0.007). Gender, tumor size, or the presence of a prolactin-secreting tumor was not associated with difficulty. Of note, Cushing’s disease, which is associated with obesity, the presence of a “buffalo hump,” and obstructive sleep apnea, also was not associated with a difficult airway. The investigation only focused on cases with unanticipated difficult intubation; specifically, their analysis did not evaluate patients in whom proactive measures were taken to accommodate expected airway difficulty. As such, their data underestimate the overall incidence of challenging airway management for pituitary surgery patients.

Koyama et al described the use of the new AirWay Scope (Pentax Corporation, Tokyo, Japan) to facilitate tracheal intubation in neurosurgical patients (Fig. 4). Advantages of the device include: 1) a shape based on computerized tomograms of healthy humans, allowing the device to fit in the oropharynx with minimal neck extension, 2) a rotating color display, 3) a guide function that stabilizes tube direction, 4) a port that allows passage of a 12-French suction catheter, and 5) portability. The authors reported rapid and safe tracheal intubation in 10
consecutive, non-obese, otherwise healthy neurosurgical patients with apparently grossly normal airways [Mallampati 1 (n = 1), Mallampati 2 (n = 4), Mallampati 3 (n = 1), Mallampati class not stated (n = 3)]. Further investigations will be required to determine the device’s safety and effectiveness in patients with difficult airways or cervical spine anomalies.

Coughing during emergence from anesthesia can have many adverse affects such as hypertension, increased intracranial pressure, and promotion of intracranial bleeding. The IV administration of various drugs (ie, beta1-adrenergic antagonists, local anesthetics, short acting narcotics, and calcium channel antagonists) immediately prior to extubation can reduce the incidence of coughing or hypertension.52–55 Further, lidocaine solution, placed into the cuff of the endotracheal tube, in lieu of air, is also reported to attenuate coughing and hypertensive episodes.56 It is believed that lidocaine diffuses out of the cuff and into the tracheal mucosa. In a randomized, double-blinded, prospective trial, Venkatesan et al compared the incidence of coughing and effects on hemodynamics, in 82 patients undergoing craniotomy.57 Patients were randomly treated with either 4% lidocaine infused into the cuff of the endotracheal tube or 1.5 mg/kg IV lidocaine administered as a bolus dose, given immediately following administration of neuromuscular blockade-reversing agents. No difference was found between groups with regard to the incidence of coughing or change in vital signs (ie, heart rate and blood pressure) just prior to and during endotracheal extubation. Further, no adverse effects we observed in either group. Unfortunately, the authors did not include a placebo group; therefore, it is not possible to comment on absolute efficacy of either technique. Further, they did not measure lidocaine concentrations, so the diffusion of meaningful doses of lidocaine through the tracheal tube cuff remains speculative.

**Intracranial Procedures in Awake Patients**

Monitored anesthesia care, including mild sedation, is commonly used to facilitate neurosurgical procedures on eloquent regions of brain. However, its safety versus standard general anesthesia (GA) is currently unknown. Skucas et al retrospectively compared the incidence of complications in patients undergoing seizure focus resection via monitored anesthesia care (n = 332) versus GA (n = 129).58 Those receiving monitored anesthesia care had: 1) more episodes of mild oxyhemoglobin desaturations, 2) greater arterial carbon dioxide partial pressure, 3) more episodes of hyper- and hypotension, 4) more episodes of tachycardia, but 5) less frequent episodes of bradycardia (Table 4). Of note, there were 6 patients (1.8%) in the monitored anesthesia care group that required rescue airway management. Most were obese, 1 suffered laryngospasm, and the remainder experienced unacceptable oxygen desaturations. Of these, the tracheas of 2 were intubated fiberoptically, a laryngeal mask was used in 1, and the remainder were conservatively managed.

Manninen et al prospectively compared fentanyl boluses (0.5 to 1 mcg/kg then 25 to 50 mcg as needed) to a remifentanil infusion (0.03 to 0.05 mcg/kg/min) during propofol sedation (75 to 100 mcg/kg/min) in 50 patients during monitored anesthesia care for craniotomy.59 They found no difference between groups with regard to: 1) intra-operative or post-operative hemodynamics, 2) intra-operative or post-operative complications, 3) post-operative pain or sedation, or 4) patient satisfaction. The authors concluded that either narcotic, supplemental to a propofol infusion, provides for a safe and effective means of sedation during awake craniotomy.

Bilgin et al prospectively compared the use of fentanyl, alfentanil, or remifentanil, as a primary sedative for stereotactic brain biopsy during monitored anesthesia care.60 135 patients undergoing brain biopsy via burr
hole were randomized to received, in addition to meto- 
clopramide IV 10 mg and midazolam IV 0.03 mg/kg, 
either fentanyl (1 mcg/kg boluses as needed), alfentanil 
(7.5 mcg/kg bolus then 0.25 mcg/kg/min), or remifentanil 
(0.05 mcg/kg/min). Although there were differences with 
regard to heart rate (slower heart rate, but not clinical 
bradycardia, was more common in the fentanyl group) 
and oxygen saturation (lowest in the alfentanil group but 
still generally above 94%), there were no differences 
among groups regarding other hemodynamic or respira-
tory data or the rate of complications. The authors 
concluded that either narcotic, in addition to midazolam, 
provides for a safe and effective technique for brain 
biopsy via monitored anesthesia care. Unlike the study by 
Manninen et al, the Bilgin et al report did not evaluate 
patient satisfaction post-operatively.

Dexmedetomidine is an α₂-adrenergic receptor 
agonist with rapidly titratable sedative, sympathetic, 
and analgesic effects, but without meaningful respiratory 
depression.⁶¹–⁶³ Given the effective sedation and analgesic 
profile without the respiratory depressant effects com-
monly seen with other sedation agents, dexmedetomidine 
has proven a useful adjunct for patients undergoing 
craniotomy via monitored anesthesia care.⁶⁴ Moore et al 
reported on the use of a dexmedetomidine infusion, in lieu 
of conversion to general anesthesia, in a 57 year-old 
patient who was unable to tolerate light sedation. The 
patient was undergoing craniotomy during propofol and 
remifentanil infusions, but complained of discomfort 
related to positioning. She was unable to tolerate deeper 
sedation due to concerns about hypercapnia and clinically 
increased brain tension. Both the propofol and remifen-
tanil infusions were discontinued, and dexmedetomidine 
was started, after which the patient was able to tolerate 
her procedure, underwent successful awake cortical 
mapping, and subsequently had an uneventful periopera-
tive course.

Rozet et al also reported on their experience with 
dexmedetomidine as a sedative agent during implantation 
of deep brain stimulators for treatment of Parkinson’s 
disease.⁶⁵ Prior to 2003, patients undergoing this proce-
dure were given no sedation at the authors’ institution 
(Harborview Medical Center, Seattle, WA), however, 
in 2003, a clinical protocol involving dexmedetomidine 
sedation was instituted. The authors, therefore, compared 
the outcome of their practice involving dexmedetomidine 
(n = 11) to that without (controls, n = 8). A 0.3 to 
0.6 mcg/kg/hour infusion of dexmedetomidine: 1) did not 
interfere with microelectrode recordings, 2) did not 
impair the patient’s movement disorder, 3) allowed for 
patient cooperation, and 4) decreased antihypertensive 
medication requirements during the procedure. Overall, 
both patient and surgeon satisfaction were good to 
excellent. The authors reported on three complications 
attributable to dexmedetomidine: 1) one case (0.9%) of 
dyspnea, 2) one case (0.9%) of respiratory arrest, and 3) 
one case (0.9%) of agitation after discontinuing dexam-
etomidine. The authors did not report on complications 
that occurred in the control group so it is unknown if the 
27% complication rate attributed to dexmedetomidine is 
superior to other sedation techniques.

Endoscopic third ventriculostomy is used to treat 
various types of obstructive hydrocephalus. In this 
procedure, the floor of the third ventricle is surgically 
fenestrated so that CSF is able to drain directly into the 
basal cisterns. The procedure is often performed under 
general anesthesia; however, in patients with multiple or 
severe comorbidities, monitored anesthesia care might be 
a better option. Longatti et al⁴⁶ report the common 
ocurrence (100% of 24 patients) of bilateral orbital pain 
during coagulation and dilatation of the floor of the third 
ventricle when the procedure was performed in awake 
patients. The authors had no definite mechanistic 
explanation for this finding other than to suggest that it 
may be related to the stimulation of pain structures in 
that region, such as periaqueductal gray matter, the 
hypothalamus, or some other yet undiscovered pain-
mediating tract.

---

### TABLE 4. Incidence of Complications in Craniotomy Performed via Monitored Anesthesia Care and General Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Monitored Anesthesia Care</th>
<th>General Anesthesia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>332</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Episodes of SpO₂ = 91%-95% (%)</td>
<td>16.9</td>
<td>0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Episodes of SpO₂ ≤90% (%)</td>
<td>1.5</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>47.5 ± 1.2</td>
<td>35.0 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertensive episodes (%)</td>
<td>11.1</td>
<td>3.9</td>
<td>0.0149</td>
</tr>
<tr>
<td>Hypotensive episodes (%)</td>
<td>56.3</td>
<td>26.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tachycardic episodes (%)</td>
<td>14.2</td>
<td>2.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bradycardia episodes (%)</td>
<td>0.3</td>
<td>3.1</td>
<td>0.0092</td>
</tr>
<tr>
<td>Seizures (%)</td>
<td>3</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Brain swelling (%)</td>
<td>0.6</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Intraoperative bleeding (%)</td>
<td>0.6</td>
<td>0.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

This was a retrospective review of the records from patients, aged from 10 to 70 y, who underwent craniotomy for seizure focus resection. Anesthetic techniques consisted of either general anesthesia for the duration of the procedure or monitored anesthesia care consisting of IV sedation before and after mapping with spontaneous ventilation throughout and without a secured airway (ie, laryngeal mask airway, endotracheal tube).

Bradycardia indicates heart rate < 45 beats per minute; hypertension, systolic blood pressure > 150 mm Hg; hypotension, systolic blood pressure < 90 mm Hg; ns, not significant; PaCO₂, arterial carbon dioxide partial pressure; SpO₂, oxyhemoglobin saturation; Tachycardia, heart rate > 110 beats per min.

Adapted with permission from Anesth Analg. 2006;102:882-887.
Carotid Endarterectomy—Anesthetic Techniques and Outcomes

In 2001, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) demonstrated that in patients with both symptomatic and asymptomatic carotid disease, who were randomized to either endarterectomy or endovascular treatment, risks of major complications (ie, disabling stroke or death) were similar. However, the risk of restenosis after 1 year was more common after endovascular treatment, but the risk of minor complications (ie, cranial nerve injury, hematoma) was more common after endarterectomy. Similar to CAVATAS, Mas et al performed a prospective randomized multicenter trial, except they included only patients with symptomatic and severe (≥60%) carotid stenosis. In the endovascular treatment group, all patients underwent stenting (unlike the CAVATAS trial where patients had angioplasty with or without stenting). With 257 and 247 patients who completed the study in the endarterectomy and endovascular arms, respectively, the incidence of disabling stroke or death within 30 days of the procedure was 3.4% after stenting and 1.5% after endarterectomy (P = 0.26). The incidence of any stroke or death at 30 days was greater in those who underwent stenting (9.6% vs. 3.9% for endarterectomy; P = 0.01) and there was a significantly greater incidence of stroke or death within 6 months of stenting (11.7% vs. 6.1% for endarterectomy; P = 0.02) despite an increased incidence of preprocedural stroke in those who underwent endarterectomy (20.1%) compared with endovascular treatment (12.6%) (P = 0.02). Overall, the incidence of local complications (ie, hematoma, infection, pseudoaneurysm, limb thrombosis) was not different between groups (P = 0.22 overall); however, the incidence of cranial nerve injury was less with stenting (1.1% vs. 7.7% for endarterectomy; P < 0.001). Long-term follow-up in this group of patients will determine if these effects are sustained.

Although dexmedetomidine has many attractive qualities, one of the theoretical concern is its effects on cerebral hemodynamics. Specifically, dexmedetomidine produces direct vasoconstriction of the cerebral vasculature without a concomitant decrease in cerebral metabolic rate. These hemodynamic effects can potentially increase the risk of cerebral ischemia upon carotid cross-clamping. Bekker et al prospectively estimated the incidence of new-onset cerebral ischemia upon carotid cross-clamp in patients receiving regional anesthesia, with dexmedetomidine (0.1 to 0.5 mcg/kg/h) used at the primary sedative agent. The criteria for shunt placement were the development of either new neurologic deficits (ie, contralateral weakness, slurred speech, and confusion) or nausea on carotid occlusion. In 123 patients, 5 patients (4.3%) required shunting. Although there was no control group in this study, the authors report that the incidence of ischemic symptoms upon cross-clamp was similar to that published in other sources, 5% to 12.4%.

In 54 patients undergoing carotid endarterectomy via regional anesthesia and sedation, McCutcheon et al compared dexmedetomidine with a fentanyl and midazolam-based protocol where intraoperative sedation was titrated to a Ramsey Sedation Score of 2–4. Patients who received dexmedetomidine had fewer intraoperative tachycardia and hypertensive episodes and had less hypertension and lesser narcotic requirements in the postanesthesia recovery unit. There was no difference between groups with regard to arterial carbon dioxide partial pressure, antiemetic requirements, need for shunting owing to the development of cerebral ischemic symptoms upon carotid cross-clamping, or overall patient satisfaction. Similar findings were demonstrated by Bekker et al in 2004.

When viewed collectively, the data of Bekker et al and McCutcheon et al suggest that, despite theoretical concerns, dexmedetomidine probably does not increase the incidence or severity of cerebral ischemic events during carotid endarterectomy.

It has long been appreciated that cerebral and myocardial ischemia are common complications following carotid endarterectomy. In a retrospective study involving 1201 patients who underwent carotid endarterectomy at a single institution, McGirt et al reported on risk factors for new-onset stroke or myocardial infarction. Overall rate of stroke, transient ischemic attack, myocardial infarction, and death were 3.8%, 1.6%, 1.6%, and 1.4%. Hyperglycemia (blood glucose >200 mg/dL) was an independent predictor for stroke, myocardial infarction, and death. Other results can be found in Table 5. Although this study used a high cut-off value to define hyperglycemia (ie, >200 mg/dL), it provides the following results:

### TABLE 5. Predictors of Stroke, Transient Ischemic Attacks, Myocardial Infarction, and Death After Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/transient ischemic attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative blood glucose &gt; 200 mg/dL</td>
<td>2.78 (1.37-5.67)</td>
<td>0.005</td>
</tr>
<tr>
<td>Postoperative blood glucose &gt; 200 mg/dL</td>
<td>1.67 (0.59-4.71)</td>
<td>0.333</td>
</tr>
<tr>
<td>Combined coronary artery bypass/carotid</td>
<td>3.52 (1.59-7.78)</td>
<td>0.002</td>
</tr>
<tr>
<td>endarterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic carotid disease</td>
<td>2.19 (1.15-4.18)</td>
<td>0.018</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative blood glucose &gt; 200 mg/dL</td>
<td>4.29 (1.28-14.39)</td>
<td>0.018</td>
</tr>
<tr>
<td>Postoperative blood glucose &gt; 200 mg/dL</td>
<td>0.776 (0.14-3.05)</td>
<td>0.716</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>2.87 (0.93-8.88)</td>
<td>0.067</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>6.28 (2.25-17.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative blood glucose &gt; 200 mg/dL</td>
<td>3.29 (1.07-10.09)</td>
<td>0.037</td>
</tr>
<tr>
<td>Postoperative blood glucose &gt; 200 mg/dL</td>
<td>2.24 (0.59-8.42)</td>
<td>0.233</td>
</tr>
<tr>
<td>Combined coronary artery bypass/carotid</td>
<td>6.16 (2.17-17.43)</td>
<td>0.006</td>
</tr>
<tr>
<td>endarterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>7.17 (2.37-21.63)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

This retrospective study was conducted in 1201 patients with both asymptomatic and symptomatic carotid artery atherosclerotic disease, who underwent carotid endarterectomy at a single institution.

Adapted with permission from *Neurosurgery*, 2006;58:1066–1073.
additional support for the current trends for tighter
glycemic control in patients at risk for cerebral ischemia.

The risk of frank stroke after carotid endarterectomy is low, usually less than 1% to 4%.77,78 However, approximately 25% of patients who undergo carotid endarterectomy develop postoperative neurocognitive deficits.79,80 The mechanism of injury leading to these new cognitive deficits is currently poorly understood. In 34 patients undergoing carotid endarterectomy, Heyer et al.81 reported that the development of new postoperative cognitive deficits is not associated with new radiographic lesions in the brain as assessed by diffusion-weighted magnetic resonance imaging. Specifically, 8 (24%) patients had new-onset postoperative cognitive dysfunction and 3 patients (9%) had new radiographic lesions; only 1 patient had both new cognitive deficits and new lesions. Because embolic phenomena lead to the appearance of lesions on diffusion-weighted imaging and hypoperfusion does not, the authors conclude that cognitive deficits may be more dependent on hypoperfusion and not emboli. Further, the only risk factor identified as contributory to new cognitive deficits was carotid cross-clamp time (44.2 ± 16.2 min vs. 63.1 ± 16.9 min for the absence and presence of new cognitive deficits, respectively; P < 0.008). Such an observation also supports hypoperfusion as a source of neurologic deterioration. Further investigation will be needed to determine the clinical relevance of the new hypodensities.

Mocco et al.82 prospectively evaluated 186 symptomatic and asymptomatic patients undergoing carotid endarterectomy, both preoperatively and postoperatively at 1 day and 1 month, for the development of new cognitive deficits. They report an overall incidence of cognitive dysfunction of 18% and 9% at postoperative days 1 and 30, respectively. In a multivariate logistic analysis, only age (73.2 ± 7.7 y vs. 69.1 ± 8.5 y for presence and absence of new deficits respectively, odds ratio = 1.93, CI = 1.15-3.25; P = 0.01) was an independent predictor of cognitive dysfunction on postoperative day 1. On postoperative day 30, both age (73.2 ± 7.6 y vs. 69.8 ± 8.2 y for the presence and absence of new deficits, respectively, odds ratio = 2.57, CI = 1.01-6.51; P < 0.05) and the presence of diabetes mellitus (57% vs. 22% for the presence and absence of new deficits, odds ratio = 4.26, CI = 1.15-15.79; P = 0.03) were associated with the development of cognitive dysfunction. Factors that were not associated with the development of new cognitive deficits at either time point included sex, body mass index, smoking history, hypertension, hyperlipidemia, use of statin medications, need for intraoperative carotid shunt placement, surgical duration, or whether the patient’s carotid disease was symptomatic or asymptomatic.

CEREBRAL HEMODYNAMICS

In 2006, a great deal of the neuroanesthesia literature addressing cerebral hemodynamics focused on the effects of various anesthetic agents on cerebral blood flow, autoregulation, and reactivity to carbon dioxide. Other studies addressed additional items that affected hemodynamics: diabetes mellitus, body position, presence of tumors, aging, and the use of hyperventilation after injury.

Carbon dioxide reactivity refers to the changes in cerebral blood flow in response to changes in the partial pressure of carbon dioxide in arterial blood (PaCO2). Some prior data suggest that volatile anesthetics may alter the reactivity of the cerebral vasculature to carbon dioxide.83,84 It has also been reported that cerebrovascular carbon dioxide reactivity is altered in those with diabetes mellitus during propofol anesthesia.85 As diabetes mellitus is a common disease and volatile agents are commonly used anesthetics, it is important to characterize the response of the cerebral vasculature to carbon dioxide in diabetic patients during a volatile-based anesthetic because carbon dioxide reactivity is often exploited clinically (ie, to control intracranial pressure). Kadoi et al.86 randomized 40 diabetic patients undergoing elective orthopedic, cardiac, or thoracic surgery to maintenance with 67% inspired nitrous oxide with 1 minimum alveolar concentration (MAC) equivalent of either sevoflurane or isoflurane. Middle cerebral artery blood flow velocity was assessed via transcranial Doppler sonography at normocapnia (end-expired CO2 35 to 37 mm Hg) and at hypercapnia (end-expired CO2 42 to 44 mm Hg). Absolute and relative reactivity to carbon dioxide were determined on the basis of the equations in Figure 5. The degree of cerebrovasodilation in response to hypercapnia was decreased in: (1) patients in whom diabetes was managed with insulin compared with those managed with oral agents or diet, irrespective of the volatile anesthetic used and (2) those patients who received sevoflurane with diet and oral agent-controlled diabetes compared with similar patients who received isoflurane (Table 6). The response to hypocapnia was not determined in this investigation. Of note, patients who were receiving insulin probably had more poorly controlled diabetes, as they had higher serum concentrations of hemoglobin A1c (Table 6). The authors attributed these carbon dioxide-reactivity findings to impaired nitric oxide release in hyperglycemic patients.87 One possible implication of this investigation is that the loss of reactivity of the cerebral vasculature in diabetic patients

FIGURE 5. Equations used to determine the absolute and relative reactivity of the cerebrovasculature to arterial carbon dioxide partial pressure. PaCO2 indicates partial pressure of carbon dioxide in arterial blood; Vmca, velocity of blood in the middle cerebral artery (cm/s). With permission from Anesth Analg. 2006;103:168–172.

\[
\text{Absolute CO2 reactivity} = \frac{\text{Vmca (hypercapnia) – Vmca (normocapnia)}}{\text{PaCO2 (hypercapnia) - PaCO2 (normocapnia)}}
\]

\[
\text{Relative CO2 reactivity} = \frac{\text{Absolute CO2 reactivity}}{\text{Vmca (normocapnia)}}
\]

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may correlate with a decreased capacity to vasodilate in response to decreased oxygen supply, such as during hypotension. If true, such a factor would help explain the increased severity of ischemic brain injury reported in diabetic patients.

Head position can have an important effect on cerebral hemodynamics. Specifically, elevation of the head improves venous drainage and can help to decrease intracranial pressure. A 10-degree head-up position has been reported to decrease intracranial pressure without affecting cerebral perfusion pressure in patients undergoing craniotomy for tumor resection. Tankisi et al. evaluated the effect of the 10-degree head-up, compared with horizontal, position on cerebral perfusion pressure and intracranial pressure in 28 patients undergoing aneurysm clipping. Head-up was associated with a decrease in intracranial pressure (2.8 ± 3.6 mm Hg vs. 6.6 ± 4.6 mm Hg for horizontal, P < 0.05), a decrease in mean arterial blood pressure (72 ± 14 mm Hg vs. 77 ± 14 mm Hg for horizontal, P < 0.05), but no change in calculated cerebral perfusion pressure (70 ± 14 mm Hg vs. 70 ± 14 mm Hg for horizontal, P > 0.05). In going from horizontal to 10-degree head-up position, dural tension, as estimated on a 4-point scale by the neurosurgeon, was reduced in 15 patients and unchanged in 13 patients. These data suggest that slight head elevation can improve venous drainage without the adverse effect of decreasing cerebral perfusion pressure in patients undergoing aneurysm clipping.

It is unclear if the presence of tumor affects the reactivity of the cerebrovasculature to carbon dioxide. Umamahewsara Rao et al. prospectively evaluated the reactivity of the brain to the changes in arterial carbon dioxide partial pressure in 29 patients undergoing frontotemporal craniotomy for glioma resection during either propofol or isoflurane anesthesia. After the induction of anesthesia and before the commencement of surgery, transcranial Doppleruario of both middle cerebral arteries was obtained during a target PaCO2 of 37 ± 2 mm Hg (normocapnia) and 30 ± 2 mm Hg (hypocapnia). The responsiveness of the vasculature to the changes in carbon dioxide was estimated by determining the percent-change per mm Hg change in PaCO2 in the velocity of middle cerebral artery blood flow (Vmca) upon institution of hypocapnia. They reported that reactivity to carbon dioxide was not affected by: (1) the cerebral hemisphere (ie, the side containing tumor compared with the tumor-free side) tested, or (2) the anesthetic technique used (ie, propofol or isoflurane). This suggests that the presence of tumor does not affect carbon dioxide reactivity; however, the authors did not address other factors (ie, the presence of herniation, tumor size, tumor type, the degree of peritumor edema) that could contribute to the alterations in the reactivity of the cerebrovasculature to arterial carbon dioxide tension.

A variety of changes occur with aging that may limit the ability to optimally deliver oxygen to the brain in the setting of arterial hypoxemia. Li et al. evaluated the effect of aging on local cerebral blood flow (measured via laser Doppler sonography), and brain oxygen partial pressures in a nonhypertensive rat model of isovolemic hemodilution. In 344 rats stratified into 3 groups: (1) young (3 mo old), (2) middle-age (9 to 12 mo old), and (3) elderly (24 mo old), the authors found that the cerebral blood flow and brain oxygen partial pressure were not significantly affected by normovolemic hemodilution or by age (Table 7). There seemed to be a tendency toward increased local cerebral blood flow after hemodilution and a significant decrease in the brain partial pressure of oxygen immediately after the hemodilution. However, the latter normalized after a few minutes. Age, therefore, did not seem to affect the response of the cerebral vasculature or brain oxygen partial pressure to isovolemic hemodilution. It is possible, though, that this model did not produce enough hemodilution or does not accurately represent the human population with vascular disease.

During hyperventilation-induced cerebral vasoconstriction, cerebral metabolic rate does not change. In this setting, oxygen delivery is usually sufficient because of a compensatory increase in the fraction of oxygen extracted.

### Table 6. Comparative Effects of Sevoflurane or Isoflurane on the Reactivity of the Cerebrovasculature to Carbon Dioxide

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diet</td>
<td>Oral Agent</td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Baseline (P_{\text{ETCO}}) (mm Hg)</td>
<td>35 ± 3</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>(P_{\text{ETCO}}) during hypercapnia (mm Hg)</td>
<td>43 ± 4</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.1 ± 0.7</td>
<td>5.9 ± 1.1</td>
</tr>
<tr>
<td>Absolute CO(_2) reactivity (cm/s/mm Hg)</td>
<td>2.6 ± 0.6(\dagger)</td>
<td>2.5 ± 0.8(\dagger)</td>
</tr>
<tr>
<td>Relative CO(_2) reactivity (%/mm Hg)</td>
<td>4.8 ± 1.2(\dagger)</td>
<td>4.5 ± 1.4(\dagger)</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± SD.

This prospective investigation was conducted in adult patients with type 2 diabetes mellitus controlled either with diet, oral hypoglycemic agents, or insulin. Reactivity of the cerebrovasculature to arterial carbon dioxide tension was assessed using transcranial Doppler sonography during either isoflurane or sevoflurane anesthesia.

\(P_{\text{ETCO}}\) indicates end-expired partial pressure of carbon dioxide.

\(\dagger P < 0.05 \) compared with the corresponding group maintained with isoflurane.

\(w P < 0.05 \) compared with diet and oral agent-controlled diabetes within same volatile anesthetic group.

Adapted with permission from *Anesth Analg*. 2006;103:168–172.
from the blood. In traumatic brain injury, it has been reported that during hyperventilation, oxygen extraction can be exhausted such that cerebral ischemia may develop. After subarachnoid hemorrhage, various vasomotor changes occur (ie, vasospasm and impaired cerebral autoregulation), which could potentially lead to similar exhaustion of oxygen extraction if hyperventilation were induced. In a rat model of subarachnoid hemorrhage, Ma et al evaluated the effect of graded hyperventilation on the oxygen extraction ratio of the brain. Despite reductions in cerebral blood flow in both control animals and those following injection of autologous blood into the cisterna magna (ie, subarachnoid hemorrhage model), appropriate compensatory increases in the oxygen extraction ratios were observed such that there was no increase in lactate production by the brain. Of note, the animals in the subarachnoid hemorrhage group all received 0.07 mL of intracisternal blood. This investigation does not take into consideration the various severities of subarachnoid hemorrhage, and extension of these data in the setting of severe subarachnoid hemorrhage may not be appropriate.

**MONITORING**

Traditionally, intraoperative applications of motor-evoked potentials (MEPs) were limited by their inherent sensitivity to the depressant effects of commonly used anesthetic agents. However, with recent technical advances (eg, the introduction of repetitive high-frequency stimulation devices), safe and effective direct monitoring of motor tracts is becoming much more compatible with mainstream anesthetic techniques.

Despite the above-mentioned advances, volatile anesthetic agents still produce significant depression of MEPs. Lo et al compared desflurane (2.1 to 4.3 end-expired volume %) plus 66% inspired nitrous oxide anesthesia versus total IV anesthetic provided with a propofol infusion (10 mg/kg for 10 min, then 8 mg/kg for 10 min, then 5 mg/kg every 10 min) during an air/oxygen inhaled mixture on tibialis anterior and adductor hallucis-recorded potentials in unparalyzed patients. Multipulse transcranial electrical stimulation was conducted via a train of 5 square waves of 0.5-ms duration delivered at 250 Hz. No differences were found in peak latencies in both muscle groups between techniques. There was less suppression of the amplitudes of adductor hallucis responses with desflurane/nitrous oxide (85 ± 19 mA vs. 56.7 ± 28.4 mA with propofol, \(P < 0.05\)), and less suppression of tibialis anterior responses with propofol (59.1 ± 24.5 mA vs. 21.7 ± 10.8 mA for desflurane/nitrous oxide, \(P < 0.05\)). The authors offered no explanation for the differential effects on the 2 muscle groups other than to say that it may be because of the differences in “central nervous system or spinal cord actions” (of the anesthetic agents). Given the small number of patients enrolled in this investigation (ie, 20), the lack of meaningful differences between anesthetics may be due to type II statistical error.

Sekimoto et al compared the suppressant effects of both 0.5 MAC and 1 MAC halothane, isoflurane, or sevoflurane on MEPS obtained from the adductor pollicis and tibialis anterior muscles in 35 patients undergoing brain tumor resection. The background anesthetic consisted of 67% inspired nitrous oxide, a propofol infusion titrated to a bispectral index (BIS) of 40 ± 5 before the institution of volatile anesthetic, and a vecuronium infusion titrated to a 40% to 50% suppression of the first twitch in a train of 4 after recovery from an intubating dose. MEPS were elicited via metal electrodes screwed directly into the calvarium, with a train of 5400-ms duration square waves delivered at a 500-Hz frequency at an intensity of <200 mA. At 0.5 MAC, halothane produced less depression of peak amplitude (65.0 ± 21.2%) compared with sevoflurane and isoflurane (23.2 ± 21.2% and 25.1 ± 17.3% respectively, \(P < 0.05\) for halothane vs. sevoflurane and isoflurane, \(P > 0.05\) for sevoflurane vs. isoflurane). At 1 MAC, amplitude suppression was not different (21.2 ± 14.4%, 20.5 ± 23.4%, etc., etc.

### TABLE 7. Physiologic Parameters During Graded Hemodilution in Rats of Various Ages

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 mo (Young)</th>
<th>9-12 mo (Middle Age)</th>
<th>24 mo (Elderly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.7 ± 0.7</td>
<td>10.3 ± 0.5</td>
<td>11.0 ± 1.3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>122 ± 15*</td>
<td>129 ± 14*</td>
<td>104 ± 14.8</td>
</tr>
<tr>
<td>Laser Doppler flow (units)</td>
<td>568 ± 620</td>
<td>1167 ± 498</td>
<td>930 ± 508</td>
</tr>
<tr>
<td>PBrO₂ (mm Hg)</td>
<td>17.1 ± 4.3</td>
<td>17.6 ± 4.4</td>
<td>19.5 ± 3.4</td>
</tr>
<tr>
<td>Severe hemodilution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>6.1 ± 0.6</td>
<td>5.7 ± 0.9*</td>
<td>6.6 ± 0.9</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>107 ± 22</td>
<td>108 ± 21</td>
<td>91 ± 16</td>
</tr>
<tr>
<td>Laser Doppler flow (units)</td>
<td>1025 ± 610</td>
<td>1269 ± 640</td>
<td>1081 ± 427</td>
</tr>
<tr>
<td>PBrO₂ (mm Hg)</td>
<td>16.8 ± 7.3</td>
<td>16.3 ± 7.3</td>
<td>19.4 ± 5.9</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to 24 mo group.

Adapted with permission from J Neurosurg Anesth. 2006;18:125–131.
17.7 ± 30.5% among sevoflurane, isoflurane and halothane, respectively. \( P > 0.05 \). The effect on peak latency was not addressed in this study.

Reinacher et al\(^{101}\) characterized the effects of a sevoflurane-based anesthetic on MEPs during variations in both sevoflurane dose and the MEP technique. In 12 patients undergoing craniotomy in whom neuromuscular block following intubation had dissipated, and who were maintained on a remifentanil infusion without supplemental nitrous oxide, end-expired sevoflurane was adjusted to age equivalents of 0.5, 0.75, and 1.0 MAC while monitoring responses in the abductor pollicis brevis and abductor digitii minimi muscles. MEP stimulation profiles were varied in the following 3 manners:

1. Varying current (100, 150, 200, 250, and 300 V) for a train of 4 stimuli at 500 Hz;
2. Varying stimulation frequency (100, 200, 500, and 1000 Hz) with 4, 300 V stimuli;
3. Varying the number of 300-V stimuli (1-5) delivered at 500 Hz.

The investigators demonstrated the least suppression of MEP amplitudes with 4 stimuli of maximal current (300 V) delivered at maximal frequency (1000 Hz). Concentration effects of sevoflurane were minimal when stimuli were delivered in this manner. Although the results of this study tend to suggest that MEP monitoring can be effectively performed during sevoflurane anesthesia, the large number of study variables and potential for confounding interactions require future study for clarification.

Kamel et al\(^{102}\) retrospectively reviewed data from spine surgeries in which somato-sensory–evoked potential (SSEP) monitoring was employed to guide the surgical procedure. The objective of their study was to determine if SSEP could play any role in the prevention of perioperative peripheral nerve injury. In 1000 surgical procedures in 929 patients placed in 1109 positions, the authors found 74 cases in which SSEPs elicited in the upper extremities underwent changes. Of those, 68 responded to changes in patient position (i.e., repositioning of the extremity) and the remaining were non-position-related. These changes were significantly more common in the lateral decubitus (40%) and prone position with arms out (53%) compared to supine with arms out (1%), supine with arms tucked (3%), or prone with arms tucked (3%). Of note, no new postoperative neurologic deficits were noted in any patient, suggesting that the SSEP data provided strong false-positive results for nerve injury, regardless of whether remedial efforts were successful or not in correcting SSEP abnormalities.

Currently, a wide range of depth-of-anesthesia monitors are available for clinical use. These techniques often rely on predictable anesthetic-induced changes in electroencephalographic characteristics. Many investigations have demonstrated a reduction of anesthetic drug utilization and faster recovery from general anesthesia when depth of anesthesia monitors are used to help guide anesthetic delivery.\(^{103–106}\) Boztug et al\(^{107}\) evaluated the utility of BIS guidance on drug utilization and emergence characteristics on patients undergoing craniotomy. Fifty ASA I and II patients undergoing elective supratentorial craniotomy were randomized to receive a sevoflurane/fentanyl/cisatracurium-based anesthetic with either (1) BIS guidance such that sevoflurane concentration was titrated to maintain a BIS value of 40 to 60 during maintenance and 60 to 70 during the last 15 minutes of surgery, or (2) a standard hemodynamically and clinically titrated anesthetic. They showed that BIS-guided anesthetic delivery resulted in: (1) reduced average sevoflurane requirements during maintenance, (2) higher average BIS values in the BIS-guided group, (3) more rapid emergence from anesthesia, and (4) no difference in length of stay in the post-anesthesia care unit or hemodynamics. Such findings on emergence are interesting, when taken in the context of the 1992 data of Losasso et al\(^{108}\) in which tracheal extubation after craniotomy was accomplished on average in 2 to 3 minutes, regardless of whether or not nitrous oxide was used. Clearly, art and science are both important for the conduct of a successful anesthetic.

Paolo Martorano et al\(^{109}\) evaluated the correlation of BIS and an electroencephalographic entropy-based monitor (Spectral Entropy, GE Health Care, Helsinki, Finland) during various events in surgery in 20 patients undergoing elective supratentorial craniotomy via a propofol/sufentanil target-controlled infusion-based anesthetic. Spectral entropy is a measure of disorder in electroencephalographic activity. State entropy refers to disorder occurring in the 0.8 to 32 Hz frequency range, whereas response entropy refers to disorder in the 0.8 to 47 Hz range. The authors found excellent correlation between BIS and both state and response entropy (factors derived from the Spectral Entropy monitor) during critical times of the procedure. They also determined values for each monitoring modality that provided maximum sensitivity and specificity for discriminating between a hypnotic state and wakefulness. Those values can be found in Table 8, and at least for a comparison with BIS, correlate well with prior data.\(^{110}\)

Cerebral dysfunction is known to confound BIS assessment of anesthetic depth.\(^{111–113}\) Electroencephalographic-derived entropy monitoring is becoming more common, and the effect of cerebral dysfunction on entropy monitoring has yet to be established. Duncan

<table>
<thead>
<tr>
<th>TABLE 8. Values for Various Monitoring Modalities Which Discriminate Between Hypnosis and Wakefulness With Maximum Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
</tr>
<tr>
<td>BIS</td>
</tr>
<tr>
<td>State Entropy</td>
</tr>
<tr>
<td>Response Entropy</td>
</tr>
</tbody>
</table>

Optimal cut-off values for the hypnosis-to-wakefulness transition were assessed for the BIS and also both state and response entropy. This was a prospective study consisting of 20 patients, mean age 54 ± 5 y, undergoing elective supratentorial craniotomy during propofol/sufentanil anesthesia.

et al\textsuperscript{114} compared the correlation of BIS monitoring (Aspect Medical Systems, Newton, MA) and entropy monitoring (Datex-Omeda, Helsinki, Finland), measuring both response entropy and state entropy, during a propofol/remifentanil-based anesthetic technique in 31 patient who were grossly or nearly grossly intact after the subarachnoid hemorrhage (World Federation of Neurologic Surgeons Grades 1 and 2) and undergoing embolization of their aneurysm. BIS and entropy values were compared at 6 time points during their anesthetic care, and the degree of concordance between these 2 techniques and clinical criteria were determined. The authors found that both techniques had good concordance with clinical events; however, concordance to clinical events was stronger with BIS monitoring compared with entropy monitoring at all time points. Lowest concordance was during anesthesia emergence with both techniques. The authors also reported the median values that correlated with the transition from wakefulness to loss of consciousness (defined as loss of eyelid reflex). This occurred at 65 for BIS, 71 for response entropy, and 76 for state entropy. These values were similar to those from previous reports.\textsuperscript{109,110}

**NEUROPROTECTION**

In recent years, numerous studies have attempted to identify the origins of the mild neuroprotective effect of isoflurane. Currently, various factors such as depression of cerebral metabolic rate,\textsuperscript{115} n-methyl-D-aspartate (NMDA) receptor antagonism,\textsuperscript{116} \(\gamma\)-amino-butyric-acid (GABA) receptor agonism,\textsuperscript{117} and adenosine A1 receptor agonism\textsuperscript{118} are thought to possibly play a role. Wise-Faberowski et al\textsuperscript{119} evaluated the effects of isoflurane on a mixed neuronal/glial rat cortical cell culture after exposure to the excitotoxic agent NMDA. Under these conditions, 1.8 and 7 MAC equivalents of isoflurane failed to modulate apoptosis after 48 hours. Of note, the employed study design evaluated a single type of apoptosis, the caspase-3–mediated type. It is possible that neuronal apoptosis in their study evolved by alternate (ie, caspase-independent) pathways and was not detected by their study design.

In 1999, Mackensen et al\textsuperscript{117} reported reversal of isoflurane neuroprotection by the GABA\(\textsubscript{A}\)–receptor antagonist, trimethaphan. In 2006, Elsersy et al\textsuperscript{120} demonstrated in rat hippocampal slices exposed to oxygen and glucose deprivation that the neuroprotective effects of isoflurane are attenuated by the addition of the GABA\(\textsubscript{A}\)–receptor antagonist, bicuculline, and not by the addition of the GABA\(\textsubscript{B}\)–receptor antagonist, phaclofen. In a second experiment reported in the same manuscript, intact rats underwent focal cerebral ischemia during the following 4 conditions:

1. Fentanyl, 10 mcg/kg IV bolus followed by 25 mcg/kg/h IV plus 70% inspired nitrous oxide (\(n = 11\)) with placebo (1 mL 0.9% NaCl) given IV 30 minutes before ischemia.

2. 1.4% inspired isoflurane (\(n = 12\)) with placebo (1 mL 0.9% NaCl) given IV 30 minutes before ischemia.

3. 1.4% inspired isoflurane (\(n = 11\)) with 1 mg/kg bicuculline given IV 30 minutes before ischemia.

4. 1.4% inspired isoflurane (\(n = 13\)) with 2 mg/kg bicuculline given IV 30 minutes before ischemia.

At 5 days posts ischemia, the authors discovered better gross neurologic function in group 2 (isoflurane alone) than the other study groups. They also found significantly improved neuronal survival in group 2 compared with groups 1 and 4 and a tendency toward improved neuronal survival in group 2 compared with group 3. These data support a prior report that GABA\(\textsubscript{A}\)–mediated pharmacology may account, in part, for the neuroprotective effects of isoflurane.\textsuperscript{121}

Prior studies have suggested that the neuroprotective effects of isoflurane may be dose-dependent. Specifically, with respect to ischemic injury (as opposed to excitotoxic injury), in vivo studies in animal models have demonstrated neuroprotective effects with isoflurane at moderate doses (ie, approximately 1 MAC),\textsuperscript{16,122,123} but have failed to demonstrate isoflurane-induced neuroprotection at low doses (ie, 0.5 MAC)\textsuperscript{124} or at high doses (ie, isoflurane-induced burst suppression).\textsuperscript{125,126} Nasu et al\textsuperscript{127} investigated the neuroprotective effect of isoflurane at dose of 0.5, 1.0, 1.5, 2.0, and 2.5 MAC in a rat model of temporary focal ischemia (ie, carotid occlusion) in the setting of temporary systemic hypotension. The authors showed the following: (1) the incidence of seizures, but not mortality, were more common in rats that received higher doses of isoflurane (46% and 54% for the incidence of seizures and mortality, respectively, in the group that received 2.5 MAC) than those that received low doses (10% and 20% for the incidence of seizures and mortality, respectively, for the group that received 0.5 MAC), (2) no difference in the fraction of dead hippocampal neurons, a finding supported by prior data,\textsuperscript{128} and (3) poorer outcome both functionally and histologically in the animals that received higher doses of isoflurane. Outcome results are displayed in Table 9. On the basis of the incidence of seizures, histologic effects on cortical neurons, and effects on gross function, the authors concluded that isoflurane doses of <1.5 MAC provided better outcome compared with higher doses in this model.

Both sevoflurane\textsuperscript{129–132} and desflurane,\textsuperscript{130,133,134} are also reported to have neuroprotective effects. With desflurane, it is currently unknown if neuroprotection is mediated via cerebral metabolic depression and enhanced tissue perfusion\textsuperscript{135,136} or via other unrelated factors. In an in vitro model of hypoxic injury using rat hippocampal slices, Dimaculangan et al\textsuperscript{137} evaluated the effect of either 4% and 6%, or 12% desflurane, compared with control (ie, no desflurane) on the amplitude of the evoked potential obtained from CA1 cells in the pyramidal layer of the rat hippocampus. The authors found that there was no difference in the recovery of the spike in the presence of either 4% or 12% desflurane, compared with control; however, there was a significant recovery of the amplitude of the spike in the presence of 6% desflurane (37 ± 9% compared with spike amplitude preischemia) versus no
desflurane (15 ± 5% compared with spike amplitude preischemia). The results of this study suggest that the neuroprotective effects of desflurane may have a dose-dependent component. Further, the data suggest that neuroprotective effects of desflurane may not be entirely due to effects on cerebral hemodynamics; however, additional in vivo studies are required to confirm this finding.

Adembri et al. tested the hypothesis that neuroprotection by propofol may be influenced by its effect on mitochondrial swelling. Fanjun et al. reported that the epsilon isoform of protein kinase C and NMDA receptors may account for the neuroprotective effects of morphine.

TRAUMATIC BRAIN INJURY

Intracranial Pressure Management After Traumatic Brain Injury

Increases in intracranial pressure after traumatic brain injury are usually due to disruption of the blood brain barrier and cerebral edema. In turn, elevated intracranial pressure can cause secondary injury to the brain. Common treatments for intracranial hypertension include diuresis and hyperosmotic therapy to decrease brain water content, hyperventilation, cerebral vasoconstricting agents (eg, propofol or barbiturates), and drainage of CSF. It is currently unknown which option is superior, and multiple simultaneous treatments are often employed. Specifically, combination therapy with mannitol and furosemide leads to greater reduction in brain water content and intracranial pressure than either treatment alone. As reviewed by White et al., hypertonic saline is currently a common treatment for intracranial hypertension after traumatic brain injury. It is currently unknown if the combination of furosemide and hypertonic saline leads to synergism similar to the combination of furosemide and mannitol. In a rat traumatic brain injury model, Mayzler et al. compared brain water content in animals that received (1) 1.2 g/kg of 3% saline, (2) IV furosemide (2 mg/kg) plus 1.2 g/kg of 3% saline, or (3) no IV fluids or furosemide (ie, control group) to animals that did not undergo closed-head trauma (ie, sham group). The authors showed a significant increase in brain water content following closed-head trauma alone (81.5 ± 2.2% brain water after the injury vs. 78.9 ± 0.6% in sham animals; \( P < 0.05 \)), which was reduced by furosemide and hypertonic saline (78.0 ± 0.8%, \( P > 0.05 \) compared with sham) but not by hypertonic saline alone (80.7 ± 2.2%, \( P < 0.05 \) compared with sham) 120 minutes after the closed-head injury. Hypertonic saline, both with and without coadministration of furosemide, led to significant and similar increases in both plasma osmolality and sodium concentration. The effect of hypertonic saline and furosemide, but not hypertonic saline alone, on brain water content was attributed to: (1) decreased CSF formation induced by hypertonic saline and furosemide, (2) decreased capillary hydrostatic pressure induced by hypertonic saline and furosemide, (3) furosemide-induced inhibition of the sodium-potassium ATPase located on cells of the brain (although furosemide is a known inhibitor of the sodium-potassium-chloride transporter in the kidney and not the sodium-potassium ATPase), and (4) an effect of furosemide on mediators of cerebral edema formation. Prior studies that evaluated the effect of hypertonic saline on brain water content had conflicting results as many factors (ie, dosing, timing, injury type, and severity) probably affect the observations and outcome. Although not always feasible, prospective, controlled, human trials evaluating the effects of hypertonic saline and furosemide would be most useful to provide guidance for decision making in clinical practice.

Many factors, including use of diuretics and hypertonic therapy, can produce alterations in both sodium and water balance in critically ill patients with neurologic disease. These, in turn, can lead to significant, and preventable, morbidity and mortality. We refer the interested reader to 2 review articles. Fraser and Stieg reviewed the causes and treatment of hyponatremia. Tisdall et al. focused on the causes and treatment of both hyponatremia and hypernatremia in patients with neurologic diseases.
Hypothermia

Induced reduction of brain temperature has been shown in a variety of settings to convey neuroprotective benefits in the setting of injury or ischemia.\textsuperscript{148-151} Other investigations fail to show any benefits if hypothermia is used in the setting of potential or confirmed neuronal injury.\textsuperscript{152-154} These data may suggest that therapeutic hypothermia may be beneficial in certain select patient populations.

Inamasu et al\textsuperscript{155} reported on the use of therapeutic hypothermia in 18 acute traumatic brain injury patients as a means to control elevated intracranial pressure postoperatively after the burr hole or decompressive craniectomy for subdural hematoma with or without any evidence of cerebral contusion. All patients had a Glasgow Coma Score of \( \leq 6 \) on admission. Further, 15 historical control subjects were identified before the time at which hypothermia was used clinically at the authors’ institution. With hypothermia, there was a significant reduction in: (1) mortality (6.7% vs. 33.3% for no hypothermia and hypothermia, respectively; \( P < 0.05 \)), (2) the percentage of subjects who achieved a favorable prognosis [defined as those who did not die or remain in a persistent vegetative state (ie, includes patients with moderate disability)] (6.7% vs. 27.8% for no hypothermia and hypothermia, respectively; \( P < 0.05 \)), and (3) the percentage of subjects with uncontrollable intracranial pressure (93.3% vs. 61.1% for no hypothermia versus hypothermia, respectively; \( P < 0.05 \)). Further, there was a significant reduction in the mortality rate with the use of hypothermia in those subjects with hematoma only (100% for no hypothermia vs. 20% for hypothermia; \( P < 0.05 \)), but not in those with both hematoma and evidence of contusion (91% vs. 85%, respectively; \( P > 0.05 \)). This finding suggests that patients with less injury (ie, no evidence of cerebral contusion) may benefit from hypothermia more than those with more severe injury and is consistent with other data.\textsuperscript{150} Such an interpretation, if true, might partially explain the negative results of the earlier prospective, randomized, controlled trial by Clifton et al\textsuperscript{154} where induced hypothermia was of no benefit in a large group of patients that included all forms of closed-head injury. The limitations of the Inamasu et al\textsuperscript{155} study is the lack of subject randomization and concomitant controls plus the small number of study subjects. These factors, when added to the extensive subgroup analysis make the appearance of a type II statistical error a distinct possibility. As such, the data of Inamasu et al\textsuperscript{155} should not be viewed as providing definitive answers, but instead, should be viewed as preliminary, and of greatest use in planning future trials.

Factors Affecting Outcome After Traumatic Brain Injury

One of the primary goals for the management of critically ill patients with traumatic brain injury is the prevention of secondary injury. Physiologic states that limit the delivery of oxygen to the injured brain (eg, hypotension, hypoxia, and increased intracranial pressure) should be avoided. Additionally, there are a variety of other factors, which could prove detrimental to patients with traumatic brain injury. We identified articles from the 2006 literature that focused on the negative impact of fever and coagulopathy.

Fever following traumatic brain injury is common, occurring in about 68% of patients with closed-head injury during the initial 72 hours of hospitalization.\textsuperscript{156} Fever can be due to infectious causes (ie, aspiration, pneumonia, urinary tract infection, vascular catheter infections, sepsis) or noninfectious causes (ie, trauma-induced hypothalamic dysfunction, drugs). In both human and animal models, temperature increases in the setting of traumatic brain injury is associated with exacerbation of injury and a worse outcome.\textsuperscript{157,158} Originally, the mechanism to account for this phenomena was thought to be related to temperature-induced increases in cerebral oxygen consumption; however, glutamate excitotoxicity,\textsuperscript{159} alterations in blood-brain barrier function,\textsuperscript{160} and a variety of other factors may also play a role. Acute fever occurring in the pediatric head trauma population is also associated with poor outcome\textsuperscript{161}; however, little is known about the role that the etiology of fever plays in affecting outcome.

Suz et al\textsuperscript{162} retrospectively reviewed 93 records of patients with traumatic brain injury who were <14 years old and had a Glasgow Coma Score of <9 on admission. Fifty-two percent of patients had fever during their stay in the intensive care unit. Of those with fever, patients were febrile for 49 ± 26% of their time in the intensive care unit and the cause was due to infection in 48% (of 23 patients 18 had pneumonia, 8 had urinary tract infection, 5 had wound infection, 3 had other types of infection, and 6 had more than 1 source of infection). Fifty-two percent had a noninfectious cause of fever (of 25 patients, 1 had a drug-related fever and in the remaining 24 patients, the cause of fever was unknown). There was no difference in time of onset following admission (1.7 ± 1.1 d vs. 1.5 ± 0.7 d, \( P > 0.05 \)) or maximum temperature (39.6 ± 0.7°C vs. 39.3 ± 0.6°C, \( P > 0.05 \)) of fever in those with infectious and noninfectious causes, respectively. Patients with infectious fever had a longer intensive care unit length of stay (14.7 ± 11 d) and hospital length of stay (23.7 ± 16.7 d) compared to those with noninfectious causes (intensive care unit length of stay = 5.4 ± 5.8 d, \( P < 0.001 \); hospital length of stay = 12.3 ± 16.0 d, \( P = 0.02 \)) however, the rate of mortality (8.7% vs. 12.0% for infectious and noninfectious causes, respectively; \( P = 0.92 \)) and poor disposition (21.7% vs. 16% for infectious and noninfectious causes, respectively; \( P = 0.89 \)) did not differ between groups. Finally, each febrile episode was associated with a 2.4 increased risk of having a hospital discharge with a Glasgow Coma Score of <13 (CI = 1.2-5.0). It is unknown if treatment of fever is associated with improvement in outcome.
Coagulopathy is common after traumatic brain injury. This can manifest as mild alterations in prothrombin time and partial thromboplastin time at one extreme to frank disseminated intravascular coagulation on the other. The presence of coagulopathy has been associated with poor outcome owing to the risk of both intracranial and extracranial bleeding. The exact etiology of traumatic brain injury-associated coagulopathy is unknown, but release of brain thromboplastin into the systemic circulation and systemic lactic acidosis are thought to play a role. In an in vitro investigation using human blood, Engstrom et al. evaluated the relationship between acidosis and coagulopathy. The pH of blood obtained from healthy volunteers was adjusted ex vivo by the addition of lactic acid to reach target pH values of 7.4, 7.2, 7.0, and 6.8. pH 6.8 blood was then readjusted back to a pH of 7.4 using THAM buffer to study the reversibility of coagulation changes. Coagulation was assessed using a ROTEM thrombelastograph (Pentapharm GMBH, Munich, Germany), which measures time to start of clot formation (clotting time or the duration between initiation of clotting and y-axis inflection of 2 mm) and clot formation time (CFT or the duration between initiation of clotting and y-axis inflection of 20 mm), rate of clot formation (z angle), and maximum clot firmness (Fig. 6). On the basis of linear regression analysis, increasing lactate concentrations, and thus decreasing pH, caused a significant, dose-dependent, prolongation of CFT (P = 0.0001, r = 0.74) and decrease in z angle (P = 0.0001, r = 0.73), but no significant differences in clotting time or maximum clot firmness. Further, the lactic acid-related changes in CFT and z angle were completely restored to baseline when the pH was corrected back to 7.4. These data suggests that, in the setting of in vitro lactic acidosis, the normal coagulation cascade is still occurring, however, at a slower rate. The authors state that the phenomenon described in this investigation may account for the association between the risk of progression of hemorrhagic intracranial lesions after traumatic brain injury and coagulopathy, especially given that local acidosis usually develops in injured brain parenchyma after traumatic brain injury.

Finally, Mazzeo et al. describe a novel scoring system for assessing traumatic brain injury on the basis of the presence of factors which could exacerbate secondary neuronal injury. Calculation of an “ischemic score” is based on assigning 1 point for the presence of each of the following 5 characteristics: (1) hypoxemia (PaO2 < 60 mm Hg), (2) hypotension (mean arterial pressure < 50 mm Hg for > 30 min), (3) low hemispheric cerebral blood flow (< 20 mL/100 g/min based on xenon-enhanced brain computerized tomography), (4) presence of herniation (defined as fixed and dilated pupils), and (5) low cerebral perfusion pressure (< 50 mm Hg for > 30 min). Total possible scores range from 0 (no criteria present) to 5 (all criteria present). Scoring was based on events occurring from time of hospital admission to 5 to 10 days later. Scores were then correlated with microdialysis of lactate, pyruvate, glutamate, and glycerol, brain tissue oxygen monitoring, and clinical outcome data in 172 patients with acute traumatic brain injury. There was a significant and positive correlation between ischemic scores and both dialysate lactate (r = 0.14, P < 0.01) and pyruvate (r = 0.15, P < 0.01), but not glutamate (r = 0.1, P = 0.052), glycerol (r = 0.01, P = 0.45), or brain tissue oxygen saturation (r = −0.13, P = 0.053). There was a significant negative correlation between the ischemic score and Glasgow Outcome Score at both 3 months (r = −0.32, P < 0.01) and 6 months (r = −0.31, P < 0.01) after the initial injury. Finally, the percentage of patients with poor outcome (defined as those who died or were in a persistent vegetative state) was 52% with a score of 0; 64% with a score of 1; 70% with a score of 2; 83% with a score of 3; and 100% with a score of 4 or 5. One would question the ease at which this scoring system can be applied in clinical situations given that determination of cerebral blood flow may not be routine at many centers and might further increase cost. Further, the statistical significance achieved in this study was meaningfully influenced by a large number of measurements. Of note, the correlation coefficients were all small (ie, −0.32 to 0.22). Such values generate positive predictive values, r^2, of 0.05 to 0.10. As such, further research, in other patient populations, will need to be conducted to fully assess the utility of this scoring system in predicting outcome.

FIGURE 6. A rotational thromboelastometry registration of blood identifying the different parameters measured. Clot strength is found on the y-axis and time on the x-axis. The clot strength is arbitrary and measured in millimeters. Clotting time (CT) is the time from initiation of clotting until the clot has gained a strength of 2 mm. CFT is the time from clot strength 2 mm until clot strength 20 mm. z angle (AA) is the angle measured between a horizontal midline and a line tangential to the graph at 2-mm clot strength. Maximum clot firmness (MCF) is the maximum strength of the clot. With permission from J Neurosurg Anesthesiol. 2006;18: 200–204.
CONCLUSIONS

The 2006 literature contained numerous articles of relevance to practitioners and investigators interested in the care of neurosurgical and neurologically impaired patients. Many of the studies we reviewed contained novel, provocative finding, but suffered from design limitations that will hinder their direct utility in patient management. Instead, they are best viewed as the basis for designing future research that can provide more definitive answers.

Our overview is intended as only an introduction to the 2006 literature. Readers interested in the addressed topics are encouraged to review the referenced articles for further details.

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Anaesthetic Considerations in a Patient with Von Recklinghausen Neurofibromatosis

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Anaesthetic Considerations in a Patient with Von Recklinghausen Neurofibromatosis

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Von Recklinghausen Neurofibromatosis is associated with a variety of conditions often requiring anaesthesia for surgical treatment, including painful neurofibromas, severe kyphoscoliosis, pseudarthroses, hydrocephalus, intracranial tumors and other malignancies. The type and severity of systemic dysfunction must be considered while planning anaesthesia for a patient with von Recklinghausen neurofibromatosis.

CASE REPORT

60 yrs old, 55 kg female with known case of von Recklinghausen neurofibromatosis (Fig 1) was scheduled for dynamic hip screw fixation of left femur and intramedullary interlocking nail for humerus. There was no history of previous surgeries and drug allergies. She was poorly built & systemic examination revealed a normal cardiovascular and respiratory systems. She had protruding upper incisors with adequate mouth opening, normal neck and temporomandibular joint movements, Mallampati class 1 on oropharyngeal examination.

Pulmonary function tests revealed forced vital capacity (FVC of 1.5 lts/min), forced expiratory volume in first second (1.09l/min) and FEV1/FVC of 91%. X-ray chest (PA), CT abdomen, CT scan of head & brain were normal and other blood investigations are within normal limits.

Regional anaesthesia was planned for both the surgical procedures. The anaesthetic procedures were explained to the patient and written informed consent obtained. She was advised oral Midazolam (10mg) at bed time on the night before and 5 mg on the morning of surgery following an overnight fast. In the operating room her heart rate was 88/ min & blood pressure was 140/80 mmHg, oxygen saturation was 99%. Intravenous access wit 18G canula was obtained. The patient was positioned for subarachnoid block in a sitting position. After preparation of back of the patient, appreciation of the tips of the spinous processes and interspinous spaces, sub-arachnoid space was located in L2-L3 space with midline approach. After free flow of cerebro spinal fluid, 3 ml of 0.5% Bupivacaine heavy was given into the sub-arachnoid space. The patient was put in supine position and oxygen supplementation was given with Hudsons mask at a flow rate 3 lts/min. After 5 min, level of anaesthesia was checked and patient is shifted on to the fracture table. The surgery lasted for 1½ hour during which 1500ml of crystalloids were given. The urine out put during the intra operative period was 900 ml. After the completion of hip surgery patient was shifted to another table.

The patient was explained about the procedure before giving brachial plexus block (25ml 1% lignocaine and 1 in
200000 Adrenaline) by supra clavicular route. After giving the block, the patient was monitored for 10 minutes and kept in supine position. The surgery lasted for 1 hr 20 min during which 500 ml of crystalloid & one unit of compatible blood was transfused. The urine output during the intra operative period was 600ml. Post operative period was uneventful and post-operative pain was managed with IV Tramadol hydrochloride (50 mg, 8 hourly)

DISCUSSION

Neurofibromatosis is autosomal dominant disease that have widespread effects on ectodermal & mesodermal tissue. The commonest member of the group is Neurofibromatosis type 1 (NF1) which varies in severity but affects all physiological systems. Neurofibromas are the characteristic lesions of the condition and not only occur in the neuraxis but may also be found in the oropharynx and larynx; these may produce difficulties with laryngoscopy and tracheal intubation. Pulmonary pathology includes pulmonary fibrosis and cystic lung disease. The cardiovascular manifestations of NF1 include hypertension, which may be associated with pheochromocytoma or renal artery stenosis. Neurofibromas may also affect the gastrointestinal tract and carcinoid tumours may be found in the duodenum.  

Painless dislocation of cervical vertebrae has been reported in a patient with multiple cervical neurofibromas and it has been suggested that radiographic examination of the neck should be performed before administering anaesthesia in these patients in order to avoid spinal cord damage during laryngoscopy and tracheal intubation.  

Hypertension presenting in the young NF1 sufferer is usually because of renal artery stenosis, which may be bilateral. The arterial lesions are of variable morphology with fusiform intimal narrowing or nodular or aneurysm formation.  

Tumors of the central nervous system (CNS) account for the major portion of the morbidity and mortality of patients with neurofibromatosis. Anaesthetic assessment of such patients should take into account the increased incidence of epilepsy, learning difficulties and possibility of undiagnosed CNS tumors. Involvement of brain stem structures by neurofibroma or glioma may result in central hypoventilation syndromes. Such patients may exhibit protracted weaning from mechanical ventilation post-operatively.  

The genitourinary tract may be involved in NF1 and retroperitoneal neurofibromas may result in ureteric obstruction and hydronephrosis. Similarly out flow obstruction has been reported and bladder catheterization may be difficult.  

There have been many reports suggesting an increased sensitivity of patients with NF1 to non-depolarizing neuromuscular blocking drugs.  

This is especially pertinent in NF1 patients with renal impairment or those on concurrent medication (e.g. anticonvulsant drugs), which may interfere with the normal pharmacokinetics or pharmacodynamics of neuromuscular blocking drugs.  

In conclusion, the neurofibromatosis is a group of conditions that vary in their severity but which have fundamental implications for the anaesthesiologists. Manifestations of neurofibromatosis are often mild; there may be associated pathology of direct relevance and importance to the anaesthetic management of patients with the disease. It is therefore important to have a working knowledge of the clinical manifestations of the disease, so that a systemic approach to the pre-operative assessment of these patients can result in rational perioperative management.

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Figure 1

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