Neuroprotection in traumatic brain injury: a complex struggle against the biology of nature
Joost W. Schouten

Purpose of review
Translating the efficacy of neuroprotective agents in experimental traumatic brain injury to clinical benefit has proven an extremely complex and, to date, unsuccessful undertaking. The focus of this review is on neuroprotective agents that have recently been evaluated in clinical trials and are currently under clinical evaluation, as well as on those that appear promising and are likely to undergo clinical evaluation in the near future.

Recent findings
Excitatory neurotransmitter blockage and magnesium have recently been evaluated in phase III clinical trials, but showed no neuroprotective efficacy. Cyclosporin A, erythropoietin, progesterone and bradykinin antagonists are currently under clinical investigation, and appear promising.

Summary
Traumatic brain injury is a complex disease, and development of clinically effective neuroprotective agents is a difficult task. Experimental traumatic brain injury has provided numerous promising compounds, but to date these have not been translated into successful clinical trials. Continued research efforts are required to identify and test new neuroprotective agents, to develop a better understanding of the sequential activity of pathophysiologic mechanisms, and to improve the design and analysis of clinical trials, thereby optimizing chances for showing benefit in future clinical trials.

Keywords
clinical trial, head injury, neuroprotection, neurotrauma, traumatic brain injury

Introduction
Traumatic brain injury (TBI) is a major cause of death and disability worldwide, leading to immense personal suffering to victims and relatives, and high costs to society. Injuries are the leading cause of death between the ages of 15 and 44, and head trauma accounts for the majority of all trauma deaths. Today, at least 11.5 million people live with TBI-related disability, impairment, complaint or handicap in Europe (6.2 million) and the USA (5.3 million) alone [1**,2].

Depending on the severity of injury, the medical management of brain-injured patients currently includes specialized prehospital care, clinical (intensive) care, and, for some, long-term rehabilitation, but lacks clinically proven effective management with neuroprotective agents to limit pathophysiologic cascades or enhance repair. The enormous burden of TBI, however, clearly supports the need for such neuroprotective agents. Translating promising experimental results into clinical benefit has proven an extremely complex issue. First, although many pathophysiologic cascades inducing secondary damage have been identified, it remains uncertain which of these are active in individual patients and at what time after injury. Moreover, many pathways may initially have detrimental effects, but at later stages can be protective. Second, clinical trials have suffered from inadequacy in their design and analysis, not in the least part due to heterogeneity of the population and variability in treatment approaches [3].

Rationale for treatment: primary and secondary injury
Brain trauma results in brain damage and dysfunction from both primary injury (due to biomechanical effects) and subsequent secondary damage due to activation of pathophysiologic cascades. These are further aggravated by secondary insults. Early detection of such secondary insults, including intracranial insults (e.g. mass lesions, increased intracranial pressure) and systemic insults (e.g. hypoxia, hypotension), followed by appropriate intervention currently forms the basis of clinical management [4].

Secondary damage consists of seemingly innumerable complex biochemical and cellular pathways that influence progression of the primary injury. The primary goal of neuroprotection is to prevent and/or reduce secondary...
damage and to enhance repair [5]. Over the past decades our understanding of the pathophysiology of TBI has greatly increased and based on this understanding numerous pharmacological therapies have been developed, tested and proven effective in the treatment of experimental TBI. To date, however, promising experimental results have not been translated into successful clinical trials, and hence the cornerstone of management of TBI patients remains the prevention of initial injury and the minimization or reversal of secondary insults. The excitement about the new knowledge of the neurobiology and neuropharmacology of TBI should not detract from the absolute importance of correcting hypoxia, hypotension, raised intracranial pressure and other causes of secondary ischemic insult [6,7]. On the other hand, we should not be discouraged by negative results and difficulties in previous clinical trials, but continue our search for effective neuroprotective drugs for TBI patients in order to further improve outcome of this devastating disease.

Neuroprotective strategies
The complex pathobiology of TBI offers numerous targets for potential neuroprotective agents. Many of these have been or will be investigated in experimental models of TBI (Table 1 [8**,9–13]). The few that made it into clinical trials join a growing list of neuroprotective agents without proven clinical benefit (Table 2 [14–24]). The focus of this review is on neuroprotective agents that have recently been evaluated in clinical trials and are currently under clinical evaluation, as well as on those that appear promising and are likely to undergo clinical evaluation in the near future.

Excitatory neurotransmitter antagonism
Disturbances in neurotransmitter concentration occur frequently following TBI. Excitotoxicity refers to an excessive release of excitatory neurotransmitters (primarily glutamate) initiating various pathophysiological processes including excessive calcium influx in neurons, resulting in neuronal cell death [10]. High concentrations of extracellular glutamate have been demonstrated in both experimental models and clinical patients with TBI. Experimental research has elucidated many aspects of excitotoxicity and identified a number of glutamate antagonists acting either pre- or postsynaptically on \( \text{N-methyl-D-aspartic acid (NMDA), } \text{\( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolyl-propionic acid (AMPA/kainate and metabotropic receptors, in a competitive, noncompetitive or modulating way. However, glutamate receptors are of utmost importance to normal functioning, so antagonism of excessive excitotoxic activity must be achieved.

Table 1 Neuroprotective strategies evaluated in experimental traumatic brain injury

<table>
<thead>
<tr>
<th>Pharmacological target</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>Excitatory amino acids</td>
<td>Numerous compounds have been evaluated and reviewed elsewhere [8**,10]. New compounds with different pharmacological profiles (e.g. memantine) require further experimental evaluation.</td>
</tr>
<tr>
<td>Calcium channels</td>
<td>Extensively studied, also in clinical TBI (Nimodipine and SNX-111); the short time frame following injury seems to limit further clinical use.</td>
</tr>
<tr>
<td>Scavenging oxygen radicals</td>
<td>Tirilazad Mesylate, PEG-SOD and Lelubazole have been clinically evaluated; many new compounds are at least promising in experimental TBI.</td>
</tr>
<tr>
<td>Inflammation</td>
<td>A double-edged sword in TBI, both detrimental and beneficial. The massive inflammatory response is a high potential target for neuroprotection, with special attention for NO inhibitors, nitrates and nitroxides.</td>
</tr>
<tr>
<td>Caspases</td>
<td>Caspases are important enzymes in apoptotic cell death known to occur following TBI. It is however still a matter of debate whether apoptosis is a good or bad thing compared to necrosis following TBI.</td>
</tr>
<tr>
<td>Calpains</td>
<td>Calcium-dependent proteases involved in cytoskeletal remodeling. Calpain inhibitors in experimental TBI reduce damage to fiber tracts, and therefore are of major interest in axonal injury.</td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td>Progesterone is currently being evaluated in a clinical trial. Steroids have been extensively studied in the past. Experimental compounds attracting a lot of attention are dehydroepiandrosterone, thyrotropin-releasing hormone and their analogs.</td>
</tr>
<tr>
<td>Neurotransmission</td>
<td>Widespread changes in neurotransmitters occur following TBI. All compounds interfering in catecholamine, serotonin, histamine, ( \gamma )-aminobutyric acid (GABA) and acetylcholine metabolism are therefore of potential interest following TBI. Cognitive problems and depression frequently present following TBI, which might benefit from this approach, although a rationale for more acute administration exists.</td>
</tr>
<tr>
<td>Neurotrophic factors</td>
<td>These growth/survival factors effectively reduce apoptosis and improve functional outcome in experimental TBI. Many questions about dosage, time-window and route of administration remain to be answered.</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Recombinant human factor VII has been evaluated in a clinical trial. Coagulation disorders are common following TBI, relate to outcome, and will be a hot topic for future research. Controversies regarding treatment of microvascular thrombosis and progressive hemorrhagic contusions require attention [11].</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Seizures occur frequently following TBI, and anticonvulsants may reduce early seizures. In addition, acute administration can be neuroprotective [12,13].</td>
</tr>
<tr>
<td>Immunosuppressive ligands</td>
<td>Cyclosporin A is currently being evaluated in a clinical trial, other compounds are under experimental investigation.</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Minocycline is a broad-spectrum antibiotic, shown to be neuroprotective in experimental studies. In experimental research additional hot topics far from translation into clinical trials are neurogenesis, improvement of axonal outgrowth and stem-cell transplantation, although for the latter a small clinical trial in pediatric TBI has been initiated.</td>
</tr>
</tbody>
</table>

TBI, traumatic brain injury. Neuroprotective strategies are discussed more extensively in [8**,9].
<table>
<thead>
<tr>
<th>Study and agent</th>
<th>Study population</th>
<th>No. of patients</th>
<th>Start of treatment</th>
<th>Year of study</th>
<th>Status</th>
<th>Published</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin inhibition</td>
<td>GCS 3–8</td>
<td>139</td>
<td>≤12 h</td>
<td>1996</td>
<td>Completed [14]</td>
<td>12% improvement in favorable outcome (P = 0.26)</td>
<td></td>
</tr>
<tr>
<td>Calcium-mediated damage</td>
<td>Not obeying commands</td>
<td>351</td>
<td>24 h</td>
<td>1987–1989</td>
<td>Completed [15]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>HIT II Nimodipine</td>
<td>Not obeying commands</td>
<td>852</td>
<td>12 h of not obeying commands within 24 h of injury</td>
<td>1989–1991</td>
<td>Completed [16]</td>
<td>No significant effect overall population</td>
<td></td>
</tr>
<tr>
<td>HIT intravenous Nimodipine</td>
<td>GCS &lt;15 + traumatic subarachnoid hemorrhage</td>
<td>592</td>
<td>≤12 h</td>
<td>1997–1999</td>
<td>Completed</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Glutamate excitotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliprolil study</td>
<td>GCS 4–8</td>
<td>452</td>
<td>≤12 h</td>
<td>1993–1995</td>
<td>Completed</td>
<td>No significant effect reported</td>
<td></td>
</tr>
<tr>
<td>Selfotel</td>
<td>GCS 4–8</td>
<td>693</td>
<td>≤8 h and within 4 h of admission</td>
<td>1994–1996</td>
<td>Terminated [18]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Cerestat/Aptiganel</td>
<td>GCS 4–8; GCS 3 if pupils reactive</td>
<td>532</td>
<td>≤8 h</td>
<td>1996–1997</td>
<td>Terminated</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Saphir/D-CPP-ene</td>
<td>Not obeying commands, ≥ one reactive pupil</td>
<td>924</td>
<td>≤12 h</td>
<td>1995–1997</td>
<td>Completed</td>
<td>No significant effect reported</td>
<td></td>
</tr>
<tr>
<td>Lipid peroxidation/free radical damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer/CP-101606</td>
<td>GCS 4–8</td>
<td>416</td>
<td>≤8 h</td>
<td>1997–2000</td>
<td>Completed</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>PEG-SOD</td>
<td>GCS &lt;8</td>
<td>1562</td>
<td>Within 8 h</td>
<td>1993–1995</td>
<td>Completed [19], in part</td>
<td>No significant difference</td>
<td></td>
</tr>
<tr>
<td>Tinlazad domestic trial</td>
<td>GCS &lt;8, 70%; GCS 9–12, 30%</td>
<td>1155</td>
<td>≤4 h</td>
<td>1991–1994</td>
<td>Terminated</td>
<td>No significant effect reported</td>
<td></td>
</tr>
<tr>
<td>Tinlazad international trial</td>
<td>GCS &lt;8, 85%; GCS 9–12, 15%</td>
<td>1120</td>
<td>≤4 h</td>
<td>1992–1994</td>
<td>Completed [20]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Severe head injury, not further defined</td>
<td>396</td>
<td>≤4 h</td>
<td>1985–1990</td>
<td>Completed [21]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone mega dose trial</td>
<td>GCS &lt;13</td>
<td>300</td>
<td>≤3 h</td>
<td>1986–1989</td>
<td>Completed [22]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Pharmos/dexanabinol</td>
<td>Motor score 2–5 + CT abnormalities</td>
<td>861</td>
<td>≤6 h</td>
<td>2000–2004</td>
<td>Completed [27*]</td>
<td>No significant effect</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>GCS 3–12 and/or intracranial surgery</td>
<td>499</td>
<td>≤8 h</td>
<td>1998–2004</td>
<td>Completed [32*]</td>
<td>Poorer outcome at low dose; higher mortality at high dose</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; GCS, Glasgow Coma Score.

* Currently included in the IMPACT database.

* Planned for inclusion in the IMPACT database.
without interference in normal function [25]. Some highly neuroprotective NMDA antagonists have not been evaluated in clinical trials because of concerns of psychotropic side effects whereas for other compounds trials were terminated prematurely due to excess mortality in concomitant stroke trials. Recently, Traxoprodil, a second-generation NMDA antagonist that selectively targets NMDA receptors containing the NR2B subunit, has been evaluated in a clinical trial. Traxoprodil treatment was well tolerated and, although not statistically significant, resulted in increased favorable outcome and reduced mortality, which was more pronounced in the more severe subset of patients [26]. Dexamabinol is a synthetic cannabinoid devoid of psychotropic activity, but with strong neuroprotective potential due to antioxidant, anti-inflammatory and antiexcitotoxic properties. This compound was recently evaluated in a phase III trial and found safe, but not efficacious in the treatment of TBI [27]. Efficacy of blocking excitotoxic responses following TBI as well as other insults to the central nervous system, to date, remains unproven [28,29]. Termination of trials before definitive evidence could be obtained, incomplete publication of data and underpowered studies limit definitive conclusions for this group of neuroprotective drugs. New drugs with different pharmacological profiles are currently under investigation in experimental TBI and show promising results. Translation into clinical trials should only occur in well designed trials based on what we have learned from previous trials.

Magnesium
Magnesium plays an important role in normal cellular functioning, and has demonstrated neuroprotective properties in experimental studies in models of cerebral ischemia as well as TBI. Magnesium treatment results in reduction of cerebral edema and neuronal cell death, and attenuated motor impairment and cognitive dysfunction following experimental TBI [30,31]. One of the seemingly great advantages of magnesium, besides being inexpensive and widely available, is its multidirectional effect. Where other neuroprotective compounds usually interfere with just one pathophysiological mechanism, magnesium exerts its neuroprotective effects among others by noncompetitive NMDA receptor blockade, inhibition of presynaptic excitatory neurotransmitter release, suppression of cortical spreading depression, and blockade of voltage-gated calcium channels. Despite the solid amount of experimental evidence concerning the neuroprotective effects of magnesium, a recently completed randomized double-blind trial evaluating the efficacy of a 5-day continuous magnesium administration in 499 patients with moderate or severe TBI was unable to show neuroprotective effects and even indicated a possibility of harm [32]. The absence of efficacy is consistent with a recently reported stroke trial [33]. Possible statistical and methodological causes (e.g. lack of power to detect differences) of these negative results have not been identified. Even though magnesium administration (dose, start time, duration, concentration) in these studies was based on positive preclinical data, and targeted serum levels of magnesium were achieved, availability of magnesium in cerebrospinal fluid (CSF) or cerebral extracellular fluid might be a concern [34–36]. Further studies to elucidate the relationships between total and ionized concentrations of magnesium in serum and CSF at different times following clinical TBI may hopefully provide an explanation for the negative results of recent clinical trials.

Mitochondrial dysfunction
Mitochondria, as the centers of aerobic metabolism, show marked dysfunction following experimental and clinical TBI, contributing to cell death through several mechanisms. Increased mitochondrial calcium results in decreased ATP production and generation of reactive oxygen species as well as increased permeability of the inner mitochondrial membrane. The opening of the mitochondrial permeability transition pore is responsible for mitochondrial swelling and membrane rupture, resulting in cell death. Mitochondrial dysfunction can be attenuated by inhibitors of mitochondrial permeability transition such as cyclosporin A and its derivatives [37]. Based on preclinical data cyclosporin A has been evaluated in two phase II clinical trials, and was found to improve cerebral perfusion pressure and cerebral metabolism, as evaluated with microdialysis. Cyclosporin A is considered safe in TBI patients, and its CSF pharmacokinetics in the injured central nervous system have been elucidated, supporting the initiative for a phase III clinical trial, which is currently being designed [38,39,40].

In experimental research, blockage of N-type voltage-gated calcium channels by ziconotide (SNX-111) has been shown to induce partial restoration of mitochondrial function, but a clinical trial was terminated prematurely because of increased mortality in the treatment group. Newly developed, more selective N-type voltage-gated calcium-channel blockers like SNX-185 have better bioavailability, and appear neuroprotective in experimental models, but will need additional preclinical evaluation [41].

Erythropoietin
Erythropoietin is a kidney-derived cytokine regulating hematopoiesis, and has recently been recognized as being neuroprotective. Abundant expression of erythropoietin and its receptor in most of the cell types in the central nervous system exists, and in response to hypoxia or excitotoxicity this expression is increased, suggesting a central role in endogenous protection from deleterious stimuli [42]. Erythropoietin has been shown to be
neuroprotective in experimental models of stroke, and following experimental TBI treatment with erythropoietin leads to decreased lesion volume and improved functional outcome, possibly by limiting the inflammatory reaction [43]. Based on these experimental data clinical trials were initiated and the safety of erythropoietin administration in stroke patients was confirmed. A double-blind proof-of-concept trial showed no adverse events, and suggested improved functional outcome in erythropoietin-treated patients [44]. These results prompted further clinical research, which is currently being conducted as a multicenter phase II/III trial in stroke patients, as well as an additional pharmacokinetic study evaluating CSF erythropoietin following systemic administration [45]. In TBI, a randomized phase II clinical trial is currently ongoing in Wisconsin, USA. This trial focuses primarily on moderate TBI patients, and instead of using the Glasgow Outcome Score evaluates neuronal cell-death markers as a primary outcome measure.

**Hormones**

There has been considerable debate about sex differences in outcome following TBI, but a large meta-analysis suggests that no differences in outcome between men and women exist in outcome following TBI [46]. This debate, however, together with gender difference in treatment response and outcome in experimental TBI, stimulated research directed at the role of sex steroids following TBI. Both progesterone and estrogen may exert neuroprotective effects [47]. Based on experimental research, progesterone is thought to exert its neuroprotective effects through a variety of mechanisms including a decrease of edema formation due to changes in the blood–brain barrier and modulation of γ-aminobutyric acid (GABA)-ergic neurotransmission resulting in decreased excitotoxicity. In addition progesterone inhibits apoptosis and reduces gliosis and the postraumatic inflammatory response [48,49]. Allopregnanolone, a metabolite of progesterone, has also been shown to be neuroprotective, and might even be more effective than progesterone [50]. Both progesterone and allopregnanolone improve neuronal survival and functional recovery following experimental TBI [51].

In experimental TBI estrogen has shown to possess antioxidant and antiapoptotic properties, and improves cerebral blood flow. However, estrogen supplementation in females increased mortality following experimental brain injury [47], and most studies evaluating estrogen used pretreatment paradigms, raising questions about the value of estrogen in clinical TBI.

The wealth of experimental data on neuroprotective effects of progesterone together with adequate pharmacokinetic studies [52] resulted in a phase II clinical trial which concluded that no serious adverse events occurred due to progesterone administration in TBI patients. Even more interesting was the observation that, in moderate TBI survivors treated with progesterone, the outcome was better than in those treated with placebo [53]. A large multicenter study to prove what this study suggests has been initiated by the authors.

**Bradykinin antagonists**

Increased production of kinins has been reported following brain trauma, and their interaction with the constitutive B2-bradykinin receptor has been shown to be important in the development of postinjury inflammation-induced secondary damage. Specific inhibition of the B2-bradykinin receptor is considered a promising strategy for neuroprotection. Experimental data support this strategy, and recently a phase I clinical trial to investigate the pharmacokinetics of Anatibant, a selective potent bradykinin receptor antagonist, was conducted and published [54]. Currently a phase II safety study is being conducted on 500 patients with TBI.

**Nitric oxide and inhibitors of nitric oxide synthases**

Nitric oxide is a key factor in the development of secondary injury, regulating the dilation of blood vessels and acting as chemotoxin during inflammatory processes. Nitric oxide is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS), of which four isoforms have been identified. Three of these are constitutive and one inducible [55]. The three constitutive isoforms are neuronal NOS, endothelial NOS and mitochondrial NOS.

The fourth isomorfp is the inducible NOS (iNOS), which is induced under pathological conditions [55–57].

In excess, nitric oxide is potentially neurotoxic because it contributes to excitotoxic neuronal death, generates cytotoxic peroxynitrites, damages DNA directly, inhibits DNA synthesis, inhibits mitochondrial respiration, and has been associated with apoptotic cell death [58]. In addition to producing nitric oxide, NOSs are also known to produce considerable amounts of the free radicals superoxide and hydrogen peroxide. This occurs particularly when substrate levels fall below those required to saturate the enzyme. This mechanism is called uncoupling of NOS [59,60]. Following TBI, nitric oxide synthesis is also activated by inflammation, which is initiated by both primary and secondary injuries. Proinflammatory cytokines can induce iNOS, thereby promoting persistent iNOS over-activation for several days after injury [61]. iNOS is mainly expressed in macrophages, microglia and infiltrating neutrophils recruited from the blood and thus has a substantially greater capacity to synthesize nitric oxide than endothelial NOS [58,61]. During the course of the pathophysiological process triggered by TBI, nitric oxide accumulates in the brain immediately after injury, as well as several hours or days later.
Various studies have shown that nitric oxide and the NOS pathways are involved, both positively and negatively, in the secondary injury cascade following injury. These pathways, and the recognition of the importance of nitric oxide in modulating regional cerebral blood flow, indicate a promising treatment target. Overall, experimental studies with inhibitors of NOS have shown beneficial effects, in particular with inhibitors of neuronal NOS and iNOS [8**]. Other studies, however, failed to show benefit and a few even show deleterious effects (see [8**] for references). These differences may reflect differential effects of agents investigated on the different isoforms of NOS as well as time-dependent influences. A new drug currently under investigation is the compound VAS203, a structural analog of 5678-tetrahydro-l-biopterin (BH4), the endogenous cofactor of NOS, and one of the most potent inhibitors of NOSs discovered so far. This compound competitively displaces BH4 from NOS and thus inhibits the formation of nitric oxide, but does not interact with the binding site of the substrate (L-arginine) [62]. Further, VAS203 is capable of reducing uncoupling of NOS, with an additional effect, the inhibition of increased superoxide production.

**Translational neuroprotection: neuroprotection from bench to bedside**

The neuroprotective agents that fail in clinical trials have all been proven effective in experimental models. One could question whether the current models of TBI adequately mimic human TBI. Many aspects of human TBI, either focal or diffuse, are reflected by the different experimental models, but experimental models cannot reproduce the entire heterogeneous spectrum of clinical TBI [63]. Additional concerns exist about the severity of experimental injuries as well as ultra-early or even pretreatment paradigms in experimental TBI. Extrapolation of results obtained in animals to clinical setting will remain problematic.

In ‘early’ TBI trials patient inclusion was primarily based on Glasgow Coma Score on admission (Table 2). The actual presence of the pathophysiological mechanism that was targeted with the neuroprotective compound that was studied, however, has hardly or never been confirmed. The presence of certain pathophysiological mechanisms in patients should be the basis of inclusion in a clinical trial evaluating the compound that interferes with this mechanism in a hopefully beneficial manner. In other words: diffuse axonal injury patients and subdural hematoma patients should not be included in the same trial even though their Glasgow Coma Scores on admission are identical. We should select and include patients in trials that are likely to benefit from the evaluated treatment [64].

Similarly, mild and moderate TBI may be considered completely different diseases than severe TBI. Unsuccessful clinical trials in which the subpopulation of moderately injured patients responded to therapy (e.g. [53]) raise the question of whether trials should not focus more on moderate or even mild TBI patients whose brains actually are ‘salvageable’. This population remains poorly represented in clinical trials, but constitutes the majority of all TBI worldwide.

To date, both clinical trials and experimental research have focused on the evaluation of a single potential neuroprotective compound at a time when it is considered unlikely that one ‘magic bullet’ will improve outcome in all subtypes of TBI. Serious consideration should be given to the possibility of combination therapies in which multiple compounds are administered sequentially, each in their own appropriate therapeutic time window.

Another major concern in clinical trials is the uncertainty about pharmacokinetics in the TBI patient, which are considerably different from the normal physiological situation. In recent phase III trials drug administration was based on specifically designed phase II trials [32*,40]. More detailed pharmacokinetic studies are advocated by some, in which, in addition to the target, serum concentrations in CSF or cerebral extracellular fluid should be monitored [34,57]. In this development, cerebral microdialysis is likely to become an increasingly important monitoring tool for diagnosis (presence of a pathophysiological mechanism in a patient), drug monitoring (measurement of drug concentration in the target organ) and outcome (surrogate outcome markers) in clinical TBI [65].

**Outcome**

Pharmaceutical clinical trials in TBI, to date, have been largely unsuccessful [66**]. To improve the quality of future clinical trials it is imperative that all data, including negative data, are published. Unfortunately, studies with negative results have not always been published (Table 2). In addition, trials have been prematurely terminated by sponsors because of interim analysis or (primarily psychomimetic) adverse effects in concurrent stroke trials. The question remains whether adverse effects leading to termination of clinical trials in stroke should have the same consequence in TBI trials because the average TBI patient, in contrast to the average stroke patient, is younger and – more importantly – comatose and fully sedated at the time of drug administration.

The primary end point in most TBI trials to date has been the dichotomized Glasgow Outcome Score (favorable/unfavorable). The use of this scale, together with the hypothesis of most trials that a 10% increase in favorable outcome is considered a positive result, has led to negative trial results. Although reported as negative, many trials showed some improvement in outcome,
but this was not statistically significant, indicating that neither efficacy nor inefficacy of the tested compound was proven.

In the recently published Dexamabinol trial, a new statistical method to reduce the effect of differences in initial prognostic risk factors on outcome analysis has been introduced. This so-called sliding dichotomy reduces the effect of differences in initial prognostic risk on outcome analysis, and thereby improves statistical power [27,67]. Somewhat similar, an improved outcome measure was introduced in the recently published magnesium trial. A composite outcome measure consisting of mortality, seizures, functional measures and neuropsychological tests was used as a primary outcome in this study, and is suggested to be more sensitive for the detection of a treatment effect [32]. The value of such composite outcomes, however, remains to be further evaluated in additional clinical trials.

In addition to clinical outcome markers there is an argument that surrogate outcome markers, like intracranial pressure, improved lactate/pyruvate ratio, or other biochemical markers, can be used to reflect therapeutic efficacy. Such surrogate outcome markers, however, would have to correlate with outcome, and this has not been proven to date, even for the most studied surrogate outcome marker, intracranial pressure.

A further complicating factor in clinical trials to date has been the limited standardization of treatment. Analysis of multicenter trials has shown heterogeneities in the patient population and treatment approaches, which have not been corrected for by covariate adjustment [68,69]. In contrast, generalization of results from single-center trials is not necessarily valid, as a result of differences in treatment. Adherence to treatment protocols using evidence-based guidelines is likely to reduce heterogeneity in multicenter clinical trials [4].

Conclusion
TBI is a major central-nervous-system disorder, with enormous burden to individual patients and society. Although extensive preclinical research has identified numerous effective neuroprotective agents, none of these agents has been proven to be effective in clinical trials. Before translation into clinical trial, experimental evidence should be strong, based on multiple experiments, preferably in multiple models, and include pharmacokinetic analysis. Successful translation of compounds into clinical trials will probably require a more mechanistic approach, in which only patients with the proven presence of a certain pathophysiological mechanism are included in trials evaluating a compound that interferes with this particular mechanism. Extensive pharmacokinetic evaluation of the potential neuroprotective agent in the injured brain should be required, ensuring adequate tissue penetration once the agent is studied in efficacy trials. A more sensitive analysis of outcome in new types of clinical trials is advocated, with an important role for surrogate outcome measures as well as new types of outcome analysis. Further standardization in treatment is likely to benefit from further development of evidence-based treatment guidelines. Implementation of these suggestions, even though a complex challenge, is likely to improve the chance that experimentally effective agents will show positive results in future clinical trials.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 226–227).


This paper summarizes the current knowledge on the epidemiology of TBI in Europe and serves to highlight the lack of standardized data.


This is an excellent and extensive review of almost all preclinical research in TBI research.


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66 Wang KK, Lamer SF, Robinson G, Hayes RL. Neuroprotection targets after traumatic brain injury. Curr Opin Neurol 2006; 19:514–519. This is a brief review with the same topic as the current review. There is some overlap in the drugs discussed, some points of view are different.


Airway Management in Adults after Cervical Spine Trauma
Edward T. Crosby, M.D., F.R.C.P.C.*

Cervical spinal injury occurs in 2% of victims of blunt trauma; the incidence is increased if the Glasgow Coma Scale score is less than 8 or if there is a focal neurologic deficit. Immobilization of the spine after trauma is advocated as a standard of care. A three-view x-ray series supplemented with computed tomography imaging is an effective imaging strategy to rule out cervical spinal injury. Secondary neurologic injury occurs in 2–10% of patients after cervical spinal injury; it seems to be an inevitable consequence of the primary injury in a subpopulation of patients. All airway interventions cause spinal movement; immobilization may have a modest effect in limiting spinal movement during airway maneuvers. Many anesthesiologists state a preference for the fiberoptic bronchoscope to facilitate airway management, although there is considerable, favorable experience with the direct laryngoscope in cervical spinal injury patients. There are no outcome data that would support a recommendation for a particular practice option for airway management; a number of options seem appropriate and acceptable.

The provision of acute medical care to patients with cervical spinal injuries (CSIs) is a complex, challenging, and rewarding task. It is also an anxiety-provoking endeavor because care is provided in a milieu where there is constant concern about medical interventions resulting in the conversion of a spinal injury without neurologic sequelae to one in which the two are now concurrent. It is also a topic of continuous debate because care providers struggle in an environment of limited data and incomplete answers to try to craft clinical care paradigms designed to optimize preservation and return of neurologic function, while minimizing the risk of creating additional injury and neurologic compromise. Many questions regarding the initial care of these patients, particularly as they relate to airway management, remain unresolved, but there has been great effort, energy, and enthusiasm expended during the past two decades searching for these answers. This article reviews the literature that has been generated on the topic of airway management after CSI, particularly that published in the past 10 yr, identifying new areas of knowledge and evolving practice patterns. It also attempts to address and resolve controversy surrounding areas of care that have proven more contentious, most particularly the use of the direct laryngoscope to facilitate direct tracheal intubation in these patients.

The Adult Cervical Spine: Stability, Injury, and Instability

Movement and Stability of the Upper Cervical Spine
Flexion–extension occurs in the upper cervical spine at both the atlanto-occipital and atlantoaxial articulations, and a combined 24° of motion may be achieved.1 Flexion is limited by contact between the odontoid process and the anterior border of the foramen magnum at the atlanto-occipital articulation and by the tectorial membrane and posterior elements at the Cl–C2 level. Extension is limited by the contact of the posterior arch of the atlas with the occiput superiorly and with the arch of the axis inferiorly. The distance from the posterior arch of the atlas to the occiput is termed the atlanto-occipital gap, and a narrow atlanto-occipital gap has been cited as being a cause of difficult intubation.2 Nichol and Zuck2 suggested that attempts to extend the head in patients with a narrow atlanto-occipital gap result in anterior bowing of the cervical spine, forward displacement of the larynx, and a poor view during laryngoscopy. This concept, although offering an elegant anatomical explanation for the clinical experience of difficult laryngoscopy, has yet to be validated, and the truth may be simpler. Calder et al.3 have reported that limited separation of the occiput from the atlas and the atlas from the axis yields an immobile upper spine and reduces both cervical spine extension and mouth opening, resulting in difficult direct laryngoscopy.

The ligaments contributing to the stability of the upper complex are the transverse, apical, and alar ligaments as well as the superior terminations of the anterior and posterior longitudinal ligaments (fig. 1). In adults, the transverse ligament normally allows no more than 3 mm of anteroposterior translation between the dens and

* Professor.

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Address correspondence to Dr. Crosby: Department of Anesthesiology, The Ottawa Hospital—General Campus, Room 2600, 501 Smyth Road, Ottawa, Ontario, Canada, K1H 8L6. ecrosby@sympatico.ca. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.
the anterior arch of the atlas. This may be measured on lateral radiographs of the neck and is termed the atlas–dens interval. If the transverse ligament alone is disrupted and the alar and apical ligaments remain intact, up to 5 mm of movement may be seen. If all the ligaments have been disrupted, 10 mm or more of displacement may be seen. Destruction of these ligaments is a common consequence of severe and long-standing rheumatoid arthritis.

Significant posterior displacement of the dens reduces the space available for the spinal cord (SAC) in the vertebral column. The SAC is defined as the diameter of the spinal canal measured in the anteroposterior plane, at the Cl level, that is not occupied by the odontoid process. The SAC represents the area composed of both cord and space. The area of the spinal canal at Cl may be divided into one third odontoid, one third cord, and one third “space.” The one third space allows for some encroachment of the spinal lumen without cord compromise. However, when this margin of safety has been exhausted, compression of neural elements will occur; persistent compression will eventually lead to myelopathy and neurologic deficit. The cord occupies a greater proportion of the available SAC in the subaxial spine; at the C6 level, approximately 75% of the SAC is occupied by the cord.

**Movement and Stability of the Lower Cervical Spine**

A further 66° of flexion–extension may be achieved in the lower cervical spine, with the C5–C7 segments contributing the largest component. There is an inverse relation between age and range of motion, i.e., as age increases, mobility decreases. However, most of the decrease occurs at the C5–C7 motion segments, and this usually does not have a significant impact on the ease of direct laryngoscopy. With the head in the standard sniffing position, the cervical spine below C5 is relatively straight; there is increasing flexion from C4 to C2, and the occipitoatlantoaxial complex is at or near full extension.

In the lower cervical spine, the structures contributing
Cervical Spinal Instability after Injury: Mechanisms and Consequences

White et al. have defined stability as “the ability of the spine to limit its pattern of displacement under physiologic loads so as not to allow damage or irritation of the spinal cord or nerve roots.” Instability occurs when physiologic loading causes patterns of vertebral displacement that jeopardize the spinal cord or nerve roots. Instability may result from congenital anomalies, acquired conditions related to chronic disease, and acutely after trauma. The following discussion will primarily relate to traumatic instability.

One element in the injured column must be preserved to achieve spinal stability. Clinically, to ensure a margin of safety, preservation of elements in the injured column cannot be assumed, and the spine must be considered to be potentially unstable until proven otherwise. The anterior column contributes more to the stability of the spine in extension, and the posterior column exerts its major forces in flexion. Therefore, the anterior elements tend to be disrupted in hyperextension injuries, and the posterior elements tend to be disrupted in hyperflexion injuries. With extreme flexion or extension or if either a compressive or rotational force is added, both columns may be disrupted.

Flexion injuries usually cause compression of the anterior column and distraction of the posterior column (fig. 4). Pure flexion trauma may result in wedge fracture of the vertebral body without ligamentous injuries. These injuries are stable and are rarely associated with neurologic injuries. With more extreme trauma, elements of the posterior column are disrupted as well, and facet joint dislocation may result. These injuries are unstable and are associated with a high incidence of cord damage. Flexion–rotation injuries also commonly disrupt the posterior ligamentous complex and may also produce facet joint dislocation. They tend to be stable and are not usually associated with spinal cord injury, although cervical root injury is common. Hyperextension injuries cause compression of the posterior column and distraction of the anterior column (fig. 4). Hyperextension combined with compressive forces (e.g., diving injury) may result in injury to the lateral vertebral masses, pedicles, and laminae. Because both anterior and posterior columns are disrupted, this injury is unstable and is associated with a high incidence of cord injury. Violent hyperextension, with fracture of the pedicles of C2 and forward movement of C2 on C3, produces a traumatic spondylolisthesis of the axis, or hangman’s fracture. The fracture is unstable, but the degree of neurologic compromise is highly variable, because the bilateral pedicular fractures serve to decompress the spinal cord at the site of injury.

Burst fractures are caused by compressive loading of the vertebrae of the skull in the neutral position and are not as common as flexion–extension injuries. Compression forces in the lower cervical spine result in the explosion of intervertebral disc material into the vertebral body. Depending on the magnitude of the compression loading and associated angulating forces, the resulting injury ranges from loss of vertebral body height with relatively intact margins, to complete disruption of the vertebral body. Posterior displacement (retropulsion) of comminuted fragments may result, producing cord injury; the spine is usually stable. Pure distraction injuries are uncommon but, if severe, may result in ligamentous disruption causing both cord trauma and an unstable spine.

Determining Stability of the Cervical Spine after Injury

Because spinal instability usually results in vertebral displacement, it may be detected in many instances by radiography. White and Panjabi identified the upper limit of vertebral displacement and that which is beyond the physiologic range. They concluded that a normal adult spine would not permit horizontal motion greater than 2.7 mm between vertebrae. Therefore, if horizontal displacement exceeding 3.5 mm (corrected for x-ray magnification) or 20% of the vertebral body width was
found on lateral radiographs of the neck (or with flexion-extension views or dynamic fluoroscopy), this motion was deemed abnormal and the spine was considered unstable. With respect to angular displacement, the upper limit of physiologic angular displacement of a vertebral body compared with adjacent vertebrae was 11°. If there is greater angulation of the vertebra in question demonstrated on imaging studies, the spine is deemed unstable at the site of the excessively rotated vertebra.

The ligamentous structures, intervertebral discs, and osseous articulations have been extensively studied, and their major role in determining clinical stability has been demonstrated. Although the muscles in the neck exert some stabilizing forces, the contribution that they make toward clinical stability has not been studied. The repeated observation that secondary neurologic injuries occur frequently in spine-injured patients who are not immobilized suggests that muscle splitting is not highly protective after injury.9,10

Not all cervical spine injuries result in clinical instability. Generally, fractures are considered to be clinically insignificant if failing to identify them would be unlikely to result in harm to the patient or, alternatively, recognizing the injury would prompt no specific treatment. Two groups have categorized, by expert consensus, a number of injuries as not clinically important.11,12 The National Emergency X-Radiography Utilization Study (NEXUS) group identified the following injuries as not clinically significant: spinous process fractures, wedge compression fractures with loss of 25% or less of body height, isolated avulsion fractures without ligament injury, type 1 odontoid fractures, end-plate fractures, isolated osteophyte fractures, trabecular fractures, and isolated transverse process fractures.11 Similarly, the Canadian CT Head and Cervical Spine Study group identified the following injuries as not significant: simple osteophyte fractures, transverse process fractures, spinous process fractures, and compression fractures with loss of less than 25% of body height.12

Mechanisms of Spinal Cord Injury

There are a number of mechanisms implicated in primary spinal cord injuries. Immediate neural damage may result from shear, compressive, ballistic, or distracting forces, which primarily avulse and devitalize tissues. Persistent cord compression from fracture-dislocation may lead to ischemia. The cord may be injured by bone fragment or missile injury with resultant laceration, contusion or concussion.13 Secondary and progressive injury may also result from local perfusion deficits due to vascular compression by deranged anatomy (e.g., tissue damage or edema) or from global perfusion compromise caused by systemic hypotension. In addition, tissue hypoxemia leading to secondary injury may also occur as a result of hypoventilation caused by head or cord injury or by primary lung trauma. Finally, there are multiple mechanisms at the cellular and subcellular level that may result in exacerbation of the injury resulting in an extension of the clinical deficit.14

The impact of persistent cord compression and the benefits of urgent decompression of injured cord have been assessed by a number of authors. Carlson et al.15 determined the relation between the duration of sustained spinal cord compression and the extent of spinal cord injury and the capacity for functional recovery after immediate decompression. Sixteen dogs underwent spinal cord compression for 30 or 180 min. Sustained cord compression was associated with a gradual decline in the amplitude of evoked potentials. Within 1 h of decompression, dogs that had experienced 30 min of compression had recovery of the evoked potentials, but no animal that had been subjected to 180 min of compression had similar recovery. Motor tests demonstrated rapid recovery of hind-limb function in the 30-min group, but there was considerable impairment in the 180-min group, and this impairment was persistent. In a similar model, Delamarter et al.16 demonstrated that neurologic recovery after 1 h of cord compression occurred after immediate decompression but not when cord compression persisted for 6 h or more.

Despite the basic science support for early decompression after spinal cord injury, two recent reviews have concluded that the evidence supports decompression as a practice option only.17,18 The authors of these reviews concluded that the data assessing the impact of early decompression on neurologic outcomes was limited, consisted of primarily class III (case series, retrospective reviews, and opinion) and limited class II (prospective cohort studies or controlled studies with comparison cohorts) evidence, and demonstrated a possible benefit to patients with incomplete injury only. Both early decompression and conservative management were associated with neurologic improvement in some patients and deterioration in others. Both groups of authors acknowledged the need for randomized, controlled trials to better delineate the role of surgery in the management of acute spinal cord injury.17,18

Biomechanics of the Spinal Cord and Canal

For proper functioning of the spinal cord, a minimum canal lumen is required, both at rest and during movement. Cord compromise will result if the canal space is less than that required for cord function; neurologic injury will occur if this reduction in canal space is persistent. The neurologic injury results from sustained mechanical pressure on the cord leading to both anatomical deformation and ischemia. A reduction in canal size is often seen with age-related changes in spinal anatomy such as disc degeneration, osteophyte formation, hypertrophy of the ligaments of the spinal column, and the vertebral subluxations common in the chronic arthriti-
Fig. 5. The Poisson effect: schematic representation. The axis of rotation is indicated by the small squares superimposed on the vertebral bodies. In the neutral position (A), the gentle arc of the normal lordotic curve is transcribed. In extension (B), the elements posterior to the bodies, including the canal, transcribe the arc of a smaller circle than that of the vertebral bodies, indicated by the small circles. In flexion (C), the opposite effect is seen, and the arc of a larger circle is transcribed by the posterior elements. The Poisson effect dictates that as the length increases (the arc is of a larger circle), the cross-sectional area (lumen) of the column will decrease.

des. Canal size may also be reduced acutely with traumatic injury to the spinal column. Although neurologic deficits do not directly correlate with the degree of posttraumatic reduction of the spinal canal, canal impingement is more commonly observed in patients with both spinal injury and neurologic deficit than in patients who do not have a deficit after spinal injury.19

The functional size of the spinal canal may be further reduced with movement. The spinal canal is a column of relatively fixed volume.20 As it lengthens, its cross-sectional area will be reduced, and as it is shortened, its area will be increased; this behavior is termed the Poisson effect. With flexion, the canal length is increased and its area is reduced; the cord is stretched. This occurs because the axis of rotation of the spine is centered in the vertebral body.21 As the spine flexes, the rotation points will transcribe an arc; posterior spinal elements, including the canal, will also transcribe an arc, but that of a larger circle and will axially lengthen (fig. 5).22 The Poisson effect dictates that both the lumen of the canal and the spinal cord will narrow as they lengthen. The cord will tolerate a degree of elastic deformation while maintaining normal neurologic function.20 It may be further stretched and deformed if there is a local anomaly such as an osteophyte, prolapsed disc, or subluxed vertebral body projecting into the canal. These deformations may, over time, result in the application of strain and shear forces to the cord and ultimately result in axonal injury and myelopathy.25

With extension, the canal length is decreased and its area is increased; the cord is shortened. Again, this is an effect of the axis of rotation being centered in the vertebral bodies and the posterior spinal elements including the canal now transcribing the arc of a smaller circle; the Poisson effect will dictate canal widening. However, the shortening and folding of the cord when the spine is in extension may result in a relative increase in the ratio of cord size to canal lumen, despite the potential increase in the lumen. As well, there is posterior protrusion of the disc annulus and buckling of the ligamentum flavum in extension, which may further reduce canal dimensions and the space available for the cord at any given vertebral level. A number of age-related pathologic processes, including osteophyte formation and ossification of the posterior longitudinal ligament, may lead to further impingement on the canal lumen; these typically manifest a greater impact during spinal extension.

Ching et al.24 measured the impact of different positioning on canal occlusion in a cervical spine burst fracture model. Extension increased the canal occlusion to levels normally associated with the onset of neurologic injury. Flexion did not result in a significant increase in canal occlusion. These observations run counterintuitive to what might be expected on the basis of the Poisson effect and are likely manifestations of both the soft tissue buckling and bone fragment retropulsion which occur during extension. Prone positioning is also often associated with modest degrees of extension, and there is evidence that canal stenosis is increased with patients with cervical myelopathy who are positioned prone compared with supine positioning.25 Again, this is likely a manifestation of the soft tissue encroachment on the spinal canal with extension and aggravated by the preexistent canal compromise. The clinical relevance of these findings is that a persistent malposition of an abnormal neck may result in a degree of cord compression. If the abnormality is modest, it is likely that the malposition will need to be of greater magnitude and more prolonged to cause harm; as the anatomical derangement is increased, the duration of positional stress required to cause harm is shortened.15,26 Prone positioning is also associated with increases in vena caval pressures that may further reduce cord blood flow already compromised by cord compression.27

Dominguez et al.28 reported the occurrence of irreversible tetraplegia in a 21-yr-old woman without cervical pathology whose neck was maintained in extreme flexion after tracheal reconstruction; a magnetic resonance imaging (MRI) study was consistent with cord infarction. Deem et al.29 reported the occurrence of quadriplegia in a 60-yr-old man with severe cervical stenosis after thoracolumbar surgery in the prone position. The patient’s trachea was intubated, and he was positioned prone while still awake; anesthesia was in-
duced after his cervical spinal positioning was ascertained to be near neutral, and neurologic examination results were deemed normal. When he awoke from anesthesia after 6 h of surgery, there was evidence of a central cord syndrome. The authors acknowledge the possibility that, even though extreme degrees of flexion and extension were avoided, more subtle degrees of malpositioning may have been present. Unfortunately, cord injury may occur when positions detrimental to canal architecture are persistent; the greater the degree of underlying spinal pathology is, the lesser the magnitude of malpositioning required to cause harm is. The prone position may be especially threatening in these instances for the reasons already outlined.

Patients with severe cervical spondylosis may manifest such severe positional intolerance that they develop symptoms of cord compromise with degrees of malposition that may be imperceptible to the caregivers. Miller et al.30 described exacerbation of neurologic symptoms in a 74-yr-old women with an osseous bar at C3–C4 who presented with signs of cord compression and was booked for cervical laminectomy. On the first surgical occasion, after awake tracheal intubation accomplished with sedation, she was considerably weaker than before intubation. Surgery was cancelled, and her trachea was extubated; her neurologic condition returned to baseline within 2 h. Four days later, she presented for surgery in halo traction, and after sedation with intravenous diazepam, her neurologic condition deteriorated. A joint decision was made to induce anesthesia and proceed with tracheal intubation and surgical laminectomy at the C3–C5 spinal levels. Although she awoke with signs of neurologic deterioration, she recovered to her baseline condition by the fourth hour. The authors of this report postulated that the increased neurologic symptoms were an effect of the medications administered to facilitate awake intubation. Whether the drugs actually caused deterioration in the patient’s neurologic status or made the neurologic assessment less reliable is not certain. Equally unknown is whether, in general, patients might be more likely to overlook or underreport neurologic changes that occur if they were sedated during awake intubation. The reliability of a neurologic assessment in a sedated patient might be questioned, especially if one is seeking evidence of subtle changes.

Bejjani et al.31 reported the case of a 54-yr-old woman with cervical spondylosis and canal stenosis from C4 to C7 who developed signs of cord compression while her head was restrained in a plastic head-holder for the purpose of cerebral angiography. Approximately 45 min after the procedure had begun, she reported neck pain and upper extremity weakness; her symptoms were attributed to anxiety, and she was sedated. At the termination of the procedure, she was hemiparetic on the left side; an MRI study revealed a high-signal lesion consistent with edema. She recovered completely over the next 6 weeks. The potential for general anesthesia to permit positioning for MRI in postures not tolerated by awake patients with resultant neurologic injury has also been reported.52

Magnaes measured cerebral spinal fluid pressure with the neck in the extended position for tracheal intubation, in eight patients with a compromised spinal canal due to cervical spondylosis. Pressures up to approximately 140 cm H2O were recorded. Longitudinal skeletal traction with the tong placed frontally significantly reduced the pressure on the spinal cord in all patients. This finding would suggest that there is likely a benefit, in terms of decreased intracanal pressures, in maintaining the compromised cervical spine in as close to the neutral position as possible at all times after injury. As has already been noted, it may be very difficult to determine neutral position in some patients.

Persistent severe malpositioning at the extremes of the spinal range of motion has the potential to cause harm even in the normal spine–cord complex. In patients with disease processes that result in spinal canal compromise, minor degrees of malpositioning may also result in severe stress to the cord. If these positions are enforced, especially for prolonged periods, neurologic injury may result. As well, the use of sedation or anesthesia to allow patients to be maintained in positions that are neurologically intolerable to them while awake may also result in neurologic injury.

Cervical Spine Trauma: Epidemiology and Clinical Characteristics

The Incidence of Cervical Spinal Injury after Blunt Trauma

The incidence of CSI in victims of blunt trauma is estimated to be 0.9–3%, with a weighted average of 1.8%.34 Many of these previously published studies evaluating CSI after blunt trauma involved data from individual institutions or limited populations of trauma victims; there have been few data available regarding injury patterns at a national level. A substudy of NEXUS was designed to provide such data regarding the prevalence, spectrum, and distribution of CSI after blunt trauma.35 A total of 34,069 patients with blunt trauma undergoing cervical spine radiography at 21 US institutions were enrolled. Consistent with past reports, 818 (2.4%) of trauma victims had a total of 1,496 distinct CSIs. The second cervical vertebra (C2) was the most common level of injury (24.0% of all fractures), and 39.3% of fractures occurred in the two lowest cervical vertebral (C6, C7). The vertebral body was the most frequent anatomical site of fracture; nearly one third of all injuries (29.3%) were considered clinically insignificant.
Cervical Spine Injury and Associated Craniocerebral Trauma

Although it has been reported that patients with craniocerebral trauma had an incidence of CSI similar to that of the general trauma population, review of the large databases evolving at major trauma centers now dispute this finding. Holly et al. 36 reviewed 447 consecutive, moderately to severely head-injured patients presenting to two level I trauma centers. Twenty-four patients (5.4%) had a CSI; patients with an initial Glasgow Coma Scale (GCS) score less than 8 were more likely to sustain both a CSI and a cord injury than those with higher scores. Demetriades et al. 37 conducted a similar review of all CSI patients admitted over a 5-yr period at a major trauma center. During the study period, there were 14,755 admissions and 292 patients with CSI, for an overall incidence of 2.0%. Again, the incidence of CSI varied with the GCS score, being 1.4% if the GCS score was 13–15, 6.8% when it was 9–12, and 10.2% when it was less than 8. Hackl et al. 38 used a large computerized database to assess the association between CSI and facial injuries in 3,083 patients with facial injuries. Two hundred six (6.7%) of these patients had experienced a concomitant CSI, an incidence substantially higher than would be expected after blunt trauma. Blackmore et al. 39 reviewed their institutional experience with 472 patients with trauma (168 with cervical fractures, 302 without fractures) to delineate the characteristics of trauma patients with cervical fracture. The clinical predictors of cervical spine injury included severe head injury (odds ratio, 8.5; 95% confidence interval [CI], 4–17) and focal neurologic deficit (odds ratio, 58; 95% CI, 12–283). In patients with head injury, those who were persistently unconscious had an even higher likelihood of spinal injury (odds ratio, 14; 95% CI, 6–35) than those with head injury who were not unconscious. Therefore, new evidence has emerged that consistently suggests a higher incidence of cervical injury in patients who have experienced craniocerebral trauma, especially among those with increasing severity of craniocerebral injury as determined by low GCS score and unconsciousness. The finding of a focal neurologic deficit has been identified as a highly important clinical finding predicting spinal injury. 40

Systemic Injuries Associated with Cervical Spine Injury

The majority of patients with CSI also have other injuries; in only 20% of instances are traumatic injuries restricted to the cervical spine. 41 Although 2–10% of patients with craniocerebral trauma have CSI, 25–50% of patients with CSI have an associated head injury. Patients with additional injuries are more likely to experience hypoxia and hypotension, both of which may not only prompt urgent airway intervention, but may also predispose to secondary neurologic injury. There is data to suggest reduced neurologic recovery and increased mortality in cord-injured patients who have concurrent injury. It is not clear whether these patients experienced more severe primary injury or whether they are more likely to experience secondary injury leading to the poorer outcome.

Defining the Low-risk Trauma Patient

The National Emergency X-Radiography Utilization Study. The majority of patients who have experienced a blunt traumatic injury do not have a CSI. Enormous resources are currently expended to clear the spine (determine the absence of injury when injury does not exist) in these patients. The NEXUS project attempted to derive a set of clinical criteria to identify blunt trauma victims at low risk for CSI. 42 The decision instrument required patients to meet five criteria to be classified as having a low probability of injury: (1) no midline cervical tenderness; (2) no focal neurologic deficit; (3) normal alertness; (4) no intoxication; and (5) no painful, distracting injury. Distracting injuries were defined as including long bone fractures; visceral injuries requiring surgical consultation; large lacerations; burns; degloving or crush injuries; or any injury that might impair the patient’s ability to participate in a general physical, mental, or neurologic examination. The decision instrument was applied to 34,069 patients and identified as high risk all but 8 of the 818 patients who had a CSI (sensitivity, 99%; 95% CI, 98–99.6%). The negative predictive value was 99.8% (95% CI, 99.6–100%), the specificity was 12.9%, and the positive predictive value was 2.7%. Only two of the eight patients missed by the screening protocol had a clinically significant injury. In the NEXUS study, plain radiographs alone revealed 932 injuries in 498 patients but missed 564 injuries in 320 patients. 43 The majority of missed injuries (436 injuries in 237 patients) occurred in cases in which plain radiographs were interpreted as abnormal (but not diagnostic of injury) or inadequate. However, 23 patients had 35 injuries (including three potentially unstable injuries) that were not visualized on adequate plain film imaging. In the absence of all five clinical risk factors identified by the NEXUS study as predicting an increased risk of CSI, the likelihood of a significant injury is low. The practice of withholding imaging for patients who meet these exclusionary criteria has been endorsed by recent neurosurgical guidelines. 44

The Canadian C-spine Rule for Radiography after Trauma. The Canadian CT Head and Cervical Spine Study Group attempted to derive an optimally sensitive clinical decision rule to allow for selectivity in the use of radiography in alert and stable trauma patients. 45 A prospective cohort study was conducted in 10 large Canadian hospitals and included 8,924 consecutive adult patients presenting to emergency departments after...
sustaining acute blunt trauma to the head or neck. Patients were eligible for enrollment if they were alert (GCS of 15), if they had stable vitals signs, and if they had either neck pain after injury or had no neck pain but visible injury above the clavicles after a dangerous mechanism of injury. The patients were assessed using 20 standardized clinical findings from the history, general physical examination, and an assessment of neurologic status. Patients then underwent diagnostic imaging at the discretion of the treating physician; this imaging consisted of a minimum of three views of the cervical spine.

Among the study sample, 151 patients (1.7%) had an important cervical injury. The resultant rule that was derived comprises three questions: (1) Is there any high-risk factor present that mandates radiography? (2) Are there low-risk factors that would allow a safe assessment of a range of motion? and (3) Is the patient able to actively rotate the neck 45° to the left and to the right? When applied to the study population, the derived rule had 100% sensitivity and 42.5% specificity for identifying patients with clinically important injuries. The rule also identified 27 of 28 patients with clinically unimportant cervical injuries (primarily avulsion fractures), defined as those not requiring stabilization or follow-up.

The NEXUS Low-Risk Criteria were compared prospectively with the Canadian C-Spine Rule in 8,283 patients presenting to Canadian hospital emergency departments after trauma. Two percent of patients had clinically important cervical injuries, and the C-Spine Rule was both more sensitive than the NEXUS criteria (99.4% vs. 90.7%) and more specific (45.1% vs. 36.8%) for injury. The C-Spine Rule would have missed one patient, and the NEXUS criteria would have missed 16 patients with important injuries.

Strategies to define a low-risk clinical population continue to evolve. It must be emphasized that the primary focus and utility of these strategies is to allow for selective use of diagnostic imaging in patients who have a low-risk of injury, thus reducing imaging use and patient exposure, conserving resources, and allowing for expedited and simplified care for this patient group. A criticism leveled at the NEXUS protocol is that application would have a limited impact in reducing imaging because only 12.9% of patients presenting after trauma would be deferred; most would not meet at least one deferral criteria. Application of the C-Spine Rule would allow for the exclusion of 42.5% of trauma patients from radiographic imaging. The original rationale for the derivation of the protocols, to provide more efficient care and conserve imaging resources, is satisfied to a very limited degree by the NEXUS protocol but to a greater degree by the C-Spine Rule. Application of either protocol will still demand imaging in a large portion of the trauma patient population at low risk for CSI.

There will be a small population of patients presenting for urgent surgical intervention after minor injury who are fully evaluable using either the NEXUS criteria (12.9%) or the C-Spine Rule (42.5%); it is likely not necessary to delay surgery to clear the cervical spine of these patients with detailed imaging. Unfortunately, many patients presenting for urgent operative interventions after trauma will manifest more severe injuries; it will not be possible to clinically rule out injury in this patient cohort, and they will still require diagnostic imaging. As well, application of these protocols is complicated by the fact that there is a lack of agreement on the definitions of both distracting injury and intoxication. Failure to appreciate the degree of both distraction and intoxication may reduce the clinical index of suspicion for injury, resulting in missed diagnosis.

**Patterns of Practice in Evaluating and Clearing the Cervical Spine after Trauma**

Two authors have recently reported descriptions of patterns of practice in the United States and the United Kingdom obtained through postal surveys regarding evaluation and clearance of the cervical spine after trauma. Grossmann et al. surveyed 165 US trauma centers and reported that between 26 and 73% had written protocols for cervical spine clearance after trauma. It was more common for level I and academic centers to have protocols. In most instances where a protocol existed, it also described the radiographic approach to clearance; most centers did not consider that either computerized tomography (CT) or MRI was the standard of care in this setting. The use of a five-view series was moderately prevalent in response to specific scenarios, and the problem of visualizing the cervicothoracic junction was dealt with in most centers (68%) using an axillary/swimmer’s radiographic view. For patients with a head injury who are comatose or who have altered mental status and who have normal plain films, 21% of level II and 10% of level I centers advocated removal of the cervical collar without further testing beyond a five-view series.

Jones et al. surveyed 27 United Kingdom neurosurgical and spine injury units to determine the methods of cervical spine clearance used in unconscious, adult trauma patients and the point at which immobilization was discontinued. Most centers did not have either a written protocol to perform clearance or one regarding discontinuing cervical immobilization (78%). All units relied to some degree on plain radiography for clearance; 10 units (37%) performed only a single lateral view as the initial evaluation, and the remainder performed two more views. Five units routinely used CT imaging, and 17 units (63%) made no use of CT to screen for cervical injury. If the initial investigations were normal, 12 units (44%) would discontinue immobilization, and 10 units continued it until the patient could be evaluated.
clinically irregardless as to the results of the screening imaging.

The Eastern Association for the Surgery of Trauma recently reported the results of a survey of 31 large American and Canadian trauma centers. Centers were asked to identify their routine practice for determining cervical spinal stability in obtunded or comatose patients. Twenty-four centers (77%) reported using three views of the cervical spine (lateral, odontoid, and antero-posterior views) supplemented by CT through suspicious or poorly visualized areas. Three centers (9.7%) relied on three views only, and three centers (9.7%) added a swimmer’s view to visualize the lower cervical spine and the cervicothoracic junction.

There is considerable variation in the approach that different centers take in the performance of radiographic evaluation of at-risk patients, making the determination that the spine has been cleared, and reaching the decision that immobilizing devices can be safely removed. The most common pattern of practice in North American centers is to rely on multiple (at least three views) plain radiographs; the use of supplementary CT is also common.

**Radiographic Assessment after Blunt Trauma: Evolving a Best Practice**

An evaluative approach that would provide timely and accurate assessment of cervical stability in patients who may not be reliably examined clinically so that immobilizing devices can be safely removed is desirable. This would minimize the potential for sequelae related to prolonged immobilization. The reader is referred to three excellent reviews on the topic of evaluating and clearing the cervical spine in high-risk patients; these reviews form the basis of the subsequent discussion.

The cross-table lateral radiograph, of acceptable quality and interpreted by an expert, will disclose the major-ity of injuries. However, the sensitivity of the cross-table view is such that up to 20% of patients with cervical injury will have a normal study. Half of cross-table views are deemed inadequate to properly assess the entire cervical anatomy; injuries at both the craniovertebral and the cervicothoracic junctions are often not well visualized in the cross-table view. Too many injuries are missed when only a cross-table view is used for it to be considered an acceptable study to rule out injury in a high-risk patient. The sensitivity of three views (cervical series) approximates 90%; the cervical series was long regarded as an acceptable radiologic evaluation in patients deemed at risk for CSI. Similar technical concerns apply to the cervical series as to the cross-table lateral view with respect to both anatomical limitations at the cervical junctions and inadequate studies being issues. It is estimated that 1% of clinically important injuries will be missed even with a technically adequate cervical series.

A three-view cervical series supplemented by CT through areas that are either difficult to visualize or suspicious on plain radiography will detect most spinal injuries. The negative predictive value of this combination of studies is reported to be 99–100% in several class II and III evidence studies. In the obtunded patient with a normal cervical series and appropriate supplemental CT of the cervical spine, the incidence of significant spine injury is less than 1%. High-resolution CT scanning with sagittal reconstruction of the entire cervical spine rather than directed scanning of only at-risk areas may be even more effective in capturing virtually all injuries.

The use of MRI in addition to plain radiography and supplemental CT has been advocated to perform spinal clearance; the significance of a positive MRI study in the setting of normal CT imaging is currently unclear because many false-positive findings are reported with MRI. As well, MRI is less sensitive than CT for injuries in the upper and posterior cervical spine. Shuster et al. studied the role of MRI in assessing the spines of patients with persistent cervical pain and no motor deficits after trauma when the CT imaging was negative for injury. Ninety-three patients (3.4%) had a normal admission motor examination, a CT result negative for trauma, and persistent cervical spine pain; they underwent MRI examination. All MRI examinations were negative for clinically significant injury, and no patient subsequently experienced a neurologic deterioration. Hogan assessed the role of magnetic resonance imaging in 366 obtunded or unreliable patients who had normal CT imaging after trauma. Magnetic resonance images were negative for acute injury in 354 of 366 patients; the most common injury seen was a cervical cord contusion, identified in 7 patients. Magnetic resonance images were also negative for spinal ligament injuries in 362 of 366 patients; 4 patients had ligament injuries, but in all cases, the injury was limited to the ligaments of a single column. CT had negative predictive values of 98.9% for ligament injury and 100% predictive value for unstable cervical injury; MRI identified a small number of patients with ligament injuries not diagnosed with CT, but none of these were deemed to be unstable injuries.

In summary, in a patient at high risk for cervical injury, who cannot be evaluated clinically, a three-view cervical series supplemented by high-resolution CT scanning with sagittal reconstruction will reduce the likelihood of an occult fracture to less than 1%. After a technically adequate imaging series has been reviewed and cleared by a radiologist, it is prudent to remove cervical immo-
bilization. If there is evidence of a neurologic deficit referable to the cervical spine despite the finding of normal cervical radiography and CT imaging, MRI should be considered.

**Spinal Ligament Injuries and Spinal Cord Injury without Radiographic Abnormality**

Spinal ligament injuries are of particular concern because of the high incidence of resultant spinal instability, the potential for cord injury, and the hemodynamic instability common at presentation in this subpopulation. In Demetriades'\(^3\) review of CSI patients admitted during 5 yr to a major trauma center, 31 patients (10.6%) had a ligament injury (subluxation without fracture), and 11 patients (3.8%) had an isolated spinal cord injury without fracture or subluxation (spinal cord injury without radiographic abnormality). Of the 31 patients with ligament injury, one third required tracheal intubation before clinical evaluation of the spine was completed. Of the 11 patients with spinal cord injury without radiographic abnormality, 27.3% required intubation before spinal evaluation occurred. The diagnosis of cord injury was made on admission in only 5 patients (45.5%) with spinal cord injury without radiographic abnormality. In 3 patients, the neurologic examination on admission was normal, and neurologic deficits appeared a few hours later. In the remaining 3 patients (2 intubated, 1 intoxicated), the diagnosis was missed initially. Patients who required urgent airway intervention were less likely to have had a complete neurologic evaluation and were more likely to have neurologic injury than those who did not require urgent interventions. Chiu et al.\(^5\) also investigated the incidence of cervical spinal ligament injury in 14,577 blunt trauma victims. Six hundred fourteen patients (4.2%) had CSI, and 87 (14% of CSI) had dislocation without evidence of fracture. There were 2,605 (18%) patients who could not be assessed for symptoms, and 143 (5.5%) of these unreliable patients had a CSI; 129 (90%) had a fracture, and 14 had no fracture.

Trauma patients with greater severity of injury are more likely to have had a CSI; clinical evaluation is more difficult in these patients, typically because of depressed consciousness. Patients with ligament injury of the cervical spine without fractures frequently require urgent intubation, and not uncommonly, clinical evaluation is either not possible or not complete at the time that intervention is required; delay in the diagnosis of injury is common in these patients.

**Failure to Diagnose Cervical Spine Injury at Initial Assessment: Factors and Consequences**

Patients with decreased mental status from trauma, alcohol, or drugs and patients with other painful or distracting injuries have an unreliable history and physical examination for CSI; patients with these characteristics have spinal injuries that are also more likely to be missed on initial presentation. The commonest reasons for missed diagnosis are failure to obtain radiographs, poor quality of the imaging study, or misinterpretation of the radiographs. Failure to impede the spine in patients whose injuries are missed at the initial assessment is considered to be a leading cause of secondary injury.

Poonnoose et al.\(^5\) conducted a detailed review of the experience of a specialty spinal cord injury unit to determine both the incidence of missed injury and the clinical mismanagement that occurred in the setting of missed injury. The medical records of 569 patients with neurologic deficits secondary to traumatic spinal cord injury were reviewed. In 52 instances (9.1%), the diagnosis was initially missed, and 26 of these patients (50%) had evidence of neurologic deterioration after admission to care. The median time to recognition of the injury was 4 days. Therapeutic interventions were performed in 34 patients that were deemed inappropriate to their condition before the diagnosis was made. In 19 patients, there were significant neurologic findings present on initial assessment, and in 7, the initial neurologic deficit was minimal. Nine patients eventually developed paralysis, and 6 died with the deaths attributed to the delay in diagnosis. Again, the major cause for delayed diagnosis was related to radiographic assessments: In 18 cases, the initial images were of poor quality; in 11 patients, the area of concern was not adequately visualized; in 10 cases, an obvious fracture was missed; in 11 cases, facet joint malalignment was not recognized; and in 10 cases, prevertebral hematoma went undetected. It was common for the clinicians to consider the spine cleared when the radiographs “failed” to reveal injury and to attribute neurologic findings to either preexistent conditions (e.g., ankylosing spondylitis) or peripheral traumatic injuries. As well, 7 patients with evidence of neurologic deficits were initially labeled as “hysterical” and not managed as at-risk.

It is unfortunately the case that patients with CSI are frequently not correctly diagnosed at the time of initial presentation.\(^9\)\(^,\)\(^10\)\(^,\)\(^37\)\(^,\)\(^54\) This may occur in a small percentage of CSI patients because the injury is a ligamentous one and the screening imaging seems on initial review to be negative. However, it more commonly occurs because there is a low index of suspicion for injury despite high-risk mechanisms, inadequate radiographic studies are deemed acceptable, and neurologic signs or symptoms are either attributed to other causes or ig-
nored entirely. Delayed diagnosis is associated with a very high incidence of secondary injury, and the magnitude of that injury is often considerable.9,10,53,54

Secondary Neurologic Injury after Cervical Spine Injury
Secondary injury may be precipitated in CSI victims when management is suboptimal, and in particular when the injured spine is not immobilized. However, there is also evidence that neurologic deterioration occurs after acute injury despite appropriate management paradigms; the reported incidence of neurologic deterioration in this setting ranges from 2 to 10%.55 Frankel56 reported the occurrence of an ascending myelopathy 2–18 days after spinal cord injury despite appropriate clinical management. Only patients with ascension of injury level of at least four levels were included in this analysis; despite the high threshold for inclusion, this magnitude of secondary injury occurred in 1% of 808 patients admitted to the center. Frankel attributed the deterioration to either vascular catastrophes (arterial insufficiency or venous thrombosis) or inflammation; this report predated MRI, so no imaging is available in these patients to support the clinical conjecture. Marshall et al.57 reported the experience of a US regional spinal cord center regarding neurologic deterioration in cord-injured patients conducted in five US trauma centers. Deterioration occurred in 4.9% of patients and was consistent across the five centers. Although the deterioration was often associated with a specific intervention (surgery in 4 patients, traction application in 3, halo vest application in 2, Stryker frame rotation in 2, and rotobed rotation in 1), there was no evidence that these procedures were performed poorly or that they could have been performed in an altered fashion to prevent the deterioration. There were 375 such interventions recorded among the 283 patients. The authors concluded that deterioration is an inevitable consequence of providing care to cord-injured patients and will occur in some patients despite acceptable care practices.

Farmer et al.57 reported the experience of a US regional spinal cord center regarding neurologic deterioration after cervical cord injury. Deterioration was evident in 1.84% of 1,031 patients assessed. The average time from injury to deterioration was 3,95 days, and deteriorations were associated with early surgery (< 5 days after injury), sepsis, ankylosing spondylitis, and tracheal intubation. Tracheal intubation was associated with two minor and two major deteriorations, but no further details were offered regarding this cohort; it is possible that the intubation was necessitated by the neurologic deterioration and not the cause of it. In the patients who experienced deterioration and survived, 92% of patients eventually had improvement in their neurologic status. Harrop et al.58 analyzed the cases of 12 of 186 patients (6%) with acute traumatic cord injuries who demonstrated neurologic ascension within 30 days after injury. Three subgroups were defined: an early deterioration group who worsened within 24 h, a delayed deterioration group (1–7 days), and a late (beyond 7 days) deterioration group. Two patients in the late group had vertebral artery injury; vertebral artery injury is common after midcervical injury, and its clinical significance is uncertain.59,60

Yablon et al.61 described 14 cases of ascending myelopathy (involving 1–4 levels) that occurred in the first 4 weeks after injury. These cases were attributed to spinal cord edema; MRI studies demonstrated evidence of this as well as diffuse intrathecal hemorrhage. Belanger et al.62 identified a similar occurrence of ascending myelopathy, which they labeled as subacute post-traumatic ascending myelopathy, occurring within the first 2 weeks after injury. This syndrome occurred in three patients who experienced neurologic deterioration with a secondary injury ascending six or more levels (6, 9, and 17 levels) from the initial level after an uneventful early course. No etiologic factors could be identified. In all three patients, T2-weighted MRI studies revealed a high signal intensity located centrally within the cord and extending rostrally from the site of injury. T2-weighted images are sensitive to the presence of edema and effectively distinguish pathologic from normal tissue; the high signal intensity identified indicates injury and edema.

The above reports suggest that there is a progressive postinjury course in some patients leading to a secondary neurologic injury and ascension of injury level, sometimes to a striking degree. In some instances, this deterioration has been associated with clinical interventions, including immobilization, traction, surgery, intubation, and sepsis. In other instances, no clear factors are associated, and in particular, both extrinsic cord compression and vascular interruptions have been excluded. This syndrome, when witnessed early in the course after injury, has usually been attributed to vascular perturbations or cord edema and inflammation; MRI studies have been consistent with this attribution. More recent work has also suggested a role for apoptosis in the causation and progression of ascending myelopathy.63 A diagnosis of ascending myelopathy must be considered when a secondary injury has occurred; there is natural temptation to attribute the deterioration to temporally related clinical interventions but, in fact, these interventions are rarely associated with neurologic sequelae. Progressive neurologic injury after CSI may be inevitable in some patients because of pathophysiologic processes initiated at the time of the application of the injuring forces and may occur despite the provision of appropriate management paradigms and interventions.
Clinical Care of the Spine-injured Patient

Spinal Immobilization in Trauma Patients: The Overview

During the past 30 yr, the neurologic status of spinal cord-injured patients arriving in emergency departments has dramatically improved, and the odds of dying during the first year after injury have been significantly reduced. The improvement in the neurologic status of patients has been attributed to improved initial care and retrieval systems, recognition of the importance of instituting prehospital spinal immobilization, maintaining immobilization until clearance is obtained or definitive therapy is applied, and hospital practices designed to prevent secondary injury. The routine use of spine immobilization for all trauma patients, particularly those with a low likelihood of spinal injury, has been challenged on the basis that it is unlikely that all patients rescued from the scene of an accident or site of traumatic injury require spine immobilization. A Cochrane systematic review also concluded that the impact of immobilization on mortality, neurologic injury, and spinal stability was uncertain and that direct evidence linking immobilization to improved outcomes was lacking. The Cochrane review further concluded that the potential for immobilization to actually increase morbidity or mortality could not be excluded based on a review of the literature. However, the current consensus among experts remains that all patients with the potential for a CSI after trauma should be treated with spinal column immobilization until injury has been excluded or definitive management for CSI has been initiated.

The benefits, consequences, and sequelae of spinal immobilization in at-risk patients have been recently analyzed, and the reader is referred to these reviews for more detailed discussions. The chief concern during the initial management of patients with potential CSI is that neurologic function may be further compromised by pathologic motion of the injured vertebrae. Management of the potentially traumatized spine emphasizes three principles: (1) restoration and maintenance of spinal alignment, (2) protection of the cord with preservation of intact pathways, and (3) establishment of spinal stability. To achieve these principles, immobilization of the cervical spine before radiographic assessment and clearance is the accepted standard of care. The rationale behind early immobilization is the prevention of neurologic injury in the patient with an unstable spine. Establishment of the clinical care paradigm that features immobilization as a core element has resulted in improved neurologic outcomes in spine-injured patients during the past three decades. Failure to immobilize in the context of missed or delayed diagnosis is also associated with an increased incidence of neurologic injury. Lack of immobilization has been cited as a cause of neurologic deterioration among acutely injured trauma patients being transported to medical facilities for definitive care.

A number of complications to prolonged immobilization have been identified. Cutaneous ulcerations (pressure sores) are common, and the incidence increases when immobilization is prolonged beyond 48–72 h. Airway management, central venous access and line care, provision of oral care, enteral nutrition, and physiotherapy regimes are all made more difficult when immobilization must be maintained. The need for multiple staff to allow for safe positioning and transfer of immobilized patients makes barrier nursing more difficult and may result in higher rates of cross-contamination and infection in high-dependency units.

The application of cervical collars has also been associated with increased intracranial pressure (ICP) in both injured patients and healthy volunteers. Davies prospectively analyzed ICP in a series of injured patients treated with a rigid collar. The ICP increased a mean of 4.5 mmHg when the collar was firmly in place. Koll also examined changes in ICP after the application of a rigid Philadelphia collar in 20 adult patients. ICP averaged 17.68 cm H$_2$O initially and increased to an average of 20.15 cm H$_2$O after collar placement. Although the difference in ICP of 2.47 mm H$_2$O was statistically significant, it remains uncertain that it has clinical relevance. Nonetheless, this modest increase in pressure may be magnified in patients who already have increased ICP and poor intracranial compliance. The potential for complications should not discourage the use of immobilization where indicated. Rather, because many of the complications are time dependent, they should encourage attempts to promptly assess the patient for cervical injury to expedite the discontinuance of immobilization in those patients whose spines can be cleared.

Techniques and Devices for Preadmission Spinal Immobilization

The position in which the injured spine should be placed and held immobile, the "neutral position," is poorly defined. De Lorenzo et al., in an MRI study of 19 adults, found that 2 cm of occiput elevation produced a favorable increase in spinal canal/spinal cord ratio at the C5 and C6 levels, a region of frequent unstable cervical spine injuries. Podolsky et al. evaluated the efficacy of cervical spine immobilization techniques. Hard foam and hard plastic collars were better at limiting cervical spine motion than soft foam collars, although the use of collars alone did not effectively restrict spinal motion. The use of sandbag-tape immobilization was more effective at reducing spinal movement than any of the other individual methods tested. Adding a Philadelphia collar to the sandbag-tape construct reduced neck extension but had no effect on any other motion of the cervical spine. These authors found that sandbags and tape combined with a rigid cervical collar was the most effective con-
struct of those evaluated to limit cervical spine motion, restricting movement to approximately 5% of the normal range. The sandbag-tape-backboard-collar and variations thereof have become the most commonly used extrication and transport assembly in prehospital trauma care to provide spinal immobilization.

Bednar assessed the efficacy of soft, semirigid, and hard collars to immobilize the neck in a destabilized elderly cadaver model. Bednar’s experiment involved creation of unstable motion segments at the C3–C4, C4–C5, or C5–C6 levels; isolated posterior column, combined column, and then anterior column injuries were sequentially assessed. Soft, semirigid, and rigid collars were used in an attempt to restrict neck movements, and then the spines were subjected to unrestrained gravitational forces with flexion, lateral side-bending, and extension. The collars were not effective in reducing spinal movement; in fact, there was evidence for increased spinal movement. Bednar hypothesized that the increased movement resulted from the levering of the mobile head and proximal cadaver neck over the collar edge. The model described allowed for the application of forces that would rarely be applied or permitted in clinical settings but did emphasize the very limited role that collars would play in limiting spinal movement if the spine were subjected to very hostile forces.

Goutcher and Lochhead measured maximal mouth opening (interincisor distance) in 52 volunteers, before and after the application of a semirigid cervical collar. Three collars were assessed: the Stifneck (Laerdal Medical Corp., Wappinger’s Falls, NY), the Miami J (Jerome Medical, Moorestown, NJ) and the Philadelphia (Philadelphia Cervical Collar Co., Thorofare, NJ). Application of a collar significantly reduced interincisor distance from a mean of 41 ± 7 mm in the control state to 26 ± 8 mm with the Stifneck, 29 ± 9 mm with the Miami J, and 29 ± 9 mm with the Philadelphia. There was a wide variation between subjects, and a significant proportion had an interincisor distance reduced to less than 20 mm after application of the collar (Stifneck, 25%; Miami J, 21%; Philadelphia, 21%). Goutcher and Lochhead concluded that the presence of a semirigid collar significantly reduced mouth opening and would likely often interfere with airway management; removal of the anterior portion of the collar before attempts at tracheal intubation was encouraged by these authors.

**Manual In-line Immobilization**

The goal of manual in-line immobilization (MILI) is to apply sufficient forces to the head and neck to limit the movement which might result during medical interventions, most notably, airway management. MILI is typically provided by an assistant positioned either at the head of the bed or, alternatively, at the side of the stretcher facing the head of the bed. The patient is positioned supine with the head and the neck in neutral position. Assistants either grasp the mastoid processed with their fingertips and cradle the occiput in the palms of their hands (head-of-bed assistant) or cradle the mastoids and grasp the occiput (side-of-bed assistant). When MILI is in place, the anterior portion of the cervical collar can be removed to allow for greater mouth opening, facilitating airway interventions. During laryngoscopy, the assistant ideally applies forces that are equal in force and opposite in direction to those being generated by the laryngoscopist to keep the head and neck in the neutral position.

Avoiding traction forces during the application of MILI may be particularly important when there is a serious ligamentous injury resulting in gross spinal instability. Lennarson et al. noted excess distraction at the site of a complete ligamentous injury when traction forces were applied for the purposes of spinal stabilization during direct laryngoscopy. Similarly, Kaufmann et al. demonstrated that in-line traction applied for the purposes of radiographic evaluation resulted in spinal column lengthening and distraction at the site of injury in four patients with ligamentous disruptions. Bivins et al. reported that traction applied during orotracheal intubation in four victims of blunt traumatic arrest with unstable spinal injuries resulted in both distraction and posterior subluxation at the fracture site. It is possible that the fracture site distraction that was observed resulted from application of traction forces not appropriately axially aligned.

Majernick et al. demonstrated that MILI reduced total spinal movement during the process of laryngoscopy and tracheal intubation; movement was not reduced to a similar degree by collars. Similarly, Watts et al. measured a reduction of spinal movement with the application of MILI during tracheal intubation in patients with normal spines during general anesthesia. However, Lennarson et al. were unable to demonstrate that application of MILI resulted in any significant reduction in movement during intubation in a cadaver model with a posterior column injury. In a cadaver model with complete ligamentous instability, Lennarson et al. reported that application of MILI minimized distraction and angulation at the injured level but had no effect on subluxation at the site of injury.

Manual in-line immobilization may be effective in reducing overall spinal movements recorded during airway maneuvers but may have lesser restraining effects at the actual point of injury. This may be because spinal movement is restricted by the weight of the torso at the caudal end and the MILI forces at the cephalad end but is unrestricted by any force at its cervical midpoint. It is possible that application of traction forces during MILI would also reduce midcervical movement in some patients, but traction forces may also result in distraction at the site of injury; the use of such forces during applica-
tion of in-line immobilization continues to be discouraged.

**Impact of MILI on the View Obtained at Laryngoscopy**

The application of MILI during airway maneuvers may result in decreases in overall spinal movement, but the evidence also suggests modest, if any, effect at individual motion segments. However, the use of MILI may have lesser impact on the view obtained during direct laryngoscopy than relying on other immobilization techniques, such as axial traction or a cervical collar, tape, and sandbags. Heath examined the effect on laryngoscopy of two different immobilization techniques in 50 patients. A grade 3 or 4 laryngoscopic view (partial or no view of the glottic structures) was obtained in 64% of patients immobilized with a collar, tape, and sandbags compared with 22% of patients stabilized with MILI. The laryngeal view improved by one grade in 56% of patients and by two grades in 10% when MILI was substituted for the collar, tape, and sandbags. The main factor contributing to the increased difficulty of laryngoscopy when patients were wearing cervical collars was reduced mouth opening. Gerling et al. reported the findings of an analogous study using a cadaver model with a C5-C6 destabilization and arrived at similar findings. MILI allowed less spinal movement than did cervical collar immobilization during laryngoscopy and intubation and was associated with improved laryngeal visualization.

Hastings and Wood measured the degree of head extension required to expose the arytenoid cartilages and glottis and determined the impact of applied MILI. The subjects were 31 anesthetized patients (24 study, 7 control) with normal cervical spines and Mallampati 1 views on preoperative airway assessment. Two methods of immobilization were assessed. Either axial traction was applied, wherein the assistant pulled the head in a caudal to cephalad direction as strongly as he or she thought was necessary to immobilize the neck, or force was applied to the head in a downward direction to hold the head onto the table. Without stabilization, the best view of the glottis was achieved with 10°-15° of head extension. Head immobilization reduced extension angles of 4°-5° compared with no stabilization, and it was more effective than axial traction immobilization in limiting extension. In 4 of the 24 study patients (17%), 2 in each immobilization group, the laryngoscopic view deteriorated from grade I or II to grade III with the application of immobilizing forces. Therefore, the use of MILI reduced the amount of head extension that was necessary for laryngoscopy but resulted in a poorer view in a portion of the patients studied.

Although MILI seems to have the least impact of all immobilization techniques on airway management, it may make direct laryngoscopy more difficult in some patients than if no immobilizing forces are being applied.

Nolan and Wilson assessed the impact of MILI with cricoid pressure on the view obtained at laryngoscopy in 157 normal patients and compared it with the view obtained in the same patients while in the sniffing position. With application of MILI and cricoid pressure, the view remained the same in 86 patients (54.8%), was worse by one grade in 56 (35.6%), and was worse by two grades in 15 (9.5%). A grade 3 view (partial glottic view) was obtained in 34 restrained patients (21.6%) compared with 2 (1.3%) in the sniffing position. Wood et al. also studied the effect of cervical stabilization maneuvers on the view obtained at laryngoscopy in 78 uninjured, elective surgical patients and concluded that cervical immobilization commonly worsened laryngoscopic view. The effects of MILI on laryngeal view were in a similar direction to those reported by Hastings but occurred more commonly in Wood’s study. Anterior laryngeal or cricoid pressure often improved the view of the larynx when the neck was immobilized. Concern has been expressed in the past regarding the use of anterior cervical pressure in patients at risk for CSI, but Donaldson et al. reported that application of cricoid pressure did not result in movement in an injured upper cervical spine in a cadaver model.

Manual in-line immobilization may have lesser impact on airway interventions than do other forms of immobilization. The experience supports routinely removing at least the anterior portion of collars to facilitate airway interventions provided that cervical spinal immobilization is maintained by MILI. Removal of the anterior portion of the collar improves mouth opening and facilitates airway management; reapplication of the mechanical immobilization should occur promptly when airway interventions are complete. MILI may increase laryngoscopic grade in some patients; this may be countered with anterior laryngeal or cricoid pressure.

**Spinal Movement during Airway Interventions**

The early biomechanical analyses of spinal motion typically used static radiography to determine the relations between the vertebral elements of the cervical spine and to quantify spinal movements. Unfortunately, no standardized technique of measurement has been used in the works since published, which have evaluated spinal movement during airway interventions. Both static radiography and dynamic fluoroscopy have been used; study findings have been reported movement as absolute distances, relative distances (typically a percentage of vertebral body width), and degrees of motion and have further been categorized relative to individual motion segments or upper and lower cervical spinal divisions or summated across the entire cervical spine. There is also little guidance available as to the clinical importance of the movements recorded, especially as they relate to the injured spine. Those spinal movements that fall within physiologic ranges have usually been considered to be
nonthreatening to the cord; whether they are in fact and remain so in a spine with a canal lumen already compromised by an acute, a chronic, or an acute superimposed on chronic anatomical derangement is by no means certain. Unfortunately, as we analyze the published works, we typically find ourselves in the position of comparing the recorded results with physiologic norms and then drawing an empiric conclusion as to the potential risk of such movements.

The Effects of Basic Airway Maneuvers on the Injured Neck. Aprahamian studied the effect of both airway maneuvers on a human cadaver, unstable spine model. The anterior and most of the posterior column were surgically disrupted; the interspinous and supraspinous ligaments were spared. Lateral cervical spine radiographs were taken during both basic and advanced airway maneuvers. Basic maneuvers included chin lift, jaw thrust, head tilt, and placement of both oral and esophageal Airways. Advanced maneuvers included placement of the following: an esophageal obturator airway; an orotracheal tube placed with both a straight and a curved laryngoscopic blade; and a nasotracheal tube, blindly placed. Chin lift and jaw thrust resulted in expansion of the disc space more than 5 mm at the site of injury. When blind nasotracheal intubation was facilitated by anterior pressure to stabilize the airway, 5 mm of posterior subluxation occurred at the site of injury. The other advanced airway maneuvers produced 3–4 mm of disc space enlargement. The study was repeated after the application of both soft and semirigid cervical collars; collars did not effectively immobilize the neck for either basic or advanced airway maneuvers.

Hauswald also determined the impact of basic airway maneuvers on cervical spine movement. Eight human traumatic arrest victims were studied within 40 min of death. All subjects were ventilated by mask, and their tracheas were intubated orally with a direct laryngoscope, over a lighted oral stylet and using a flexible laryngoscope, and nasally. Cinefluoroscopic measurement of maximum cervical displacement during each procedure was made with the subjects supine and immobilized by a hard collar, backboard, and tape. The mean maximum cervical spine displacement was found to be 2.93 mm for mask ventilation, 1.51 mm for oral intubation, 1.85 mm for guided oral intubation, and 1.20 mm for nasal intubation. Ventilation by mask caused more cervical spine displacement than the other procedures studied. It was concluded that mask ventilation moves the cervical spine more than any of the commonly used methods of tracheal intubation.

Airway maneuvers will result in some degree of neck movement, both in general and specifically at the sites of injury. The amounts of movement are small, typically well within physiologic ranges, and their impact on secondary neurologic injury has not been defined. However, as will be subsequently discussed, airway interventions are frequently performed on at-risk trauma patients, and there seems to be a very low incidence of secondary injury in these patients associated with airway clinical interventions.

Cervical Spinal Movement during Direct Laryngoscopy in Normal Patients. Sawin et al. determined the nature, extent, and distribution of segmental cervical motion produced by direct laryngoscopy and orotracheal intubation in normal human subjects. Ten patients underwent laryngoscopy while paralyzed and during general anesthesia. Minimal displacement of the skull base and cervical vertebral bodies was observed during laryngoscope blade insertion; elevation of the laryngoscope blade to achieve laryngeal visualization caused superior rotation of the occiput and Cl and mild inferior rotation of C3–C5. The largest magnitude motions were at the atlanto-occipital and atlantoaxial joints, but there was extension at each motion segment assessed. Tracheal intubation created slight additional superior rotation at the craniovertebral junction but caused little alteration in the postures of C5–C6. Horton et al. conducted a similar experiment in volunteers during topical anesthesia only. Subjects in a supine, sniffing position underwent direct laryngoscopy, and at full glottic exposure, a lateral radiograph of the head and neck was performed. The radiographs indicated that extension at the craniovertebral junction was near maximal and that there was progressively increasing extension from C4 to the base of the skull, but that the position of the lower cervical spine remained static during laryngoscopy. Both Sawin et al. and Horton et al. agreed that, during laryngoscopy, in both awake and unconscious subjects, most cervical motion occurs at the craniovertebral junction; the subaxial cervical segments subjacent to and including C4 are minimally displaced (fig. 6).91,92

Spinal Movement during Laryngoscopy in Injured Spine Models. Donaldson et al. studied the motion that occurred during intubation in a cadaver model with an unstable C1–C2 segment. The following were measured in the intact specimen and then again after creation of the unstable segment: angulation, distraction, and the space available for the cord (SAC). With maximum flexion and extension, the SAC was narrowed...
1.49 mm in the intact cervical spine but 6.06 mm in the unstable spine. Chin lift and jaw thrust reduced the SAC by 1 mm and 2.5 mm, respectively; oral intubation and nasal intubation created a similar (1.6 mm) reduction of SAC. Distraction at the unstable injured level was similar for chin lift, jaw thrust, and crash intubation (1–2 mm); distraction during gentle oral intubation and nasal intubation was less than 1 mm. Chin lift and jaw thrust created similar angulations (4°–5°) to those of the oral intubation techniques, but nasal intubation caused less (2.5°). Cricoid pressure resulted in no significant movements when it was applied in either the stable or unstable model. Donaldson et al. concluded that (1) the SAC was narrowed to a greater degree by preintubation maneuvers than it was by intubation techniques, (2) nasal and oral intubation techniques resulted in similar amounts of SAC narrowing, and (3) application of cricoid pressure produced no significant movement at the craniocervical junction.

### Stabilization during Airway Interventions in Cadaver Models of an Injured Spine

Lennarson et al. evaluated the impact of commonly used immobilization techniques in limiting spinal motion in an injured-spine model; the model involved the creation of a posterior ligamentous injury at the C5 level and compared the effects of MILI and Gardner-Wells traction. The predominant motion measured at all spinal levels during laryngoscopy and intubation in the intact spine was extension; this was consistent with the findings of Donaldson et al., Sawin et al., and Horton et al. Subluxation in the anterior–posterior dimension remained less than 1 mm in both the intact and the partially destabilized spine; rotatory or angular movements were the only significant movement recorded. Application of Gardner-Wells traction limited rotatory motion at the craniocervical junction after destabilization; MILI did not have a similar effect.

Lennarson et al. conducted a similar experiment assessing the efficacy of immobilization maneuvers in a model of complete C4–C5 segmental instability. Movement was measured at the injured level during the application of traction, during MILI, and without stabilization. Traction resulted in distraction at the site of injury when instability was complete; the magnitude of these movements was not reduced by MILI, although they remained within physiologic limits. Gerling et al. also evaluated the effect of both MILI and cervical collar immobilization on spinal movement during direct laryngoscopy in an unstable C5–C6 cadaver model. Although there was less displacement (2 mm) measured with application of MILI compared with collars, the magnitude of movement was small overall and within physiologic ranges.

Brimacombe et al. assessed spinal movement in a cadaver model with a posterior injury at C3, with MILI applied as various airway interventions (facerisk venti-

### Influence of Laryngoscope Blade Type on Spinal Movement during Direct Laryngoscopy

Three authors have assessed the influence of the type of laryngoscope blade on the spinal movements generated during direct laryngoscopy. MacIntyre et al. compared the Macintosh and McCoy blades in patients with normal spines during general anesthesia with cervical collars applied. There were no significant differences between the two blades with respect to the amount of spinal movement generated during intubation. Hastings et al. compared head movement occurring during laryngoscopy in patients with normal spines using Macintosh and Miller laryngoscopes, and again, there were no differences in the amount of movement measured. Finally, Gerling et al. compared spine movement in a cadaver model with a C5–C6 transection injury while performing laryngoscopy with Miller, Macintosh, and McCoy-type blades. There was no difference in the movements recorded with the different blades with regard to either anteroposterior displacement or angular rotation. Less axial distraction was measured with the Miller blade compared with the other two blade types; in absolute terms, the differences was 1.7 mm. Overall, there seems to be little difference in the spinal movement resulting from direct laryngoscopy relative to the type of blade used during laryngoscopy.

### Cervical Spinal Movement with Indirect Rigid Fiberoptic Laryngoscopes

Watts et al. compared cervical spine extension and time to intubation with the Bullard (ACMI Corp., Southborough, MA) and Macintosh laryngoscopes during a simulated emergency with cervical spine precautions taken. Twenty-nine patients were placed on a rigid board, and anesthesia was induced. Laryngoscopy was performed on four occasions, twice each with the Bullard and Macintosh laryngoscopes, both with and without MILI applied (MILI was applied with cricoid pressure). Cervical spine extension (from the occiput to C5) was greatest with the Macintosh and was reduced both when the Macintosh was used with MILI and when the Bullard was used with or without stabilization. Times to intubation were similar for the Macintosh with MILI and for the Bullard without MILI. MILI applied during laryngoscopy with the Bullard resulted in further reduction in cervical spine extension but a prolonged the time to intubation, although it still was achieved in less than a minute. In a study design similar to that of Watts et al., Hastings et al. found that cervical spine extension from the occiput to C4 was
decreased when comparing the Bullard with both the Macintosh and the Miller laryngoscope blades.

The times to achieve intubation using the Bullard laryngoscope, in the study of Watts et al., were similar to others reported in the literature. Twenty-two of 29 patients (76%) were intubated in less than 30s when using the Bullard under standard conditions. In a study using the dedicated intubating stylet, Cooper et al. found 70% of patients were intubated in less than 30s. There was also better exposure of the larynx during laryngoscopy with the Bullard than with the direct laryngoscope. Application of MILI resulted in deterioration in the grade view of the larynx when using the Macintosh in 19 of 29 patients (65%). In contrast, only 2 patients (7%) presented an inferior view of the larynx after application of MILI and cricoid pressure when using the Bullard laryngoscope.

Rudolph et al. compared movement in the upper cervical spine in 20 patients scheduled to undergo elective surgery, when laryngoscopy was performed with the Bonfils intubation fiberscope (Karl Storz Endoscopy Ltd., Tuttinglen, Germany) and the Macintosh laryngoscope. With the patient’s head in neutral position on the table and no pillow used, a baseline lateral radiograph was taken. The head was extended, laryngoscopy was performed using the Macintosh, a second radiograph was taken, and the head was returned to the neutral position. Laryngoscopy was then performed with the Bonfils fiberscope, and the trachea was intubated. With the Macintosh, views at laryngoscopy were class I in 8 patients, II in 5, and III in 7; all views obtained with the Bonfils fiberscope were class I. The time between insertion of the instrument and achievement of optimum view was similar for both instruments. Laryngoscopy with the Macintosh resulted in spinal movement that was greater in magnitude than that measured during Bonfils fiberscopy.

The Glidescope (Saturn Biomedical Systems, Burnaby, British Columbia, Canada) is a new video laryngoscope that incorporates a high resolution digital camera in the blade tip; the image is transmitted to a liquid crystal display monitor via a dedicated video cable. Agro et al. compared the laryngeal view obtained initially with a Macintosh and then with the Glidescope in 15 normal patients presenting for general anesthesia who were wearing cervical collars. The laryngeal view was reduced by one Cormack grade in 14 of the 15 patients (93%) studied when the Glidescope was used compared with the Macintosh; the average time to intubation with the Glidescope was 38s. Turkstra et al. compared cervical spine movement, measured fluoroscopically, during intubation with a Macintosh, a light wand, and the Glidescope. In-line immobilization was achieved by taping the patients’ heads into a Mayfield-type headrest; movement was measured at the Oc–C1, C1–C2, C2–C5, and C5–Th levels. The largest amount of motion measured was at the Oc–C1 complex with all devices. Cervical spinal movement was reduced 57% overall (all segments combined) comparing the light wand with the Macintosh; reduced movement was apparent at each level. Spinal movement was reduced only at the C2–C5 segment when the Glidescope was compared with the Macintosh; 6.9° ± 5.2° of flexion was measured during Macintosh laryngoscopy, and this was reduced by 50% using the Glidescope. Motion was not significantly altered at the three other segments studied. The time to intubation was longest with the Glidescope (27 ± 12 s) but similar with the light wand (14 ± 9 s) and the Macintosh (16 ± 7 s).

Cervical spine movements are generally less when rigid indirect laryngoscopes are used compared with the ML direct laryngoscope. Visualization of the glottis is also improved with the use of the rigid laryngoscopes, but the time to achieve the best view is somewhat longer; these times tend to be short, and the difference compared with the direct laryngoscope is likely to be of little clinical relevance.

**Cervical Spinal Movement and Laryngeal Mask Airways.** Kihara et al. measured cervical movement produced by the intubating laryngeal mask airway during MILI in 20 anesthetized patients with cervical pathology undergoing cervical spine surgery. During the insertion of the intubating laryngeal mask airway, C5 and superior segmental levels were flexed by less than 2°. During intubation, C4 and superior segmental levels were flexed by 3° or less, and C3 and levels above were flexed by an average of 1° during removal. There was some posterior displacement at the C2–C5 levels during insertion and intubation but not during removal.

Keller et al. implanted microchip sensors into the pharyngeal surfaces of C2 and C3 in 20 cadavers to determine the pressures exerted against the cervical vertebrae by both the standard laryngeal mask airway and the intubating laryngeal mask airway during insertion and manipulation. The impact of these pressures on cervical spine movement was also determined. Keller et al. concluded that laryngeal mask devices exert high pressures against the upper cervical vertebrae during insertion, during inflation, and while in situ; these pressures could produce posterior displacement of the upper cervical C-spine. The clinical relevance of these findings as they relate to CSI has yet to be clarified.

**Cervical Spinal Movement during Surgical Cricothyrotomy.** Surgical cricothyrotomy was initially advocated as a preferred airway intervention in patients at risk for CSI compared with orotracheal intubation and now is deemed to be an appropriate alternative if oral or nasal routes cannot be used or are unsuccessful. Although long considered safe in the presence of a CSI, its application in this scenario has not been well studied with respect to either spinal movements or neurologic outcomes. Gerfling et al. used a cadaver model to...
quantify movement during cricothyrotomy. Standard open cricothyrotomy was performed in 13 cadavers with complete C5–C6 transection injuries, and cervical spine images were recorded fluoroscopically during the procedure. Peak axial distraction was measured at 4.5% of the C5 width, amounting to 1–2 mm of axial compression; peak antero-posterior displacement was measured at 6.3% of the C5 width, equivalent to 1–2 mm of displacement. Although these values were statistically significant, there clinical relevance has yet to be determined.

*The Clinical Practice of Airway Management in Patients with Cervical Spine Injury*

*Surveys of Patterns of Clinical Practice Regarding Airway Management after Cervical Spine Injury.*

Four authors have surveyed North American anesthesiologists as to their preferred methods of airway management in patients with cervical spine trauma or disease. Lord *et al.*103 compared practice preferences among surgical members of the Eastern Association for the Surgery of Trauma with anesthesiologists in US anesthesiology training programs. In the elective situation (CSI but breathing spontaneously with stable vital signs), anesthesiologists stated that they were less likely to use nasotracheal intubation (53% vs. 69%), equally likely to use orotracheal intubation, and more likely to use the fiberoptic bronchoscope than were trauma surgeons. In the urgent situation (patient with unstable vital signs), anesthesiologists tended to use both nasotracheal and orotracheal intubation in a manner similar to that of the surgeons but more frequently (16%) preferred the bronchoscope. In an emergency situation (apneic patient with unstable vital signs), both anesthesiologists and surgeons relied extensively on the direct laryngoscope (78% and 81%); anesthesiologists were more likely to use the bronchoscope (15%) than were surgeons but used a surgical airway less frequently than did the surgeons (7% vs. 19%).

Rosenblatt *et al.*104 received 472 responses from 1,000 active members of the American Society of Anesthesiologists who were surveyed as to their preferences for management methods for the difficult airway in cooperative adult patients. With respect to patients with CSI, 78% of respondents expressed a preference for an awake intubation and the use of bronchoscope; the bulk of the remainder induced general anesthesia and used a direct laryngoscope. Rosenblatt *et al.* did not request information regarding the levels of experience attained with the devices preferred but did ascertain that they were available to the practitioners who stated that they would use them. Jenkins *et al.*105 collected 833 responses from 1,702 members of the Canadian Anesthesiologists’ Society surveyed regarding their management choices for the difficult airway in Canada. When faced with a patient with a cervical cord compression and neurologic deficit presenting for discectomy, 67% expressed a preference for awake intubation, and most (63%) stated that they would use a bronchoscope. Thirty-one percent would induce general anesthesia before airway intervention, and slightly more would use a direct laryngoscope than preferred a lighted stylet in this setting. Jenkins *et al.* did not solicit information regarding the level of experience with the methods identified as being preferred by the survey respondents.

Ezri *et al.*106 surveyed 452 American-trained American Society of Anesthesiologists members attending the 1999 Annual Meeting. When faced with a cooperative adult patient with cervical spine disease (rheumatoid arthritis or ankylosing spondylitis) presenting for elective surgery, awake fiberoptic intubation was preferred by most. Although 75% stated that they would use it in some of the scenarios outlined, only 59% or respondents reported skill in the use of the bronchoscope.

The surveys are consistent in revealing that many North American anesthesiologists express a preference for the use of a fiberoptic bronchoscope during airway management in patients with cervical spine disease or injury including in apneic trauma scenarios. This preference persists despite the fact that some who state this preference also acknowledge that they are not confident regarding their skill levels with the bronchoscope. Depending on the setting and the perceived urgency of the situation, direct laryngoscopy is still commonly used, and use of the lightwand is preferred by a significant minority of anesthesiologists, at least in Canada.

*Airway Management of Cervical Spine–injured Patients: The Experience and Outcomes Reported.*

Meschino *et al.*107 reviewed their experience with 454 patients with critical cervical cord or spine injuries or both. One hundred sixty-five patients underwent awake tracheal intubation within 2 months of injury; 289 did not require intubation during the same period. The direct laryngoscope was used in 36 patients (22%), the fiberoptic bronchoscope was used in 76 (46%), and 51 patients (32%) underwent blind nasal intubation. Patients undergoing intubation were more severely impaired than those who did not require intubation. Despite this, there was no difference in the incidence of neurologic deterioration over time between the two groups, and tracheal intubation was not associated with neurologic deterioration in any patient. Holley and Jordan108 conducted a retrospective analysis of traumatic, unstable cervical spine fractures requiring operative management to determine both the airway management techniques used and the incidence of neurologic complications. One hundred thirty-three patients with 140 fractures were reviewed. Ninety-four patients underwent nasal intubation in the operating room, and 29 were intubated with direct laryngoscopy and in-line stabilization. No neurologic complications were recognized in any patient.
Rhee et al. analyzed their experience with 21 patients with cervical cord or spine injury who underwent tracheal intubation in the emergency room. Orotracheal intubation was used in 81% of CSI patients; neuromuscular blockers were used in 82% of these intubations. The authors concluded that no injury was recognized to be caused or exacerbated by airway maneuvers. However, one patient with a C7–T1 dislocation and a C7 cord transection was noted to have absent sensation below the nipples before intubation (T4 level) and motor and sensory examination results consistent with a C7 cord transection after intubation. Whether this disparity reflects an ascension in the level of injury from T4 to C7 or the difference in findings between an emergency room screening neurologic exam and a more precise examination performed later is not certain; the authors’ conclusions seem to prefer the latter explanation. Scanell et al. reviewed their experience with 81 patients with CSI, including 58 with unstable fractures, who received emergency orotracheal intubations performed by experienced anesthesiologists. Neurologic assessment was documented before and after intubation, and in no instance was there a recognized deterioration of neurologic functions after tracheal intubation. Shatney et al. reviewed their experience with 81 patients with CSI, including 58 with unstable fractures, who received emergency orotracheal intubations performed by experienced anesthesiologists. Orotracheal intubation was performed in 48 patients, and no neurologic deteriorations were recognized. In-line immobilization was used during the airway maneuvers, and agitated or combative patients were sedated, paralyzed, or both. Talucci et al. reviewed their experience with 355 patients requiring urgent intubations. Seven patients with unstable CSI underwent orotracheal intubation after induction of anesthesia and paralysis; none experienced neurologic compromise as a result of airway management.

Suderman et al. reviewed the experience of 150 patients with traumatic CSI and well-preserved neurologic function presenting for operative stabilization. General anesthesia before intubation was induced in 83 patients, of whom 65 had their tracheas intubated with the direct laryngoscope; 22 patients were intubated while awake using the direct laryngoscope. The remainder had tracheal intubation performed with a variety of alternatives to the direct laryngoscope, most commonly the bronchoscope; the majority of those latter intubations were performed with the patient awake. Two patients experienced new neurologic deficits; one had a wire passed through the cervical cord accidentally during operative stabilization and was rendered quadriplegic, the second recovered from a new single level radiculopathy attributed to the operative decompression. Both of these patients had their tracheas intubated with a direct laryngoscope while anesthetized. McCrory performed a similar retrospective analysis of the records of 45 patients who presented for operative stabilization of cervical injuries resulting from trauma. Tracheal intubation was performed after induction of general anesthesia with neuromuscular block in 40% of cases; in the remainder, intubation was performed with a bronchoscope while the patient was awake. One awake tracheal intubation was abandoned as a result of patient noncompliance; this patient’s trachea was intubated after induction of general anesthesia. Weighted traction was used in all cases to immobilize the spine. No patient developed either a new neurologic finding or worsening of a preexistent deficit.

Wright et al. reviewed the records of 987 blunt trauma patients; 60 of the patients had a cervical fracture, and 53 of these were deemed to be unstable. Twenty-six patients’ tracheas were intubated orally, 25 were intubated nasally, and two were intubated by cricothyrotomy. One patient who underwent nasotracheal intubation experienced a neurologic deterioration. Lord et al. reviewed the case records of 102 patients who had a CSI and were admitted to their center after trauma. Sixty-two patients required airway management. The most common method used was orotracheal intubation facilitated by direct laryngoscopy (43%), followed by bronchoscope-assisted intubation (27%), nasotracheal intubation (22%), and tracheostomy (2%); in 4%, the method could not be determined. No patient was recognized to have experienced a neurologic deterioration associated with airway management. Other authors have reported similar findings in smaller series of trauma patients with CSI.

These studies are limited by both their small sample size and their retrospective nature. However, they do reveal that neurologic deterioration in CSI patients is uncommon after airway management, even in high-risk patients undergoing urgent tracheal intubation. They are not sufficient to rule out the potential that airway management provided in isolation or as part of a more complex clinical intervention, even provided with the utmost care, may rarely result in neurologic injury. To do so would require a study of enormous proportions. As noted previously, progressive neurologic deterioration occurs in a minority of CSI patients. If this incidence was set at 2% and a study was designed to prove that an airway intervention did not double this baseline incidence, approximately 1,800 patients would need to be studied. No method of airway intervention has been evaluated with such a study, or anything close to it, and therefore, statements comparing the relative safety of different methods have tenuous evidentiary support.

The Use of the Direct Laryngoscope after Cervical Spine Injury: The Debate. As part of the early efforts aimed at reducing secondary injuries in spine-injured patients, a hypothesis was generated that the tracheas of patients with unstable cervical spines could not be safely managed by direct laryngoscopy and oral intubation. Oral intubation was deemed dangerous because it alleg-
edly caused excessive spinal movement, and this movement could lead to secondary injury. Such secondary injury could theoretically be avoided by the careful performance of nasotracheal intubation or cricothyrotomy. These techniques were advocated as the emergency airway maneuvers of choice in patients at risk for spinal injury. There were no data at that time to support this thesis, and the data collected since seem to suggest that secondary neurologic injury associated with any form of airway management is exceedingly rare. The early Advanced Trauma Life Support protocols for airway management were consistent in their support for the nasal intubation/cricothyrotomy strategy, implying a lack of support for the use of direct laryngoscopy in this clinical setting. Not all practitioners agreed that the use of direct laryngoscopy was contraindicated in patients at risk for cervical injury. There was evidence made available soon after publication of these protocols that some experienced trauma centers (including our own) were ignoring the Advanced Trauma Life Support recommendations and performing direct laryngoscopy in at-risk populations.

McLeod and Calder\(^{119}\) examined the association between the use of the direct laryngoscope in patients and subsequent spinal injury or pathology. They suggested that the following five case features would add credence to the diagnosis of a laryngoscopy-induced cord injury: (1) a short period of unconsciousness, (2) myelopathy present on recovery, (3) autonomic disturbances after laryngoscopy, (4) difficult laryngoscopy, and (5) craniocervical disease or gross instability below C3. These criteria were then used to evaluate the likelihood that laryngoscopy was the causative factor for neurologic deterioration in the reports. Although they do make intuitive sense, whether these criteria discriminate well in assigning cause to injury recognized after intubation is not established. Six reports dealing with 10 patients in which it was alleged that direct laryngoscopy contributed to a neurologic injury were reviewed.\(^{57,120–124}\)

With the possible exception of one case, they concluded after review and analysis of the case reports, that the reports did not provide sufficient data to allow them to make the determination that the use of the direct laryngoscope was the cause of the neurologic injuries reported.

The first report analyzed was that of Farmer et al.,\(^{57}\) who reviewed their institutional experience with cord-injured patients. They reported that four patients had neurologic deteriorations associated with tracheal intubation. Two deteriorations were classified as minor and two were classified as major, but no further details were provided regarding the cases or the intubations. The second report was that of Muckart et al.,\(^{120}\) who reported two cases of neurologic deterioration after clinical interventions. The first patient was a 45-yr-old man involved in a motor vehicle accident who sustained bilateral femoral fractures and a closed head injury. Despite the mechanism of injury, a period of unconsciousness, and the presence of neck pain, no imaging was performed, and his spine was not immobilized. He underwent anesthesia for operative repair of the femoral fractures and was quadruplegic on awakening; a C2 fracture-dislocation was subsequently diagnosed, and he recovered completely. The second patient was a 22-yr-old man with multiple gunshot wounds to the neck; he arrived in the hospital neurologically intact. Imaging of the neck revealed no apparent injury to the cervical spine to a level of C5; the radiograph showed only the upper five vertebrae. He underwent emergency surgery during general anesthesia without neck immobilization and was quadruplegic after. A CT scan demonstrated a burst fracture of C6 with a retropulsed fragment impinging on the canal. He was placed in traction, had operative fixation, and recovered completely. Although direct laryngoscopy and tracheal intubation were component parts of the care of both patients, they were not the sole interventions; the lack of immobilization and the potential for malpositioning cannot be excluded as significant risk factors in both cases. The complete recovery in both patients suggests that malpositioning may have been an etiologic factor inducing a transient, compressive neuropraxia-like injury.

The third report analyzed was that of Redl,\(^{121}\) who described the case of an 18-yr-old man with undiagnosed spondyloepiphyseal dysplasia congenita resulting in unrecognized craniocervical instability. He underwent general anesthesia and direct laryngoscopy with tracheal intubation for removal of retained knee hardware. The intraoperative and early postoperative course was uneventful, but he developed a spastic quadripareisis the day after surgery. A CT scan demonstrated a congenitally abnormal craniocervical junction with an os odontoideum (congenitally nonfused odontoid process) in the foramen magnum compressing the spinal cord. Although he made a full recovery, he awoke quadriplegic after a subsequent craniocervical stabilization procedure for which his trachea was intubated using a fiberoptic bronchoscope. The precise role of the laryngoscopy in the development of transient neurologic symptoms in a patient with a congenitally abnormal and unstable spine is uncertain; the development of symptoms on the day after laryngoscopy reduces the strength of a causative association. The fourth report reviewed is that of Yan and Diggan,\(^{122}\) who described the occurrence of a central cord syndrome in a 42-yr-old woman with acquired immune deficiency syndrome who underwent urgent laryngoscopy and intubation for respiratory failure. Before her admission, she was using a walker and wheelchair to ambulate. Following the recognition of upper extremity weakness after intubation and resuscitation, she underwent imaging and evaluation of her central and peripheral nervous system. There was no evidence of
spinal anomaly or instability; there was imaging evidence of marked and generalized cerebral atrophy and a spinal cord contusion and electrodiagnostic evidence of both central and peripheral neuropathy. The etiology of injury was attributed to hyperextension, but there was also evidence of advanced neurologic disease likely related to infection with human immunodeficiency virus. The fifth report was that by Yaszemsks .,125 who reported the case of a 59-yr-old woman with advanced rheumatoid arthritis. She underwent a right wrist fusion during general anesthesia, and her trachea was intubated with a bronchoscope while she was awake. Her trachea was extubated at the end of the procedure, and the early postoperative course was uneventful. She had a cardiac arrest 10 h postoperatively and was intubated with direct laryngoscopy, but could not be resuscitated. At autopsy, she was confirmed to have atlantoaxial instability (recognized preoperatively), and there was microscopic evidence of focal areas of ischemia and infarction in the upper cord and lower medulla oblongata. The authors attributed the damage and the cause of death to the resuscitation intubation, although she was already dead at the time of that intubation. Further, the pathologic finding of infarction suggests that the injury likely took place remotely from the time of death, perhaps during the surgery, and may well have been a positioning injury that was progressive.

The case that MacLeod and Calder cited as being most likely (four of five features present) a laryngoscopy-induced cord injury was that reported by Hastings and Kelley.124 They reported of the case of a 65-yr-old man admitted to hospital after a motor vehicle accident. Despite reporting neck pain and exhibiting left arm weakness, CSI was not ruled out, nor was spinal immobilization enforced. His condition deteriorated some hours subsequently, and after repeated, failed attempts at direct laryngoscopy without spinal immobilization, he underwent cricothyrotomy; 3 h later, he was found to be paraplegic. A review of the original cervical spine radiograph demonstrated a widened disc space at C6–C7 suggesting disruption of the anterior longitudinal ligament. CT scans confirmed that finding as well as noting congenital spinal stenosis from C3 to C7, osteophyte fragments in the spinal canal at C6, a fracture of the C6–C7 facet joint, a C7 laminar fracture, and a C6 spinous fracture. The constellation of symptoms could not be attributed to a single cord lesion, and he was diagnosed as having both an anterior cord syndrome affecting the T11 and subjacent levels and a central cord syndrome at the cervical level. No MRI study was performed to detail the nature of the cord injuries, and it is possible that his neurologic deterioration was inevitable and perhaps the cause of his respiratory insufficiency. However, at no time from admission until the occurrence of his neurologic deterioration was his spine immobilized.

Two additional cases of intubation-associated neurologic injury not reviewed by MacLeod and Calder have been reported.125,126 Liang et al.125 reported a case similar to that of Hastings and Kelley of a man involved in a motor vehicle accident with a suspected CSI who was left quadriplegic after airway management. Despite the evidence of a CSI (nature of injury not reported) and a neurologic deficit (limited movement in both upper extremities), repeated and failed attempts were made at both nasal (five attempts) and then oral intubation with a direct laryngoscopy (five attempts). The last three attempts at oral intubation were made after removal of the cervical collar, but MILI was not used. The trachea was eventually intubated via a surgical airway. There is no discussion of the care afforded after intubation with respect to the spine injury or any description of subsequent imaging studies performed. The next day, it was recognized that he was quadriplegic. Powell and Heath126 reported the case of 59-yr-old man found collapsed and unconscious. Paramedics found him to be apneic, cyanosed, and unresponsive and attempted but failed to intubate his trachea. Tracheal intubation was performed in the emergency room, and then the spine was immobilized. A lateral cervical radiograph revealed an odontoid peg fracture, and the patient’s condition was consistent with a complete cord injury at the C2 level. Although it was inferred that the cord injury may have been caused or aggravated by the airway management, it was acknowledged by the authors that the injury was probably sustained at the time of the accident.

A number of reports detailing a relation between airway management and the occurrence of secondary neurologic injury in CSI patients have been reviewed. These reports consist typically of observations made in a single patient or in a small series of patients admitted to a single institution. Although the deterioration has often been associated temporally with airway management, in most cases, it is impossible to determine with certainty the cause of the deterioration because confounding factors are typically present and acknowledged by the reporting authors. As well, it is possible in some instances that the association between airway management and a worsening neurologic state arises not because of cause and effect but because the airway intervention was made necessary by a progressively deteriorating clinical condition such as an ascending myelopathy. It may well be that the magnitude of the deterioration does not become apparent until after clinical interventions, at which time they, themselves, become suspect culprits. As unsatisfactory as it might be, determining the true nature of the association (causal or otherwise) between airway management and adverse neurologic outcomes in CSI patients is not possible at this time, given the current state of our knowledge.
The Use of the Flexible Fiberoptic Bronchoscope in Cervical Spine Injury. There is considerable enthusiasm, particularly among anesthesiologists, for the use of the fiberoptic bronchoscope in patients at risk for cervical spine disease. The advantages are its potential for use in awake patients, the minimal cervical movement required to achieve tracheal intubation, and the ability to perform postintubation neurologic assessments in cooperative and cognitively intact patients. However, there have been relatively few reports recognized in the literature regarding the use of the bronchoscope in the emergency management of the airway after trauma. The overall success rate for intubation using the bronchoscope in the trauma setting has been cited at 83.3% (95% CI, 72–94.6%). There is a report detailing the successful use of the bronchoscope to facilitate awake intubation in 327 consecutive patients presenting for elective cervical spine surgery; the bulk of the procedures were surgeries for cervical disc prolapse, and there were no patients with traumatic injuries included in the review. Although the procedure was well tolerated by the majority of the patients, 38 (12%) developed low oxygen saturations; in this group, the mean oxygen saturation measured by pulse oximetry was 84 ± 4% (range, 72–89%). The potential for desaturation during bronchoscope-facilitated intubation seems to be as great or greater in CSI patients compromised by traumatic injury as in these elective surgical patients; the incidence and magnitude of hypoxemia in a series of CSI-trauma patients undergoing such management has not been reported.

There are no published data in the English literature that would indicate that the cited advantages of the fiberoptic bronchoscope translate into improved outcomes among CSI patients compared with other intubation techniques. As well, Ezri et al. reported, after a survey of American anesthesiologists, that more than 40% of respondents acknowledged that they were not comfortable using a bronchoscope for airway management. McGuire and El-Beheiry reported two cases of complete airway obstruction during elective awake bronchoscope-assisted intubation in patients with unstable cervical spine fractures; both patients were salvaged with emergency surgical airways. In patients with brain injury, a common concurrent injury to CSI, the use of the bronchoscope is associated with significant increases in ICP that are not prevented by the administration of morphine, midazolam, and nebulized lidocaine.

Comparing Rigid and Flexible Fiberoptic Endoscopes in At-risk Populations. Cohn and Zornow compared the fiberoptic bronchoscope and the Bullard laryngoscope with respect to rapidity of glottic visualization and intubation in patients requiring cervical immobility during tracheal intubation. Seventeen adult patients scheduled to undergo neurosurgical correction of a cervical spine problem were studied. Each patient was considered at risk for neurologic injury during tracheal intubation based on a request for awake fiberoptic tracheal intubation by the neurosurgical team, or radicular symptoms initiated or exacerbated by neck extension. Most showed evidence of spinal canal impingement on a preoperative MRI. Patients were allocated randomly to one of two study groups for tracheal intubation with the Bullard (n = 8) or the fiberoptic bronchoscope (n = 9); before intubation, glottic visualization was performed using the alternative technique. All intubations were performed with the neck in a comfortable position for the patient and with any preexisting immobilization device (e.g., collar, traction) in place. Glottic visualization was uniformly successful on the first attempt in both groups. Tracheal intubation was also uniformly successful, although one intubation in the bronchoscope group took 183 s because of difficulty passing the endotracheal tube through the glottis after an easy laryngoscopy. No new neurologic deficits were observed after tracheal intubation in either group.

Practice Options for Airway Management after Cervical Spine Injury. There is discordant opinion expressed in the literature regarding the optimal means of securing the airway in patients with CSI. Enthusiasm is expressed by some neuroanesthesia experts for the exclusive use of the fiberoptic bronchoscope to facilitate tracheal intubation in spine-injured patients. There are a number of theoretical factors that would support such a choice. The head and neck may be left in a neutral position, and little spinal movement is required to achieve laryngeal visualization and tracheal intubation. The patient’s protective reflexes are largely left intact, and the potential for deleterious movements and positioning is perhaps reduced. A neurologic assessment can be made after intubation to ensure that there has been no change in the patient’s status, although the accuracy of this evaluation may be diminished by sedation. Finally, the patient could be positioned awake to increase the likelihood that potentially injurious position could be avoided. These considerations support the use of the tracheal intubation facilitated by a fiberoptic bronchoscope and performed by an experienced care provider as a practice option in the management of the airway in spine-injured patients. Survey evidence also supports the conclusion that many anesthesiologists are of the opinion that it is the preferred option, especially in elective scenarios. This preference persists even among physicians who acknowledge limited skills with the device. However, there are no data to suggest that better neurologic outcomes are achieved with its use. In fact, the application of a technique by practitioners not expert in its use may carry risk. Failed awake intubation has been identified as a cause of morbidity and mortality in the latest analysis of difficult airway claims by the American Society of Anesthesiologists’ Closed Claims Project.

The use of a direct laryngoscope after induction of
anesthesia is also deemed an acceptable practice option by the American College of Surgeons as outlined in the student manual of the Advanced Trauma Life Support Program for Doctors; by experts in trauma, anesthesiology, and neurosurgery; and by the Eastern Association for the Surgery of Trauma. The principle advantages of the direct laryngoscope are that anesthesiologists are very experienced in its use and that it is a highly effective tool; many anesthesiologists do not consider themselves similarly skilled with other practice options. Direct laryngoscopy can also be performed more quickly than some, but not all, alternative techniques, and it does not require time to obtain and set up specialized equipment. However, it has the potential to cause greater spinal movement than indirect techniques.

In addition, if laryngoscopy is performed after the induction of general anesthesia, the potential for difficult ventilation, a failed intubation, and a cannot-intubate, cannot-ventilate scenario cannot be excluded. Finally, if there is underlying severe, chronic cervical spinal pathology, difficult laryngoscopy should be anticipated because it is more likely to occur. This is particularly true if the upper cervical spine is severely impacted by the disease process.

The use of the direct laryngoscope is a practice option accepted by expert practitioners; its use is commonly encouraged in urgent or emergent situations. Other practice options, such as light wands, rigid fiberoptic laryngoscopes, and laryngeal mask airways, are also deemed appropriate. There is no published evidence that would indicate that one intubation option is superior to others with respect to outcomes in general and, in particular, with respect to neurologic outcomes. Any comparative study that could or would support a single practice option would have to be very large to be persuasive.

Summary of the Literature

There is an incidence of CSI approximating 2% among victims of blunt trauma, and this incidence is trebled if the patient presents unconscious or with a GCS score reduced to 8 or below. A finding of a focal neurologic deficit also significantly increases the likelihood of a cervical injury. The need to evaluate all at-risk patients with a complete and technically adequate imaging series seems to be accepted as the standard of care, although there is debate as to what constitutes the at-risk population and an acceptable imaging series. A three-view spine series (lateral, antero-posterior, and odontoid views) supplemented by computerized tomographic imaging through areas that are difficult to visualize or suspicious is effective in ruling out injury in both cooperative and noncooperative patients. MRI studies may be useful in patients with neurologic symptoms but negative radiography and CT imaging; they seem to add little to the evaluation of patients with persistent pain but a normal neurologic examination and negative imaging. As well, although MRI may identify CSI not captured by CT, these injuries are not usually unstable. Failure to diagnose the injury at time of presentation is associated with a worse neurologic outcome; it occurs most commonly as a result of either failure to appropriately image the spine or misinterpretation of appropriate imaging.

Immobilization of the spine in at-risk patients at the time of first system contact and maintenance of the immobilization until the spine is cleared is accepted by expert consensus as the standard of care. However, there is some debate about the need for immobilization in patients at low risk. Prolonged spinal immobilization is costly in terms of system resources and not without risk to the patient. Strategies that permit efficient and prudent spine clearance are available and their use is encouraged so as to reduce costs, conserve resources, and, most importantly, to prevent harm.

Secondary neurologic injury occurs after CSI and may be associated with clinical care interventions. There is now recognized a syndrome of progressive, ascending myelopathy that occurs in some patients and that is characterized by a widely distributed cord injury. It may occur after a period of relative clinical stability and in the absence of both mechanical instability and canal compromise at the spinal levels to which the injury has ascended. The use of MRI (especially T2-weighted studies) has been instrumental in documenting both the occurrence and the nature of this injury. It may also present at a time when clinical interventions are ongoing to treat the original traumatic injuries. Although there has been a past tendency to attribute many secondary injuries to clinical interventions, especially in a medical-legal context, critical examination of these cases, supplemented with MRI evaluations, may reveal that some, and perhaps most, are an inevitable consequence of the primary injury.

The routine use of some form of immobilization during airway maneuvers in at-risk patients is accepted as the standard of care. All airway maneuvers will result in some degree of neck movement, both in general and specifically at the sites of injury. The amounts of movement are small and may be restrained by in-line immobilization, but they are not eliminated. The available data and the accumulated clinical experience support a conclusion at the current time that these movements are unlikely to result in neurologic injury provided that reasonable care is taken during airway interventions. However, a study of sufficient size to validate this statement has not been performed.

The most appropriate technique for performing tracheal intubation in patients with cervical spine injury continues to be debated. There are no clinical outcome data that suggest better neurologic outcomes with any
References


44. Steil IG, Clement CM, McKnight RD, Brison R, Schull MJ, Rowe BH,
AIRWAY MANAGEMENT AFTER CERVICAL SPINE INJURY


Morris GGT, McCoy E. Clearing the cervical spine in unconscious poly-trauma victims, balancing risk and effective screening. Anaesthesia 2004; 59:464–82


Heath KJ. The effect on laryngoscopy of different cervical spine immobilization techniques. Anaesthesia 1994; 49:843–5


Keller C, Brimacombe J, Keller K. Pressures exerted against the cervical spine.
vertebrae by the standard and intubating laryngeal mask airways. A randomized, controlled, cross-over study in fresh cadavers. Anesth Analg 1999; 89:1296–300
Anesthesia for neuroradiology
Jee Jian See and Pirjo H. Manninen

Purpose of review
The role of anesthesia outside the operating room is rapidly expanding and evolving alongside with the advances in interventional neuroradiology. Increasingly complex diagnostic and therapeutic neuroradiological procedures are being performed on sicker patients. This review provides an overview of the principles of anesthetic management and summarizes recent advances in interventional neuroradiology.

Recent findings
There are many new areas of development in interventional neuroradiology, but each also brings with it controversy. Use of newer agents for anesthesia and for anticoagulation may change the intraoperative management of patients. The role of neurophysiological monitoring during endovascular procedures is still to be validated. There has been increasing interest in and evidence of the efficacy of carotid artery stenting in the treatment of carotid artery disease. The utility of intraoperative magnetic resonance imaging in neurosurgery is expanding rapidly.

Summary
Providing anesthesia in the interventional neuroradiology suite continues to be a challenge to the anesthesiologist. Understanding the anesthetic constraints and complexities and keeping abreast of the current developments in neuroradiology are crucial in ensuring the maximal benefits to and safety of patients.

Keywords
cerebrovascular disorders, interventional neuroradiology, intraoperative magnetic resonance imaging

Introduction
Recent advances in the field of interventional neuroradiology have resulted in more patients with diseases of the central nervous system to be managed in neuroradiological suites. There is increasing evidence to suggest that the outcome of the patient may be improved with endovascular therapy for some cerebrovascular disorders. The aim of this review is to provide an overview of the recent developments in the anesthetic management of patients undergoing procedures in the neuroradiology suite.

General considerations
The optimal conduct of anesthesia in the neuroradiology suite requires forethought and thorough planning for each procedure [1,2]. Detailed patient evaluation and an understanding of the underlying neuropathology are essential components for a successful anesthetic. The establishment of an open channel of communication among the neuroradiologist, anesthesiologist, nurses and radiographer is essential for routine care but crucial for the management of disasters that may occur. Adherence to the basic principles of neuroanesthesia should continue in the management of patients in the neuroradiology suite. This includes the optimization of cerebral blood flow, perfusion pressure, control of intracranial pressure, and careful monitoring of the blood pressures, fluid status and temperature of the patient. The question of cerebral neuroprotection during periods of ischemia should also be considered. A smooth and rapid recovery from the procedure is desirable for early neurological assessment and safe transfer of the patient.

Conduct of anesthesia
The choice of the anesthetic agents and techniques remains largely in the hands of the anesthesiologist; however, the needs of the neuroradiologist and the procedure should be considered. Most institutions develop their own protocols for specific procedures, whether the patient is under general anesthesia or conscious sedation. There is little evidence favoring one technique over the other. The superior image quality obtained from a motionless patient during digital subtraction angiography favors the use of general anesthesia with apnea over conscious sedation techniques. The increasingly complex nature of procedures, the need for precise blood pressure control and preparation for potential catastrophic complications are considerations for general anesthesia. Conversely, when an assessment of neurological function is desired, conscious sedation techniques are required.
During procedures such as stenting of the carotid artery and balloon occlusion tests, patients should only be minimally sedated as they need to be awake periodically so that cerebral function integrity can be determined. Other factors including pediatric age group, uncooperative patients and the severity of underlying disease may play a role in the choice of anesthetic technique.

The ideal anesthetic agents should not impair cerebral autoregulation, carbon dioxide reactivity or cerebral metabolism. Sevoflurane, desflurane and propofol are all widely used. Castagnini et al. [3] compared the speed of recovery in 103 patients after sevoflurane with propofol for the maintenance of anesthesia during neuroradiology procedures. Sevoflurane was associated with a more rapid recovery. The limitations of the study were that the intraoperative depth of anesthesia was not controlled and may not have been the same for the two groups of patients. The time to discharge was also no different between the two groups. The superiority of sevoflurane compared with desflurane in neuroanesthesia is still debatable. Potential increases in cerebral blood flow and the loss of autoregulation associated with the use of higher doses of desflurane have raised questions regarding its use in neuroanesthesia [4]. Holmström and Åkeson [5*], in an experimental porcine model of intracranial hypertension, recently found that desflurane at 0.5 and 1 MAC were associated with more cerebral vasodilation and higher intracranial pressures at normocapnia compared with isoflurane or sevoflurane. However, the difference in intracranial pressure was less evident during hyperventilation. These findings were not consistently evident in human subjects. Sponheim et al. [6] did not find any significant increase in intracranial pressure in 36 children between the use of sevoflurane or desflurane.

Dexmedetomidine is a selective alpha2-adrenoceptor agonist with centrally mediated sympatholytic effects [7]. It significantly reduces the intraoperative and postoperative anesthetic requirements. Patients sedated using dexmedetomidine remain rousable and able to cooperate when stimulated. A lack of respiratory depression offers another distinct advantage over other sedatives [7–9]. The successful use of dexmedetomidine has been reported in awake craniotomy procedures in which neuropsychological tests were required [8,9]. However, Bustillo et al. [10] reported their experience with the use of dexmedetomidine for endovascular embolization of cerebral arteriovenous malformations in five patients, and found that cognitive and neurological testing were impaired when dexmedetomidine was used. The patients were unable to perform complex neuropsychological tests 45 min after the discontinuation of dexmedetomidine infusion. The use of dexmedetomidine in the neuroradiology suite, including the ‘ideal’ dosages, requires further evaluation.

**Anticoagulation**

One of the critical roles of the anesthesiologist in the interventional neuroradiology suite is to provide anticoagulation and to assist in the treatment of complications. A complication of endovascular treatment of cerebrovascular disease is the development of intraoperative thrombosis; therefore the management of anticoagulation is important [11,12]. Heparin is still the most commonly used anticoagulant. The preferred method of monitoring for the effect of heparin is the activated clotting time rather than the activated partial thromboplastin time [13]. The activated partial thromboplastin time may be inaccurate, especially when high doses of heparin are used. The United States Food and Drug Administration has recently approved the use of argatroban, a direct thrombin inhibitor, as an anticoagulant in patients with or at risk of heparin-induced thrombocytopenia undergoing percutaneous coronary interventions [14]. The potential advantages of argatroban over heparin include a more predictable anticoagulant response and a minimal effect on platelets. Its use may expand into the neuroradiology suite in the future.

In some institutions, during the treatment of patients with acutely ruptured aneurysms heparin administration is delayed until the first coil has been deployed even though rupture of the aneurysm during the endovascular procedure is a rare event [12,15]. The pretreatment of patients with antiplatelet agents in the treatment of unruptured aneurysms is another strategy to reduce the risk of intraprocedural thrombosis [12].

In spite of the use of heparin, the risk of thromboembolic events related to Guglielmi detachable coil embolization is still present. Thrombolytic agents are commonly used to treat intraprocedural thrombosis but results have been mixed. Hähnel et al. [16] described the use of local intraarterial fibrinolysis using recombinant tissue plasminogen activator, and achieved a recanalization rate of 44%. Fiorella et al. [12] examined the use of intravenous and intra-arterial abciximab (ReoPro), a GPlIb/IIIa inhibitor, and found that the results were promising. The elevation of blood pressure to increase collateral cerebral blood flow during a thromboembolic event to maintain cerebral perfusion as well as the institution of neuroprotective strategies during this time may be helpful.

**Neurophysiological monitoring**

Neurophysiological monitoring in the neuroradiology suite is desirable but may be difficult to perform routinely. The lack of space in the neuroradiology suite, the need for trained personnel, additional costs and time are constraints to be considered. Monitoring the descending corticospinal pathways by using motor-evoked potentials has been shown to be useful in preventing permanent neurological deficits during cranial and spinal procedures [17,18]. Liu et al. [19]
analysed the utility of intraprocedural neurophysiological monitoring during endovascular therapy of aneurysms in 35 patients, and found that changes were seen in nine patients, resulting in altered management in five patients including the abandonment of coiling in one patient. The authors concluded that neurophysiological monitoring may reduce ischemic complications and can be used to help guide therapeutic decisions [19]. The modification of anesthetic techniques, including the use of total intravenous anesthesia, may be needed when monitoring motor-evoked potentials [17].

**Intracranial aneurysms**

Since the publication of the International Subarachnoid Hemorrhage (ISAT) trial, comparing neurosurgical clipping with endovascular coiling in 2143 patients with ruptured intracranial aneurysms, debate regarding the optimal technique in the treatment of intracranial aneurysms continues [20]. The better results after endovascular treatment reported in that study implied that more patients will undergo coiling of their cerebral aneurysm, increasing the role of the anesthesiologist in the neuroradiology suite for the care of these patients.

Aneurysm rupture during endovascular procedures is not common but remains a potential risk. The incidence ranges from 2.3 to 3%, and may be higher in patients with ruptured aneurysms [15,21]. The rupture may be a slight leak or a massive subarachnoid hemorrhage. With increasing experience, the incidence of intraprocedural rupture should decrease. The occurrence of a rupture should be quickly communicated to the anesthesiologist by the radiologist. Treatment, which will depend on the severity of the bleed, includes maintaining cerebral perfusion pressure, lowering intracranial pressure and the reversal of anticoagulation. Transfer of the patient under general anesthesia may be needed for further scanning or for an immediate ventriculostomy in the operating room. The mortality rate after intraprocedural rupture has been reported to be as high as 20% [15].

Cerebral vasospasm continues to be the most common complication after subarachnoid hemorrhage. The effect of surgical clipping or endovascular coiling of aneurysms on the incidence of vasospasm remains unclear [22]. The theoretical advantages of surgical ligation and the ability to irrigate blood out of the subarachnoid space were balanced by ‘less invasiveness’ during endovascular coiling. Balloon angioplasty is widely considered to be the most effective procedure to treat vasospasm, despite the risk of vessel dissection and rupture [23]. It can also be utilized in combination with the delivery of intra-arterial vasodilators such as papaverine. Complications associated with the use of intra-arterial papaverine have been reported, including hypertension, tachycardia, transient elevation in intracranial pressure, paradoxical worsening of vasospasm, seizures and brainstem depression. Preliminary experiences with intra-arterial nimodipine and nicardipine to treat vasospasm in small groups of patients were recently reported to be favorable [23,24].

**Arteriovenous malformations**

Arteriovenous malformations (AVMs) of the brain are relatively uncommon and their pathophysiology remains poorly understood. Recent reviews by Fleetwood and Steinberg [25] and Soderman et al. [26] summarized the current management of patients with brain AVM. The development of newer tissue adhesives or blocking substances and in the delivery technology may herald a change in the role of interventional neuroradiology in the management of AVMs. There have been few new developments in anesthetic management for the embolization of AVMs. Deliberate hypotension to decrease the velocity of blood flow during embolization may be crucial for a successful procedure. At present, the preoperative embolization of AVMs remains largely an adjunctive therapy to surgery and radiosurgery [27,28].

**Carotid artery stenting**

The US Food and Drug Administration recently approved the use of stents for the treatment of atherosclerotic disease of the carotid bifurcation [29**]. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial results comparing carotid artery stenting using an emboli protection device with surgical endarterectomy in 334 high-risk patients were recently published. The findings showed that stenting was not inferior to surgery. In the secondary analysis, the cumulative incidence of stroke, death or myocardial infarction, as well as the cumulative incidence of cranial nerve palsy and revascularization, and hospital stay were lower in the patients who received a stent [30]. Currently, the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which is a large prospective randomized multicenter trial, is still ongoing [29**]. The results may impact on the future management of patients with carotid artery disease. These developments imply that an increasing number of elderly patients with multiple medical conditions will present for anesthesia in the neuroradiology suite. Mlekusch et al. [31] retrospectively analysed 471 patients who underwent elective carotid artery stenting for high-grade stenosis. The authors found that 7% of patients experienced bradycardia and hypotension during the procedure. The routine administration of anticholinergic agents did not eliminate the risk of bradycardia and hypotension [31]. Patients with elevated systolic blood pressure may also be at an increased risk of hemodynamic instability and neurological events during stent application [32].
Intraoperative magnetic resonance imaging
Magnetic resonance imaging (MRI) for intraoperative neuronavigation has attracted considerable attention. The ability to determine and assess the brain parenchyma immediately before, during and after therapy, the ability to assess brain perfusion and metabolism, as well as the extent of the surgical removal of tumors are reasons for rapid development in this area [33,34]. The use of intraoperative MRI has increased significantly, and thus the anesthesiologist needs to be continually involved and to update anesthetic management of patients in this area.

Schmitz et al. [34] recently reported their experience with high-field (1.5 Tesla) intraoperative MRI in 80 patients. Modifications such as the use of an MRI-compatible ventilator and infusion pumps were necessary. Monitoring devices were equipped with visual alarms as acoustic alarms may not be heard during the loud noise of the scanner. Having properly trained personnel involved in the care of patients in the MRI suite was also important [33,34]. General considerations for anesthesia in the MRI suite will continue to apply but may need further developments as more powerful MRI machines are developed and used [35]. Limitations of patient suitability for anesthesia in the MRI setting still exist. This includes the inability to monitor the ST segment on the electrocardiogram [34]. Therefore patients at risk of coronary heart disease may currently need to be excluded from intraoperative MRI. Birkholz et al. [36] reported that high-field MRI scanning could interfere with electrocardiogram monitoring, resulting in an electrocardiogram pattern that could imitate malignant arrhythmia or provoke ST segment changes. It was observed that an electrocardiogram alteration occurred when the patient’s thorax was entering the inner bore of the scanner. The observed electrocardiogram effects were possibly caused by current induction by the static magnetic field or the Hall effect.

Conclusion
The field of interventional neuroradiology is rapidly and continually evolving. This provides opportunities for the anesthesiologist to be part of this exciting branch of medicine. In order to provide safe and effective care to patients, an understanding of neuropathology as well as keeping up to date in our knowledge of interventional neuroradiology and neuroanesthesia is essential. In spite of the relatively non-invasive nature of the procedures, serious complications can occur. An ability to respond and treat these complications requires pre-planning, anticipation and close cooperation among the different disciplines involved.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
+ of special interest
++ of outstanding interest


This is an excellent review of the recent advances in the field of interventional neuroradiology.


This is a comprehensive review of fast changing trends in intraoperative MRI.


Anesthesia for neuroradiology See and Manninen 441
Spinal cord injury is a devastating event, often resulting in long-term disability. The injury may occur in isolation or in conjunction with other injuries. A thorough understanding of the pathophysiological processes involved aids management. This article aims to provide advice on understanding and managing some of the problems encountered by the anaesthetist.

**Aetiology and incidence**

There are approximately 1000 new cases of spinal cord injury per year in the UK, predominantly young males. Over 50% of spinal cord injuries occur as a result of road traffic accidents, the other major causes are sports injuries, assaults and industrial accidents.

**Classification**

**Level**

Spinal cord injury may occur at any level (Table 1) but certain areas, particularly the lower cervical spine and the thoracolumbar junction, are structurally more vulnerable. The level of the injury determines the extent of the neurological deficit with higher cervical lesions having the most serious consequences.

**Stability**

Anatomically, the vertebral column is described as being composed of anterior, middle and posterior columns. These columns include bony and ligamentous structures which are both important for maintaining stability. An isolated anterior or posterior column injury will be stable but injuries involving more than one column are not.

In the cervical spine, C1–C2 and C5–C7 cervical vertebrae are the most vulnerable to injury. These injuries are often unstable requiring immobilisation to prevent further damage. Although injuries of the cervical vertebral column are more common, the spinal canal is relatively spacious at this level and cord injury is not inevitable. However, the mid-thoracic region is much less mobile and the small circular vertebral canal leaves little space around the spinal cord making cord compression more likely. The same principle of immobilisation should be adhered to for thoracic and lumbosacral spine injuries, although, in general, these injuries are more stable.

Instability allows actual or potential abnormal movement of one vertebral segment upon another, thereby compromising neural structures. Defining the stability of a vertebral column injury is important, as it may influence the anaesthetic and surgical management. All spinal injuries should be treated as potentially unstable until proven otherwise.

**Neurological deficit**

In general, a spinal cord injury can be described as being complete or incomplete. An incomplete spinal cord injury is defined by partial preservation of neurological function more than one level below the level of spinal cord injury. Sacral sparing and preserved sensory or motor function are examples of incomplete lesions. There are several recognised patterns of incomplete lesions (e.g., anterior cord syndrome, Brown-Sequard syndrome, cauda equina syndrome). If a lesion is complete there is absence of motor and sensory function below the level of the lesion. Complete transection occurs in approximately 50% of spinal cord injuries.

**Table 1. Distribution of spinal cord injury (10% of patients sustain injuries at more than one level)**

<table>
<thead>
<tr>
<th>Level</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spine</td>
<td>48</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>41</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>11</td>
</tr>
</tbody>
</table>

**Key points**

- Spinal cord injury should be considered in every trauma patient
- Assessment and initial management of the injured patient is according to ATLS principles
- Prevention of further damage depends on protecting the unstable spine and maintaining spinal cord perfusion
- Sympathetic denervation may lead to neurogenic shock and loss of compensatory mechanisms
- Anaesthetic management is complex and challenging and depends on an understanding of the pathophysiology involved

Philippa Veale BSc MBBS FRCA
Specialist Registrar in Anaesthetics & Academic Research Fellow, Department of Anaesthetics, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH

Joanne Lamb MBBS FRCA
Consultant Anaesthetist, Queen's Medical Centre, Derby Road, Nottingham NG7 2UH
Tel: 0115 9249924 ext 41195
Fax: 0115 9783891
E-mail: jo.lamb@mail.qmcuh-tr.trent.nhs.uk (for correspondence)

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The level of the injury determines the extent of respiratory involvement (Table 2). Abdominal muscle paralysis contributes to the respiratory embarrassment and poor cough. Neurogenic cardiovascular complications are seen in higher lesions (above T7) due to the effects of traumatic sympathectomy. Loss of sympathetic vasoconstrictor tone to blood vessels results in vasodilatation. Cardiac sympathetic supply (T1–T4) may also be affected; loss of chronotropic and inotropic effects and unopposed vagal reflexes may result in severe sinus bradycardia. Profound bradycardia and even sinus arrest may occur during intubation or suction of the airway.

### Pathophysiology

#### Spinal shock

Spinal shock describes the initial phase after an insult to the spinal cord and may be defined as a temporary interruption of the physiological function of the spinal cord following injury. It may, in part, be a vascular phenomenon. All reflex activity is lost and the cord below the level of the lesion also becomes isolated from the higher centres. This accounts for the characteristic picture of flaccid paralysis. An accurate prognosis is not possible until the stage of spinal shock has ended (up to 4 weeks). If there is evidence of neurological sparing, i.e. residual sensory, motor or reflex function below the level of the lesion, full recovery may follow.

Autonomic and reflex activity gradually returns to the injured cord. Loss of descending inhibitory control leads eventually to spasticity and autonomic hyperreflexia. Respiratory function improves as spasticity of chest and abdominal wall muscles reduces paradoxical movement.

It is important not to confuse spinal shock with spinal neurogenic shock. The latter term describes the hypotension seen as a result of traumatic sympathectomy.

#### Secondary injury

Trauma to the spinal cord results in an immediate physical injury (i.e. primary injury). A combination of small intramedullary vessel damage, haemorrhage into grey matter and local vasoconstriction causes a critical fall in cord perfusion. The cord becomes ischaemic leading to the onset within minutes of secondary injury which may become progressively worse over the ensuing hours. The release of mediators of postschaemic injury is implicated in secondary damage as are hypotension, hypoxaemia and hyperthermia. After a period of ischaemia, apoptosis or programmed cell death occurs. This peaks at 8 h and results in irrecoverable damage.

Many interventions have been tried to reduce the severity of secondary injury, mainly in experimental animal work. Steroids, free radical scavengers, barbiturates, hypothermia, hyperbaric oxygen therapy and NMDA and opioid antagonists are some examples. The results of these interventions are disappointing. Many spinal centres have a spinal injury protocol that includes the early administration of high dose methylprednisolone. The evidence for this intervention comes from the National Acute Spinal Cord Injury Study (NASCIS) trials which demonstrated an improvement in long-term neurological outcome following high dose methylprednisolone. Unfortunately, there is no good evidence that this equates to an improvement in functional outcome and the risk of infection is increased.

Measures aimed at ensuring adequate oxygenation and perfusion of the injured cord and avoidance of hyperglycaemia and hyperthermia are the mainstay of prevention of secondary injury.

### Initial assessment and management

#### Presentation

The patient with an acute spinal cord injury typically presents to the accident and emergency department having already been immobilised on a spinal board. Use of pre-hospital spinal immobilisation in trauma patients is now routine but the positioning and immobilisation of the patient should be scrutinised as part of the primary survey. The correct technique is placement of a hard cervical collar of the appropriate size, sandbags either side of the head and adhesive tape across the forehead onto each side of the trolley.

Thoracic and lumbar spine injuries simply require the patient to be kept supine on a solid surface, avoiding any excessive movement. If the patient is to be moved, this should be by ‘log-rolling’, maintaining vertebral column alignment.

### Table 2 Respiratory effects of spinal cord injury

<table>
<thead>
<tr>
<th>Level of injury</th>
<th>Effect</th>
<th>Clinical signs</th>
</tr>
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<tbody>
<tr>
<td>T1–T7</td>
<td>Variable degree of intercostal nerve paralysis</td>
<td>Impaired chest wall movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor cough</td>
</tr>
<tr>
<td>C5–C8</td>
<td>Complete intercostal nerve paralysis Function of diaphragm intact</td>
<td>Ineffective or absent cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paradoxical respiratory pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of accessory muscles</td>
</tr>
<tr>
<td>C3–C5</td>
<td>Partial diaphragm paralysis</td>
<td>As above but usually requiring assisted ventilation</td>
</tr>
<tr>
<td>C3 or above</td>
<td>Denervation of diaphragm</td>
<td>Respiratory failure</td>
</tr>
</tbody>
</table>
Spinal cord injury should be considered in all trauma victims. An appropriately qualified person can rule out cervical spine injury in the fully conscious patient. Full precautions must be strictly adhered to in any patient with midline tenderness, neurological symptoms or signs, a reduced level of consciousness, or a painful 'distracting' injury.

Initial management

The initial management of the trauma victim with a spinal cord injury is as for any seriously injured patient. The ATLS approach is proven, standardised and effective and initial management should be based upon its principles.

Airway

The airway must be examined for patency and, if required, manipulated with a jaw thrust as opposed to a chin lift. This airway-positioning manoeuvre is associated with less displacement of the cervical spine. A trauma mask with high flow oxygen should be applied to the patient if the airway is patent. If not, a decision to intubate the trachea should be made earlier rather than later, in order to maximise oxygen delivery and limit secondary hypoxic damage to the injured spinal cord. A difficult intubation should be anticipated because of: (i) suboptimal positioning due to immobilisation of the cervical spine; (ii) the requirement for a rapid sequence induction with cricoid pressure; (iii) the potential for pre-vertebral swelling due to haematoma; and (iv) the potential for poor visibility at laryngoscopy due to debris or distorted anatomy in maxillofacial trauma.

There is a great deal of debate in the literature regarding the safest approach to intubation in the patient with a cervical spine injury and the likelihood of causing further damage to the spinal cord. One concern is that unstable bony fragments may be maintained in position only by muscular spasm and that muscle relaxation may contribute to the instability. The options for intubation are: (i) direct laryngoscopy and intubation in the presence of manual in-line immobilisation; (ii) blind nasal intubation if there is no compromise to the cribriform plate; (iii) blind oral intubation using the intubating laryngeal mask airway (ILMA); (iv) awake fibre-optic intubation; and (iv) surgical airway if intubation is not possible.

Awake fibre-optic intubation with adequate local anaesthesia and intubation under direct vision has the advantage of avoiding movement of the unstable cervical spine. It may be performed with the patient immobilised and in halo traction and allows neurological assessment following intubation. However, this method requires skill and specialist equipment and is often impractical in the acute situation, particularly if intubation is required urgently. The choice depends on the situation and experience of the individual.

Direct laryngoscopy with in-line immobilisation is a safe and acceptable method. It requires at least three trained personnel and involves four stages: preparation, manual in-line immobilisation, rapid sequence induction and intubation. Succinylcholine is the muscle relaxant of choice. The release of potassium associated with the use of succinylcholine in spinal cord injury has not been shown to be a problem until 3 days post-injury at the earliest. Atropine must be available immediately as should equipment for obtaining a surgical airway. The hard collar is opened at the front to expose fully the mandible and allow maximum possible mouth opening. In order to avoid displacement of the injured cervical spine by cricoid pressure, the back of the rigid collar is left in place. Otherwise, a bimanual technique should be employed. A small amount of movement of the neck may be inevitable, even with manual in-line immobilisation. This is unlikely to be significant enough to cause injury to the cord and must be allowed for in order to secure the airway.

Breathing

Adequate oxygenation is imperative in order to prevent secondary hypoxic damage. Supplemental oxygen must be administered to all patients. Ventilation must be assessed both clinically and with oxygen saturation measurements and arterial blood gas analysis. Inadequate ventilation causing hypoxaemia or hypercapnia should be rectified by tracheal intubation and ventilation. Hypoxaemia is found in about 50% of patients with high spinal cord injury, usually due to the neuromuscular deficit resulting from the injury. Associated injuries may also be the cause of inadequate ventilation or oxygenation. Chest injuries are common in polytrauma patients, pulmonary aspiration and pulmonary oedema are common in head injury and some patients may have been victims of near-drowning.

Circulation

Maintenance of an adequate circulation is essential in spinal cord injury in order to minimize secondary ischaemic damage to the injured cord. Hypotension must be treated promptly with fluid boluses in the first instance. In the polytrauma patient who is hypotensive, hypovolaemia secondary to haemorrhage from concurrent injuries must be excluded according to ATLS principles. Remember that the patient with a high spinal cord injury will not complain of pain from a fractured pelvis or other injuries. Intra-abdominal bleeding is more difficult to diagnose when the abdominal muscles are flaccid. This must be ruled out by diagnostic peritoneal lavage, abdominal ultrasound or computed tomography (CT).

Damage to the spinal cord above T6 may result in spinal neurogenic shock. Loss of sympathetic function leading to neurogenic shock should be actively managed in order to preserve the perfusion...
of the injured cord. Bradycardia affecting cardiac output should be treated with intravenous atropine or glycopyrrolate.

Fluid resuscitation is complex in these patients. Judicious volume loading with crystalloid or colloid solutions guided by central venous pressure measurement is the first step. Loss of cardiac sympathetic innervation affects myocardial contractility. In the acute phase, these patients have a limited capacity to respond to volume stress and are prone to develop pulmonary oedema if volume overloaded. If hypotension persists despite fluid loading, low doses of vasopressors are indicated to counteract the loss of vasoconstriction. If vasoconstrictors are used, care must be taken to avoid a fall in cardiac output resulting from a high systemic vascular resistance. Pulmonary artery flotation catheter or trans-oesophageal Doppler may be used to guide cardiovascular support in more complex cases.

Assessment of disability

Full neurological examination is important and, whenever possible, must be carried out before anaesthesia for intubation. It must be recorded and repeated at regular intervals. Any changes should be clearly documented and include: (i) sensory level; (ii) motor level; and (iii) anal tone and reflex activity

The neurological level of injury is designated as the most distal uninvolved segment of the spinal cord. This differs from the bone level of injury, which is the level of the spine at which bony damage is actually visualised. There is usually a correlation between the two levels but there can be some discrepancy, especially in cervical spine injuries. Ascending spinal cord oedema may result in deteriorating signs. Improvement in the deficit may be predictive of some neurological recovery.

Radiology

A detailed discussion of imaging in spinal injury is beyond the scope of this article. According to ATLS guidelines, all patients with multiple injuries or significant head injury require a lateral cervical spine X-ray. If there is a suspicion of an injury in the thoracic or lumbar spine, the relevant area should also be X-rayed. Of patients with cervical spinal injury, 10% will have spinal injury at a higher level; and this must be excluded.

The lateral cervical spine X-ray must be adequate, i.e. extending as far as the cervicothoracic junction. All anaesthetists should have a system for examining cervical spine films but an expert opinion is often required. Plain radiography of the cervical spine may also include an anteroposterior and an open mouth (odontoid peg) view. Upper thoracic spine injuries are difficult to visualize on plain radiography.

Magnetic resonance imaging (MRI) is particularly useful for imaging the spinal cord and soft tissues and for identifying cord compression and oedema. Specialist spinal units will usually perform an early CT and often also MRI of the entire spine in any patient with a spinal injury. However, it is important to avoid sending unstable patients to distant radiology departments and into inaccessible scanners.

Anaesthetic management

Indications for surgery

Surgical intervention may be indicated in the early or intermediate phase of spinal cord injury. If the clinical picture at 48 h is of a complete injury, no type of surgery has been shown to improve neurological function. Despite this, operative spinal fusion may be appropriate in order to confer stability thereby aiding rehabilitation and preventing further complications. Stabilisation procedures may be best delayed until the patient has recovered from other injuries or is more cardiovascularly stable.

Early surgery may be indicated if the neurological deficit is incomplete or due to spinal shock and there is felt to be some potential for recovery. The surgery is carried out in order to permit: (i) urgent decompression of the spinal cord, followed by stabilisation; (ii) restoration of vertebral column alignment if this has not been achieved by conservative means (halo traction); (iii) exploration for decompression and stabilisation if the neurological deficit is worsening; and (iv) exploration of open penetrating spinal wounds.

The anaesthetic management of patients with high spinal cord injury may be challenging and the potential hazards should not be underestimated. Spinal surgery should be carried out in specialist centres but an anaesthetist in any hospital receiving trauma patients may be called upon to manage a spinal injuries patient who requires urgent surgery for other injuries.

Pre-operative assessment and planning

Early assessment at presentation to hospital has been outlined above. Before surgery, it is important to re-assess the patient carefully and plan accordingly.

Airway

If the patient has not been intubated, the airway must be assessed and a plan made for airway management. The patient may be in halo traction and surgeons should be involved if this is to be removed.

Breathing

In cervical and higher thoracic lesions, respiratory function may have become compromised. Absent or impaired cough leads to the retention of secretions. Increased work of breathing means patients relying on diaphragmatic breathing may start to tire. Lung volumes reach their lowest point at 3–4 days post-injury and spirometry is
useful to monitor pulmonary function. If the vital capacity has fallen to less than 1 litre, the patient is hypoxaemic or has a high respiratory rate, arrangements must be made for assisted ventilation postoperatively.

Circulation

In the patient with a cervical or high thoracic lesion and sympathetic denervation, the systolic blood pressure will often have stabilised at 90–100 mmHg. This should be adequate in the supine position but loss of compensatory mechanisms may jeopardize cord perfusion during positioning for surgery or periods of intra-operative blood loss. Consequently, it is necessary to make plans for central venous catheterisation and the availability of infusion pumps and vasoactive drugs which may be needed to support the circulation. ECG abnormalities, including signs of subendocardial ischaemia and arrhythmias, are sometimes seen in high cord injuries.

Major blood loss should be anticipated and blood cross-matched in advance.

General considerations

A more general anaesthetic assessment must not be overlooked and all management plans discussed with the patient. A spinal cord injury is a devastating event and these patients may be in a state of considerable psychological distress. Good communication and a humane and sensitive approach are essential.

Intra-operative management

Monitoring

In addition to standard monitoring, intra-arterial blood pressure measurement and central venous pressure monitoring are required. As discussed above, a pulmonary artery flotation catheter or transoesophageal Doppler may be helpful for optimal cardiovascular management. Urine output should be measured hourly. Thermoregulation is impaired in spinal cord injury. Core temperature must be monitored and patient and fluid warming devices used.

Spinal cord monitoring may be used in specialist centres, particularly for the patient with an unstable vertebral column injury and no or partial neurological deficit. It is vital to preserve cord function in these patients and cord monitoring during, or immediately after, positioning and during surgery facilitates this. The commonest method is the use of sensory evoked potentials.

Induction and maintenance

The main goal is to maintain adequate cord perfusion and oxygenation during surgery and anaesthesia to prevent any further damage. Autoregulation of blood flow is lost in the injured cord and mean arterial blood pressure should be at least 60 mmHg. A controlled ventilation technique is appropriate due to the prolonged nature of the surgery and the position required for surgical access. Mild hypocapnia is of theoretical benefit in decompressing the spinal cord.

At induction, the anaesthetic agents may be of individual preference but should be titrated slowly. The usual precautions are taken if the patient has a potential full stomach but succinylcholine should be avoided if the patient is > 3 days post-injury.

Airway management has been discussed earlier and is not a particular issue if the lesion is below C7 or there is no chance of neurological recovery. Atropine or glycopyrrolate should be available to treat any bradycardia.

Large bore intravenous access is essential. A nasogastric tube should be placed as high acute cord injury leads to gastric stasis and gastrointestinal ileus. Spinal injury patients are at particular risk of venous thrombo-embolism. Compression stockings should be worn and calf compression devices used intra-operatively.

Most spinal decompression and stabilisation procedures involve posterior surgery with the patient in the prone position. Halo traction may be maintained during surgery. For unstable fractures, great care must be taken to maintain vertebral column alignment during positioning. For some injuries, access to the anterior spinal column may be indicated. If this is the case in a thoracic spine injury, a thoracotomy will be needed and, if possible, provision should be made for one lung ventilation. These procedures may take many hours and the usual precautions must be taken to avoid peripheral nerve injuries and pressure sores. Major blood loss is not uncommon and intra-operative blood cell salvage should be used if it is available.

A balanced anaesthetic technique is appropriate but analgesic requirements postoperatively depend on the nature of surgery and the extent of the neurological injury. The use of epidural analgesia may lead to difficulty with neurological assessment postoperatively and great care should be taken with the use of systemic opioids in patients with respiratory compromise.

Key references


See multiple choice questions 94–96.
The spectrum of spinal surgery in adult life is considerable. Anaesthesia for major spinal surgery, such as spinal stabilization following trauma or neoplastic disease, or for correction of scoliosis, presents a number of challenges. The type of patients who would have been declined surgery 20 yr ago for medical reasons, are now being offered extensive procedures. They commonly have preoperative co-morbid conditions such as serious cardiovascular and respiratory impairment. Airway management may be difficult. Surgery imposes further stresses of significant blood loss, prolonged anaesthesia, and problematical postoperative pain management. The perioperative management of these patients is discussed. The advent of techniques to monitor spinal cord function has reduced postoperative neurological morbidity in these patients. The anaesthetist has an important role in facilitating these methods of monitoring.

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Keywords: anaesthesia, general; monitoring; surgery, spinal

Pathological conditions requiring spinal surgery in adult practice

Scoliosis

Scoliosis involves a lateral and rotational deformity of the spine, which occurs in up to 4% of the population.98 Most cases are idiopathic (70%) and occur with a male:female ratio of 1:4 (Table 1). Surgery is usually considered when the Cobb angle exceeds 50° in the thoracic, or 40° in the lumbar spine (Fig. 1A and B). Surgery aims to halt progression of the condition and to at least partially correct the deformity, preventing further respiratory and cardiovascular deterioration. Left untreated, idiopathic scoliosis rapidly progresses and is often fatal by the fourth or fifth decade of life, as a result of pulmonary hypertension, right ventricular failure, or respiratory failure.95

Muscle disorders

Muscular dystrophy and cerebral palsy are important causes of scoliosis. Of the muscular dystrophies, Duchenne
Anaesthesia for spinal surgery in adults

Carcinomatosis

Patients with primary or secondary malignant disease of the vertebral column and spinal cord are increasingly being considered for surgery, the aims of which are primarily to relieve pain but also to excise the lesion, prevent further neurological deterioration, and stabilize the vertebral column. These patients have commonly lost a large amount of weight and have reduced physiological reserve.

Respiratory complications of malignancy are common in such patients, and include infection, pleural effusion, and pulmonary toxicity from alkylating agents (cyclophosphamide, chlorambucil, busulfan) or antimetabolites (methotrexate, azathioprine). Myocardial injury may also occur secondary to the use of chemotherapy (busulfan, cyclophosphamide, mitomycin). Metabolic derangements such as hypercalcaemia, and inappropriate secretion of antidiuretic hormone may develop. The latter is associated with small cell lung tumours, carcinoma of the prostate, pancreas and bladder, and central nervous system neoplasms.

It is usual for these patients to have acute-on-chronic pain problems. They are often receiving regular opioids, non-steroidal anti-inflammatory drugs, and simple analgesics. Patients may therefore have an increased requirement for intraoperative and postoperative analgesia as a result of pharmacodynamic-related opioid tolerance, and pharmacokinetic factors such as liver enzyme induction.

Spinal trauma

Patients with traumatic injury frequently present for surgical spinal stabilization during the period of spinal shock, which begins almost immediately after the insult and may last for up to 3 weeks. Some degree of spinal cord dysfunction may also be present in patients with malignant disease presenting for spinal stabilization. The clinical effects depend on the level of injury to the spinal cord. A physiological sympathectomy occurs below the level of the spinal cord lesion, possibly causing hypotension secondary to arteriolar and venular vasodilatation. Injuries at or above T6 are particularly associated with hypotension, as the sympathetic outflow to splanchnic vascular beds is lost. Bradycardia also occurs if the lesion is higher than the cardiac sympathetic outflow (T2–T6), the parasympathetic cranial outflow being preserved. A complete cervical cord injury produces a total sympathectomy and therefore hypotension will be more marked.

Table 1 Aetiology of structural scoliosis (relative frequencies). Derived from Kafer, published with permission of Anesthesiology

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Relative frequency</th>
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<tr>
<td>Idiopathic (70%)</td>
<td>Abnormal spinal cord/vertebral development</td>
</tr>
<tr>
<td>Congenital</td>
<td>Neuropathic: cerebral palsy, syringomyelia, poliomyelitis</td>
</tr>
<tr>
<td>Neuromuscular (15%)</td>
<td>Myopathic: muscular dystrophies, neurofibromatosis, Friedrich’s ataxia</td>
</tr>
<tr>
<td>Mesenchymal disorders</td>
<td>Rheumatoid arthritis, Marfan’s syndrome, osteogenesis imperfecta</td>
</tr>
<tr>
<td>Metabolic bone disease</td>
<td>Osteoporosis, Paget’s disease</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Primary and secondary tumours</td>
</tr>
<tr>
<td>Trauma/surgery</td>
<td>Fracture, radiotherapy, surgery</td>
</tr>
<tr>
<td>Infection</td>
<td>Tuberculosis, osteomyelitis</td>
</tr>
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</table>

Muscular dystrophy (DMD) is the most common, with an incidence of one in 3300 male births. It is inherited as a sex-linked recessive condition affecting skeletal, cardiac, and smooth muscle. Patients lack a membrane cytoskeletal protein, ‘dystrophin’, and typically present between the ages of 2 and 6 yr with progressive weakness of proximal muscle groups. Up to one-third of patients have intellectual impairment. DMD patients have a high incidence of cardiac abnormalities (50–70%). In the later stages of the disease, a dilated cardiomyopathy may occur associated with mitral valve incompetence. Dysrhythmias occur and up to 50% of patients have cardiac conduction defects. Cardiac arrest in DMD patients has been reported during spinal surgery, from which some patients have been resuscitated, and others have died.

Surgery improves the patient’s quality of life, slows the decline in respiratory function, and increases life expectancy.

Muscular dystrophic patients are sensitive to non-depolarizing neuromuscular blocking agents, and hyperkalaemia may occur with the use of succinylcholine.

Infection Tuberculosis, osteomyelitis

Infection

Trauma/surgery Fracture, radiotherapy, surgery

Malignancy Primary and secondary tumours

Metabolic bone disease Osteoporosis, Paget’s disease

Mesenchymal disorders Rheumatoid arthritis, Marfan’s syndrome, osteogenesis imperfecta

Neuromuscular (15%) Neuropathic: cerebral palsy, syringomyelia, poliomyelitis

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Neuromuscular (15%) Abnormal spinal cord/vertebral development

Carcinomatosis

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Above the level of the lesion, sympathetic outflow is preserved. Vasocostriction in upper body vascular beds and tachycardia may be observed in response to the hypotension resulting from reduced systemic vascular resistance (SVR) in the lower part of the body. Hypotension associated with spinal cord injury responds poorly to i.v. fluid loading, which may cause pulmonary oedema. Vasopressors are the treatment of choice. Other causes of hypotension should be excluded such as blood loss associated with other injuries. Hypoxia or manipulation of the larynx or trachea may cause profound bradycardia in these patients. Positive pressure ventilation (IPPV) causes marked arterial hypotension as the SVR cannot be raised to offset the changes in intrathoracic pressure caused by IPPV.

Mid to low cervical spine injuries (C4–C8) spare the diaphragm but the intercostal and abdominal muscles may be paralysed (Fig. 1C–E). This leads to an inadequate cough, paradoxical rib movement on spontaneous ventilation, a decrease in vital capacity by up to 50% of predicted values (as a result of a reduction in inspiratory capacity to 70% and expiratory reserve volume to 20% of predicted), a decrease in functional residual capacity to 85% of predicted, and a loss of active expiration. There is also an increased risk of venous thromboembolism in patients with spinal trauma, together with delayed gastric emptying, and impairment of thermoregulation. Administration of succinylcholine may cause hyperkalaemia from 48 h after the injury.

Autonomic dysreflexia may be present from 3 to 6 weeks after the spinal cord injury. This condition is
characterized by extreme autonomic responses such as hypertension and tachycardia after stimulation of nerves below the level of the spinal cord lesion (for example, rectal, urological, peritoneal stimulation). Injuries higher than T7 have an 85% chance of producing serious cardiovascular derangement.5

**Preoperative assessment**

When assessing patients before spinal surgery, particular care should be given to the respiratory, cardiovascular, and neurological systems; all may be affected by the pathology for which the spinal surgery is proposed.

**Airway assessment**

The potential for difficulty in airway management should always be considered, particularly in those patients presenting for surgery of the upper thoracic or cervical spine. A careful assessment should be made for previous difficulty in intubation, restriction of neck movement, and the stability or otherwise of the cervical spine. Stability is defined as the ability of the spine, under physiological loads, to resist displacement, which causes neurological injury. It is essential to discuss preoperatively the stability of the spine with the surgeon. The cervical spine may be assessed clinically (presence of pain or neurological deficits), and

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**Fig 1** (a) Thoracolumbar scoliosis and measurement of the Cobb angle. A perpendicular line is drawn from the end plate of the most caudal vertebral body involved, whose inferior end plate tilts maximally to the concavity of the curve. A second perpendicular line is drawn from the end plate of the most cephalad vertebral body, whose superior end plate tilts maximally to the concavity of the curve. The curve value is the number of degrees formed by the angle of intersection of these two lines. (b) Thoracolumbar scoliosis after surgery, showing long rods and pedicle screws. (c) Dislocation of the 5th and 6th cervical vertebrae after trauma; (d) same patient’s MRI scan, and (e) after surgery to stabilize the cervical spine. SC, spinal cord; C6, sixth cervical vertebrae.
radiographically (lateral or flexion/extension plain films, computer aided tomography, and magnetic resonance imaging). The stability of the cervical spine is dependent on ligamental and vertebral elements. Damage to these elements may not be detectable by plain x-rays alone. The adult cervical spine below C2 is unstable or on the brink of instability when one of the following conditions are met: (i) all the anterior or all the posterior elements are destroyed; (ii) there is >3.5 mm horizontal displacement of one vertebra in relation to an adjacent one on a lateral x-ray; or (iii) there is more than 11° of rotation of one vertebra to an adjacent one. Above the level of C2, examples of unstable injuries include: disruption of the transverse ligament of the atlas (a distance of greater than 3 mm in adults between the posterior corpus of the anterior arch of C1 and the anterior border of the odontoid process, when measured on a lateral plain x-ray film, is diagnostic); and a Jefferson burst fracture of the atlas following axial loading, which causes atlantoaxial instability. Disruption of the tectorial and alar ligaments and some occipital condylar fractures also cause atlanto-occipital instability.

Some inherited disorders such as DMD may lead to glossal hypertrophy, and previous radiotherapy to tumours of the head and neck can cause difficulty in direct laryngoscopy. A decision must be made, whether to intubate the patient awake or asleep.

**Respiratory system**

Patients presenting for spinal surgery frequently have impaired respiratory function. Those who have sustained cervical or high thoracic trauma or who have multiple injuries may be artificially ventilated preoperatively. Others have recurrent chest infections.

Preoperatively, respiratory function should be assessed by a thorough history, focusing on functional impairment, physical examination, and appropriate investigations (Table 2). Scoliosis causes a restrictive pulmonary deficit, with reduced vital capacity and reduced total lung capacity (TLC). The residual volume is unchanged. The severity of functional impairment is related to the angle of the scoliosis, the number of vertebrae involved, a cephalad location of the curve, and a loss of the normal thoracic kyphosis. The extent of functional impairment cannot, therefore, be directly inferred from the angle of scoliosis alone. The most common blood-gas abnormality is a reduced arterial oxygen tension with a normal arterial carbon dioxide tension, as a result of the mismatch between ventilation and perfusion in hypoventilated lung units. Respiratory function should be optimized by treating any reversible cause of pulmonary dysfunction, including infection, with physiotherapy and nebulized bronchodilators as indicated.

There is controversy over whether surgery for idiopathic scoliosis improves, or worsens pulmonary function. However, the type of surgery proposed may have a significant influence upon postoperative pulmonary function, and may explain the contradictory findings in studies of non-homogenous groups of patients. Surgery involving the thorax (anterior approach, combined approach, or rib resection) was associated with an initial decline in forced vital capacity (FVC, 19% of baseline values), forced expiratory volume in 1 s (FEV₁, 13%), and TLC (11%) at 3 months. This was followed by subsequent improvement to preoperative baseline values at 2 yr postoperatively. Surgery involving an exclusively posterior approach, however, was associated with an improvement in pulmonary function tests by 3 months (although not reaching statistical significance); and an improvement that was statistically significant at 2-yr follow-up: FVC (14% increase from baseline), FEV₁ (14%), TLC (5%).

Older studies have reported that if preoperative vital capacity is less than 30–35% of predicted, postoperative ventilation is likely to be required. A history of dependence on continuous nasal positive airways pressure at night is also a sign of severe functional impairment and of reduced physiological reserve. These findings should prompt serious consideration as to whether surgery repre-

| Table 2 Suggested preoperative investigations before major spinal surgery |
|-------------------------------|--------------------------|
| **Minimum investigations** | **Optional investigations** |
| Airway | Cervical spine lateral x-rays with flexion/extension views (for patients with rheumatoid arthritis) | CT scan |
| Respiratory system | Plain chest radiograph | Pulmonary function tests (bronchodilator reversibility) |
| | Arterial blood gas analysis | Pulmonary diffusion capacity |
| | Spirometry (FEV₁, FVC) | Dobutamine-stress echocardiograph |
| Cardiovascular system | Electrocardiograph | Dipyridamole/thallium scintigraphy |
| Blood tests | Echocardiography | Liver function tests |
| | Full blood count | |
| | Clotting profile | |
| | Blood cross match | |
| | Urea, electrolytes | |
| | Albumin, calcium (neoplastic disease) | |
represents an appropriate balance between its potential benefits and the high risk of long-term postoperative ventilation in such patients.

**Cardiovascular system**
Cardiac compromise may be a direct result of the underlying pathology, for example in patients with muscular dystrophies. Cardiac dysfunction may also occur secondary to scoliosis, which causes distortion of the mediastinum, and cor pulmonale secondary to chronic hypoxaemia and pulmonary hypertension. Assessment of functional cardiovascular impairment is difficult in patients who are wheelchair-bound. Minimum investigations should include an electrocardiograph, and echocardiography to assess left ventricular function and pulmonary arterial pressures (Table 2). Dobutamine stress echocardiography may be used to assess cardiac function in patients with a limited exercise tolerance.

**Thromboembolic prophylaxis**
Patients undergoing spinal surgery may be at increased risk of thromboembolic disease as a result of prolonged surgery, prone positioning, malignancy, and extended periods of postoperative recumbency. The use of compression stockings and/or pneumatic boots is recommended. Many surgeons prefer not to administer anticoagulants because their use may be associated with haemorrhagic complications, including increased blood loss and epidural haematoma.

**Neurological system**
A full neurological assessment of the patient should be made preoperatively. This should be documented for three reasons. First, in patients undergoing cervical spine surgery, the anaesthetist has a responsibility to avoid further neurological deterioration during manoeuvres such as tracheal intubation and patient positioning. Secondly, muscular dystrophies may involve the bulbar muscles, increasing the risk of postoperative aspiration. Thirdly, the level of injury and the time elapsed since the insult are predictors of the physiological derangements of the cardiovascular and respiratory systems which occur perioperatively. If surgery is contemplated within 3 weeks of the injury, spinal shock may still be present. After this time, autonomic dysreflexia may occur.

**Anaesthesia technique**
The type of monitoring chosen to assess spinal cord integrity has a bearing on the anaesthetic technique used.

**Premedication**
The use of bronchodilating agents may be of value in optimizing respiratory function preoperatively. In patients with a high spinal cord lesion, or those in whom fibre-optic intubation is to be undertaken, administration of anticholinergic agents such as atropine or glycopyrrolate (200–400 µg by i.v. or i.m. injection) should be considered. Many patients will have factors which increase the risk of regurgitation and aspiration of gastric contents, such as recent opioid administration, high spinal cord injury, or recent traumatic injury. In these circumstances, it may be prudent to premedicate patients with a histamine-2 receptor antagonist such as ranitidine, or a proton pump inhibitor such as omeprazole, and with sodium citrate. Some patients may have nasogastric tubes *in situ*, which decrease the competence of the upper oesophageal sphincter.

**Induction**
Choice of induction technique, i.v. or inhalation, is guided primarily by the patient’s condition and by consideration of the ease with which the trachea may be intubated. Preoxygenation is advisable in all patients. Unless there are concerns over the stability of the cervical spine or airway maintenance (see below), i.v. induction is suitable for all but the sickest patients.

The use of succinylcholine in patients with muscular dystrophies has long been known to cause cardiac arrest secondary to hyperkalaemia, and should be avoided. In patients with denervation as a result of spinal cord lesions, the increased number of perijunctional nicotinic acetylcholine receptors on skeletal muscle can cause hyperkalaemia after administration of succinylcholine. The time between denervation and the risk of a potentially fatal hyperkalaemic response is not known in humans. In animal studies, the peak increase in serum K⁺ was 14 days after injury, with a half-peak increase at 8.4 days. Changes in potassium levels began 4 days after injury. It is probably safe to use succinylcholine in the first 48 h after injury to the spinal cord. Thereafter, hyperkalaemia may occur for an indeterminate period, but most authors agree it is safe to use it again 9 months after the injury.

The use of bolus doses of i.v. induction agents reduces the amplitude of evoked potential responses, and in particular, cortical responses, but these effects do not prevent useful intraoperative recording of cortical somatosensory potentials and transcranial electrical motor evoked potentials (MEP). Inhalation agents reduce the amplitude of evoked potential responses to a greater degree than do i.v. induction agents, but no studies have compared an inhalation induction technique with an i.v. technique in this respect.

**Intubation**
A decision must be made at preoperative assessment whether to intubate the patient awake or asleep, and whether fibre-optic laryngoscopy will be required. The patient must be counselled fully about the decision at this time (Fig. 2).
Awake or asleep?
Indications for awake intubation include the risk of delayed gastric emptying, the need to assess neurology after intubation is complete (in cases such as an unstable cervical spine), or the presence of a neck stabilization device (such as halo traction), which prevents adequate airway maintenance in an unconscious patient. Otherwise, i.v. induction of anaesthesia followed by a non-depolarizing neuromuscular blocking drug is the technique of choice.

Direct or fibre-optic laryngoscopy?
There is controversy as to whether direct laryngoscopy is a major factor contributing to cord injury in patients with cervical spine instability. Other factors such as hypotension and patient positioning may be equally important. Direct laryngoscopy with manual in-line stabilization or a hard collar, is an accepted means of intubation for many patients provided this can be achieved without any neck movement. Fixed flexion deformities, which involve the upper thoracic and cervical spine may make direct laryngoscopy impossible. These patients require the use of fibre-optic laryngoscopy to facilitate tracheal intubation. The intubating laryngeal mask airway may be a useful alternative, with or without fibre-optic guidance, for anaesthetists familiar with its use.

Awake fibre-optic intubation will be required in patients wearing stabilization devices such as halo vests, which make conventional airway access impossible, and in those where difficulty is anticipated because of anatomical reasons, for example micrognathia, limited mouth opening. In patients with an unstable cervical spine, instillation of local anaesthesia into the airway to facilitate awake intubation may cause vigorous coughing. In such cases, it is preferable to use nebulized lidocaine rather than a cricothyroid injection or administration of local anaesthetic through the fibre-optic scope.

Anterior approaches to the thoracic spine may necessitate the use of a double-lumen endobronchial tube. Alternatively, the surgeon and anaesthetist may agree that a single lumen tracheal tube will suffice, allowing more limited intraoperative lung retraction.

Maintenance
A stable anaesthetic depth is required in order that changes to somatosensory or MEPs can be interpreted reliably. A technique involving nitrous oxide 60% and isoflurane less than 0.5 MAC is compatible with somatosensory evoked potential (SSEP) monitoring, but in nitrous oxide 60%, end-tidal isoflurane concentrations greater than 0.87% make MEP monitoring uninterpretable. An i.v. technique using propofol is therefore recommended. Neurophysiologists monitoring evoked potentials should be made aware of any sudden decrease in arterial pressure, or the need to
administer a bolus of opioid or change the anaesthetic depth. Sudden cardiovascular instability during anaesthesia may result from spinal cord and brain stem reflexes, from mediastinal distortion as a result of surgical manipulation, or more commonly from blood loss.

**Induced hypotension**

Hypotensive anaesthesia may be used to improve the surgical field and to reduce blood loss during major spinal surgery. A number of hypotensive agents have been studied during surgery to correct scoliosis. They include ganglion blocking agents, volatile agents,\(^7\)\(^{108}\) calcium channel antagonists,\(^38\) sodium nitroprusside, nitroglycerin,\(^121\) and, in children, the dopamine-1 receptor agonist, fenoldopam.\(^107\) Mean arterial pressure (MAP) is typically maintained at 60 mm Hg. There is little evidence that any particular agent is superior, but the avoidance of tachycardia is an essential part of a good anaesthetic technique.

Caudal epidural anaesthesia has also been shown to reduce surgical bleeding by 50% in patients undergoing lumbar spinal surgery. This was thought to be as a result of a reduction in sympathetic tone causing a measurable decrease in lumbar vertebral intrasosseus pressure.\(^50\) This technique, however, is not as controllable as continuous i.v. titration of a short-acting hypotensive agent, nor suitable for operations involving the thoracic and cervical spine. It may also hinder early postoperative neurological assessment.

**Muscle relaxation**

When myogenic motor evoked responses are to be recorded, neuromuscular block must be carefully monitored and a constant depth of block maintained. It is advisable to administer a non-depolarizing neuromuscular blocking agent such as atracurium using a continuous i.v. infusion device during major spinal surgery.

**Intraoperative monitoring and positioning of the patient**

**Cardiovascular monitoring**

Prolonged anaesthesia in unusual positions, combined with significant blood loss, the haemodynamic effects of thoracic surgery, and where appropriate controlled hypotension, necessitates detailed monitoring of the cardiovascular system. Invasive arterial pressure monitoring is mandatory.

In the prone position, central venous pressure (CVP) may be a misleading indicator of right and left ventricular end-diastolic volume. A study of 12 paediatric patients undergoing surgery for scoliosis in the prone position, compared CVP and transoesophageal echocardiography (TOE) in assessment of ventricular filling.\(^104\) Measurements were made before and after positioning. CVP rose from 8.7 (1.3) mm Hg (mean (SEM)) supine to 17.7 (2.5) mm Hg prone, but left ventricular end diastolic diameter measured by TOE, fell from 37.1 (2.9) to 33.2 (3.0) mm. In three patients in whom pulmonary artery occlusion pressure (PAOP) was also measured, there was an increase in PAOP on being turned from the supine (mean 12.7 mm Hg) to the prone position (mean 28.0 mm Hg), although there were insufficient data for statistical analysis. These results demonstrate that there is no correlation between the measurement of cardiac volume indicators by TOE and CVP or PAOP in such conditions. High CVP values may be misleading indicators of adequate cardiac filling in the prone position.\(^110\) The changes are probably a result of raised intrathoracic pressure causing reduced ventricular compliance and compression of the inferior vena cava. Dependent lower limbs cause a reduced venous return to the heart.

**Respiratory monitoring**

Respiratory system monitoring should always include end-tidal carbon dioxide concentration and peak airway pressure. In major surgery, serial measurements of arterial oxygen tension are recommended. Patients with severe respiratory dysfunction as a result of scoliosis may have an increased alveolar-arterial oxygen gradient,\(^48\) which may be further increased during prolonged anaesthesia because of regional hypoventilation.

**Temperature monitoring**

Thermoregulation may already be impaired in patients who have spinal cord lesions before surgery. Prolonged anaesthesia causes significant heat loss. The use of temperature monitoring, warming of all i.v. fluids, and a warm air mattress device is recommended.

**Positioning**

Patient position for spinal surgery varies depending on the level of the spine to be operated upon and the nature of the proposed surgery. Patients may be repositioned intraoperatively. It is important that venous pressures at the surgical site are kept low to reduce bleeding (reverse Trendelenburg tilt and a free abdomen), and peripheral nerves, bony prominences, and the eyes are protected. It is also important to avoid displacement of unstable fractures during patient positioning. Intraoperative x-ray imaging is frequently required. The relevant spinal level must, therefore, be placed away from the central support of a radiolucent operating table.

**Lumbar surgery**

Anterior approaches require a laparotomy, and general surgical input may be required in difficult cases. Posterior surgery requires a prone patient with a free abdomen to keep epidural venous pressure low (the patient supported on a Wilson frame, for example, or a raised mattress with a hole for the abdomen).\(^84\) For disc surgery, patients are placed in
The knee-chest position with a well-padded, secure support behind the upper thigh to support the patient’s weight. This gives a horizontal lumbar spine with vertical intervertebral discs.

**Thoracic surgery**
Anterior approaches to the thoracic spine are via a thoracotomy with the patient supported in a lateral position. If a double lumen endobronchial tube is used to allow deflation of one lung for surgical access, a fibre-optic laryngoscope should always be used to check tube placement after the patient is finally positioned. Posterior approaches to the thoracic spine require a prone patient with an uncompressed abdomen.

**Cervical surgery**
Patients are usually positioned with their feet close to the anaesthetic machine. This allows surgical access to the head and neck. Extensions are needed to breathing circuits and i.v. lines, and it may be useful to place an i.v. cannula in the patient’s foot. Tracheal tubes must be carefully secured without impinging on the surgical field.

For anterior surgery, a reinforced tracheal tube will reduce the risk of airway obstruction as tracheal retraction occurs during surgery. The head is supported on a padded head ring, or the ‘horseshoe’ of a Mayfield neurosurgical operating table attachment. Traction may be required by tongs and weights placed into the outer bone plate of the skull for some or all of the procedure. Reverse Trendelenburg positioning minimizes venous bleeding and provides counter traction for the weight attached to the head. Venous pooling in the lower limbs and intraoperative retraction of the carotid artery make an arterial line advisable for most patients.

For posterior approaches to the cervical spine, the head of the prone patient can be supported on the gel-padded horseshoe of the Mayfield table attachment, or placed in a skull clamp. The orbits, the superior orbital nerve and the skin over the maxilla are at particular risk of ischaemic injury if positioning is incorrect. These problems are avoided by using a skull clamp. The head height and degree of neck flexion may be adjusted intraoperatively, and pressure areas must be rechecked after such manoeuvres. Support for the tracheal tube and breathing circuitry is difficult; care must be taken if equipment has been taped to the operating table, that tubes are not dislodged as the head position is altered.

Venous air embolism is a risk for these patients because veins at the operative site are above the level of the heart. Unfortunately, methods to reduce blood loss such as reduced venous pressure increase the risk of this complication.

**Blood conservation**
Blood loss during single level procedures, especially for intervertebral disc-related disease, should not be excessive, but during more extensive spinal surgery, it can be considerable; typically losses are 10–30 ml kg⁻¹, a result of loss from decorticated bone and disruption of rich vascular networks. The degree of blood loss is associated with: the number of spinal levels fused; body weight; surgery for tumours; raised intra-abdominal pressure in the prone position, and the presence of DMD.

Blood loss is associated with increased operative time, delayed wound healing, wound infections, and increased requirement for blood transfusion. The risks of allogeneic blood transfusion include: hypothermia, impairment of coagulation, hyperkalaemia, hypocalcaemia, transfusion reactions, acute lung injury, immunomodulation, and viral and bacterial infection. Allogeneic blood transfusion should therefore be reduced to a minimum. This can be accomplished by techniques to reduce blood loss and by autologous blood transfusion.

**Reducing blood loss**

Blood loss can be minimized by careful patient positioning, good surgical technique, controlled hypotensive anaesthesia, and by the use of agents such as antifibrinolytics. When patients are placed in the prone or knee-chest positions, care must be taken to minimize intra-abdominal pressure. It has been shown that positioning devices, such as the Relton-Hall frame, which allow the abdominal viscera to hang freely, reduce inferior vena caval (IVC) pressure by one-third compared with conventional pads. Raised IVC pressure is associated with lumbar venous engorgement and increased blood loss. One study has shown minor changes to patient positioning on the Wilson frame can reduce blood loss per vertebral level by approximately 50%.

**Hypotensive anaesthesia**

Hypotensive anaesthesia has long been established as a safe and effective method for reducing blood loss by up to 58% during spinal surgery.

**Antifibrinolytic agents**

Drugs such as the synthetic lysine analogues, tranexamic acid, and aminocaproic acid, and the protease inhibitor, aprotinin, have been used to reduce blood loss during spinal surgery. Only aprotinin, however, has been shown to cause a statistically significant reduction in intraoperative blood loss. Aprotinin is a polypeptide derived from bovine lung, which is an inhibitor of plasmin and kallikrein, forming a reversible complex with the serine binding site on the enzyme. It also preserves platelet function.

Urban and colleagues compared the use of aprotinin, aminocaproic acid, or neither in 60 adult patients undergoing anterior-posterior thoracolumbar fusion under hypotensive anaesthesia using sodium nitroprusside and esmolol. Aprotinin (1 million KIU load over 30 min followed by 0.25 million KIU h⁻¹) and aminocaproic acid (5 g load over
30 min followed by 15 mg kg$^{-1}$ h$^{-1}$) were both shown to reduce blood loss when compared with control subjects, but this reduction only reached statistical significance in the aprotinin group (mean intraoperative loss in control group 3556 ml, in aminocaproic acid group 2929 ml, and in aprotinin group 2685 ml). Desmopressin has been shown to reduce bleeding times in patients with platelet disorders. In spinal surgery, it may have a tendency to reduce blood loss but this was not found to reach statistical significance.64

In major spinal surgery, it is the authors’ practice to ensure good patient positioning, use a controlled hypotensive anaesthesia technique, and to use an infusion of aprotinin.

Provision of autologous blood

Autologous blood can be made available to the patient by three methods; pre-deposit autologous transfusion, intraoperative acute normovolaemic haemodilution, and intraoperative red blood cell salvage.115

Pre-deposit autologous transfusion

The patient donates blood 3–5 weeks before surgery for use intraoperatively. This technique has been used widely in orthopaedic, general, and cardiothoracic surgery. It has been shown to reduce the requirement for allogeneic blood by up to 75% in lumbar fusion surgery.13 Disadvantages of this method include repeated visits for preoperative phlebotomy, wastage of unused blood, high cost, and possible risks of incompatibility because of clerical errors. Furthermore, difficulties arise in using the technique in children less than 30 kg and in adults with pre-existing anaemia or cardiovascular disease. Recombinant erythropoietin has been used before major surgery to raise preoperative haemoglobin levels in patients, such as Jehovah’s Witnesses, who object for ethical reasons to the use of blood products.102 It reduces allogeneic blood requirements in children undergoing scoliosis surgery,118 and it may also be used to facilitate autologous collection of blood, and intraoperative normovolaemic haemodilution.

Intraoperative normovolaemic haemodilution

This is performed immediately before surgery. Up to 1 litre of whole blood is removed, and stored in bags with anticoagulant according to the formula:31

\[
\text{Volume to be removed} = \text{EBV} \times \frac{(\text{initial Hct} - \text{target Hct})}{\text{mean Hct}}
\]

where EBV=estimated blood volume; Hct=haematocrit; mean Hct=arithmetic mean of initial Hct and the target Hct.

The removed blood is replaced by i.v. infusion of colloid or crystalloid to achieve normovolaemia with a reduced haematocrit. During surgery, less red cell mass is lost for a given volume of blood. The donated whole blood may be re-transfused once haemostasis is achieved, or a critical value of haemoglobin reached. The technique has been shown to reduce homologous blood requirements in spinal surgery.35 42

Intraoperative cell salvage

Blood lost during surgery is collected using commercially available equipment and is then anticoagulated, filtered for clots and debris, centrifuged, and resuspended in saline before re-infusion to the patient. Many litres of blood can be salvaged. It is the authors’ practice to use cell-salvaged blood where blood loss is anticipated to be greater than 15 ml kg$^{-1}$. Disadvantages are that re-infused red cells may contain residual anticoagulant, and also that coagulation factors and platelets are consumed at the wound site. Clotting factors may therefore need to be replaced using donor fresh frozen plasma. Only approximately half of the blood lost during surgery can be salvaged, and the technique is unsuitable if the operative field contains malignant cells or infection, as these may be disseminated through the body. The use of intraoperative cell salvage has been recommended by a consensus conference,3 concluding that despite the initial capital investment in equipment and disposables, ‘... it appears to be relatively inexpensive and may be cost saving...’. Nevertheless, a recent survey of UK surgeons found that logistical considerations were the main obstacles to using autologous blood transfusion, and that more surgeons were keen to use it than were actually doing so.109

Spinal cord monitoring

During surgery, when corrective forces are applied to the spine, while the spinal canal is surgically invaded, or when an osteotomy is to be undertaken, the spinal cord is at risk of injury. The incidence of motor deficit or paraplegia after surgery to correct scoliosis in the absence of spinal cord monitoring techniques has been quoted as between 3.7 and 6.9%.21 70 This figure may be reduced by intraoperative monitoring (IOM) to 0.5%.78 The American Academy of Neurology has published guidelines on IOM concluding ‘considerable evidence favours the use of monitoring as a safe and efficacious tool in clinical situations where there is a significant nervous system risk, provided its limitations are appreciated’.6 It is now considered mandatory to monitor spinal cord function for these types of procedures.

IOM ideally detects perturbations in spinal cord function early in order that the surgeon can take appropriate steps to correct them before irreversible damage occurs. The time, however, between a change in the electrophysiological recordings from the cord after over-distraction, and the onset of irreversible ischaemic damage is in the order of only 5–6 min in animal studies.80

A motor deficit is functionally more devastating to the patient than a sensory deficit. This is important to consider when evaluating the relative merits of each method of monitoring, some of which assess motor tracts, and some the sensory tracts of the cord (Fig. 3).
A knowledge of the methods of intraoperative spinal cord monitoring is important to the anaesthetist, as the anaesthetic technique can have profound effects on the ability to monitor spinal cord function accurately. There are four main methods of IOM: the ankle clonus test, the Stagnara wake-up test, SSEP, and MEP. These will be considered briefly, as there have been recent reviews on this subject.32 82

**Ankle clonus test**

Historically, this was the first test to be used. Clonus is repeated rhythmic movement elicited by the stretch reflex. The clonus test is usually performed during emergence, either at the end of surgery or during a wake-up test. All muscle paralysis must be antagonized. There is only a brief period between anaesthesia and wakefulness when it is possible to elicit clonus. The foot is sharply dorsiflexed at the ankle joint. Spinal cord injury is indicated by complete absence of repeated movements at the ankle joint.

In the neurologically intact, awake individual, higher cortical centres have a descending inhibitory influence on the reflex, and clonus is not observed after ankle stretch. In healthy individuals during anaesthesia, cortical centres are inhibited and there is a loss of descending inhibition via the spinal cord pathways on the ankle joint reflex. Clonus may, therefore, be elicited on ankle stretch, especially during emergence from anaesthesia. If the spinal cord is injured, however, the cord undergoes a period of spinal shock, and there is a loss of reflex activity accompanied by flaccid paralysis. During emergence from anaesthesia in these individuals, the ankle clonus reflex will not be present.

The test is easy to administer. Proponents of its use point to a high level of sensitivity (100%) and specificity (99.7%).40 However, the test can only be performed intermittently, and the absence of clonus could be a result of not only spinal cord damage, but also to an inadequate or too great a depth of anaesthesia. Furthermore, the presence of clonus does not exclude spinal cord damage; other parts of the spinal cord may be damaged leaving the ankle stretch reflex intact.

**Stagnara wake-up test**

This was first described in 1973.116 Preoperatively, the need for the test is explained; it will involve the patient making a specified motor response, usually in the lower limbs, to verbal command part way through the surgery. The test evaluates the gross functional integrity of the motor pathways (lower and upper motor neurons and muscles) involved in performance of this motor task (Fig. 3). The test does not assess the integrity of any part of the peripheral sensory system.

The surgeon must give the anaesthetist adequate warning of the need to perform a wake-up test as neuromuscular block must be antagonized and the plane of anaesthesia lightened. As the patient becomes more conscious, they are instructed first to perform an action involving muscle groups above the level of any potential cord damage, usually involving the upper limbs (for example, to grip the anaesthetist’s fingers). When a positive response is obtained, the patient is then instructed to move their legs.
and the response to this command noted. If the patient can move their legs, anaesthesia is deepened and surgery recommenced. If the patient is unable to move their legs, corrective measures are instituted immediately.

A wake-up test should be as easy and as rapid to institute as possible. This necessitates an anaesthetic technique that is reliable, but which may be quickly antagonized as many times as the surgeon requires. Wakening should also be smooth to minimize the risk of tracheal extubation. Furthermore, the patient should not experience any pain during the test and have no subsequent recall of intraoperative events.

A number of different anaesthetic techniques for the Stagnara wake-up test have been advocated, including volatile-based anaesthesia. A Danish group,58 in a randomized trial involving 40 patients, described the successful use of a midazolam-based anaesthetic, antagonized by flumazenil at the time of the wake-up test, compared with a propofol infusion technique. The midazolam/flumazenil group was found to have a shorter intraoperative wake-up time (mean 2.9 min vs 16 min in the propofol group), shorter postoperative wake-up times (1.8 vs 13.9 min, respectively), and a better quality of intraoperative arousal. Five patients in the midazolam group, however, became resedated in the recovery room required further doses of flumazenil. Remifentanil is a potent μ-receptor agonist. Its ester linkage renders it susceptible to hydrolysis by tissue esterases, producing a half-life at its site of action of less than 10 min. It therefore has a pharmacokinetic profile suitable for use when a wake-up test must be performed. Preliminary reports using remifentanil suggest a delay between the surgeon’s request for a wake-up test and adequate conditions for neurological assessment of only 5 min.94

Despite the use of such techniques, the test has a number of disadvantages. First, it requires the patient’s co-operation. Secondly, it poses risks to the patient of moving on or falling from the operating table and of tracheal extubation, often in the prone position. Thirdly, it requires an inconsiderable operator skill on the part of the anaesthetist. Fourthly, it is a valid measure of motor function at only the precise moment in time the test is instituted; it does not allow continuous IOM of motor pathways. The onset of a change in electrophysiological recordings and permanent neurological injury can occur more than 20 min after the last corrective force is applied to the spine.80 It is, therefore, conceivable that a wake-up test could be normal after the last corrective manoeuvre has been applied but before the onset of the resultant neurological deficit.

The place of the Stagnara wake-up test in spinal cord monitoring during spinal surgery should therefore be confined to situations in which electrophysiological monitoring techniques are not available, fail, or produce equivocal results.

The pathways involved in the recorded responses include a peripheral nerve, the dorsomedial tracts of the spinal cord and, depending on the electrode placement, the cerebral cortex (Fig. 3). The physiological role of these tracts is to

Somatosensory evoked potentials
SSEPs are elicited by stimulating electrically a mixed peripheral nerve (usually the posterior tibial, peroneal, or sural nerves), and recording the response from electrodes at distant sites cephalad to the level at which surgery is performed (Fig. 4). Guidelines on stimulation and recording methods have been published.48 1 Typically, the stimulus is applied to the peripheral nerve on the left and the right limb alternately as a square wave for 0.1–0.3 ms, at a rate of 3–7 Hz. The intensity of the stimulus varies depending upon the electrodes and quality of skin contact, but is in the 25–40 mA range. Recording electrodes are placed in the cervical region over the spinous processes or over the somatosensory cortex on the scalp, or are sited during surgery in the epidural space. Baseline data are obtained after skin incision. This allows a stable plane of anaesthesia to be established during baseline recordings as anaesthetic agents affect SSEPs. During surgery, responses are recorded repeatedly. The functional integrity of the somatosensory pathways is determined by comparing the amplitude change and the latency change of the responses obtained during surgery to baseline values. A reduction in the amplitude of the response by 50% and an increase in the latency by 10% are considered by most workers as significant.17 78 The amplitude response is considered the primary criterion.80
subserve sensations of proprioception and light touch. It must be emphasized that responses are not obtained from motor tracts, or from the anteriolateral sensory tracts of the spinal cord (subserving pain and temperature sensation). This has two important ramifications for the validity of SSEPs. First, because of the close proximity of the dorsomedial sensory tracts with the motor tracts in the cord, it is assumed that when using SSEPs, any damage to the motor tracts will be signalled by a change in SSEPs. This, however, cannot be guaranteed. Secondly, the blood supply of the corticospinal motor tracts differs from that of the dorsomedial tracts (Fig. 5). Hypoperfusion in the territory of the anterior spinal artery may cause ischaemia in the anteriolateral tracts, but not affect the dorsomedial tracts. It is, therefore, possible to have normal recordings from SSEPs throughout surgery, but to have a paraplegic patient postoperatively.82 98 Furthermore, in patients with pre-existing neurological disorders, reliable data can be recorded in only 75–85% of patients.82

Effects of anaesthetic agents on SSEPs
Anaesthetic agents can have a significant impact upon SSEPs.100 Inhalation anaesthetic agents and nitrous oxide cause a dose-dependent reduction in SSEP amplitude and an increase in latency.60 Nitrous oxide 60% with isoflurane 0.5 MAC or enflurane 0.5 MAC is compatible with effective SSEP monitoring.89 A recent retrospective study of 442 cases found that 13/60 ‘false-positives’ (abnormal SSEPs with no neurological deficit postoperatively) were attributable to an increased concentration of inhalation agent.83 I.V. anaesthetic agents also cause changes to SSEPs but to a lesser degree than inhalation agents.57 69 The cortical response appears to be most susceptible to anaesthetic agents; subcortical, spinal, and peripheral responses are less affected. A recent study of the use of propofol or midazolam as a continuous i.v. infusion combined with sufentanil was associated with maintenance of the amplitude of the cortical SSEP from baseline values to the end of surgery (propofol from 1.8 (0.6) to 2.2 (0.3) μV; midazolam from 1.7 (0.5) to 1.6 (0.5) μV). However, propofol and nitrous oxide used in combination caused a significant reduction in the amplitude of cortical SSEPs (from 2.0 (0.3) to 0.6 (0.1) μV).61 The latencies of the responses were not increased in any of the three groups of patients, but recovery was significantly delayed in the midazolam group. The authors recommended a propofol technique for surgery during which cortical SSEPs are to be recorded.

Opioids such as remifentanil and fentanyl administered via the i.v. route cause a small reduction in the amplitude and increase in the latencies of SSEPs.97 Intrathecal opioids have little effect on SSEPs.30 Neuromuscular blocking agents, as may be expected, cause no change in SSEPs.101
Effect of controlled hypotension on SSEP
MAP during spinal surgery is usually maintained at lower than pre-induction values in order to minimize blood loss. Typically, controlled normovolaemic hypotension to a MAP of 60 mm Hg is used. MAP should not be allowed to decrease to less than 60 mm Hg as, at this point, SSEPs are lost and neurological ischaemic injury may occur. Maintaining MAP greater than 60 mm Hg is, however, no guarantee of safety. SSEPs demonstrate that the feline spinal cord is more vulnerable to distractive injury during pharmacologically induced hypotensive anaesthesia than during normotensive anaesthesia. Earlier animal work has shown that peripheral nerves, which do not have an autoregulated blood flow, are more sensitive to the effects of hypotension than the spinal cord. SSEPs may, therefore, be reduced by even moderate hypotension. Papastefanou, in a retrospective series of 442 cases, found 17/60 ‘false-positive’ SSEP changes attributable to hypotension. Changes in SSEPs, whether a result of hypotension, or mechanical distractive forces, or a combination of both, must not be ignored.

Other factors
A decrease in core body temperature in animals causes a reduction in the amplitude of SSEPs by approximately 7% and an increase in latency of 3% for each 1°C reduction. There does, however, appear to be a protective effect of hypothermia on spinal cord function. It is clear from a large multicentre study that the experience of monitoring teams in spinal surgery has a significant effect on outcome. Teams with experience of less than 100 cases had more than twice the postoperative neurological complication rate of teams with greater experience.

Effectiveness of SSEP monitoring
In a large retrospective multicentre study of over 51 000 procedures, SSEP monitoring was found to have a sensitivity of 92% and specificity of 98.9%. The false negative rate was 0.127% (normal SSEPs throughout the case but a neurological deficit postoperatively), or 1 in 787 procedures. The false positive rate was 1.51% (SSEP had changed, but no new neurological deficit postoperatively), or one in 67 procedures. Other studies have found a higher false positive rate (4.7%), and that SSEP monitoring has a lower specificity, 85.33%, but a sensitivity of 100%, probably explained by the smaller number of cases. SSEP monitoring is currently the mainstay of spinal cord monitoring techniques. It is, overall, a reliable technique with a high sensitivity and specificity for early detection of intraoperative neurological compromise, and has a proven record over the last decade.

Motor-evoked potentials
As a result of the inherent problems using SSEPs as a monitoring tool during spinal surgery, and reports of postoperative paralysis despite apparently normal intraoperative SSEPs, efforts have been made to monitor motor tracts of the spinal cord (Fig. 3) as a more sensitive indicator of motor function.

MEP monitoring was first used clinically over 10 yr ago. Monitoring techniques are subdivided according to: the site of stimulation (motor cortex, spinal cord); the method of stimulation (electrical potential, magnetic field); and the site of recording (spinal cord, peripheral mixed nerve, muscle). Each variation of the technique has advantages and disadvantages. The principle is the same; stimulation by whatever means cranial to the site of surgery causes prodromic stimulation of motor tracts in the spinal cord, and of peripheral nerve and muscle caudal to the site of surgery. Perturbation of motor pathway function by surgery leads to a reduction in amplitude and an increase in latency of the recorded responses.

The motor cortex can be stimulated by electrical or magnetic means. Magnetic equipment is bulky and cumbersome but is not affected by the quality of electrode contact. Recorded responses are classified as myogenic or neurogenic. Myogenic responses result from the summed EMG activity in a muscle, such as tibialis anterior, in response to stimulation (Fig. 4). Neurogenic recordings arise from the summed electrical activity in a peripheral nerve or the spinal cord. The advantage of recording EMG responses is their large amplitude. The main disadvantage is their variable morphology. When recording EMG responses, the depth of muscle relaxation is of critical importance: if it is too deep, responses are unobtainable; if only residual block is present, there is a risk of injury to the patient, if violent movements occur in response to stimulation. Neuromuscular blocking agents should be administered by continuous infusion, and the depth of neuromuscular block monitored. The first twitch of the train-of-four response should be maintained at 10–20% of control. Neurogenic responses, however, can be recorded under complete neuromuscular block to avoid patient injury, and are more reliable in terms of amplitude, latency, and morphology.

Effects of anaesthetic agents on MEPs
Cortical evoked responses are more prone to the effects of anaesthetic agents than spinal-evoked responses. Propofol is a powerful suppressant of cortical evoked responses, causing a dose-dependent reduction in the amplitude of the response. A bolus dose of propofol 2 mg kg⁻¹ abolishes cortical MEPs. Volatile agents are also powerful suppressants of cortical evoked MEPs; MEPs are abolished or are too inconsistent to interpret at end-tidal isoflurane concentrations of 0.87 (0.08)%. Midazolam and etomidate cause a significant but smaller reduction in the amplitude of the response. Opioids such as fentanyl have been variously reported as reducing the amplitude of the response, or causing no effect. Multiple pulse transcranial electrical
stimulation techniques can improve the reliability of MEP recording further.

These findings have led to the need for significant modifications to the anaesthetic technique when cortical-evoked MEPs are measured. In the past, ketamine-based techniques have been used, but not without complications such as unpleasant hallucinations. An i.v. propofol infusion with fentanyl or remifentanil has been advocated and provides for adequate MEP recording in 97% of neurologically intact patients, when used with a multiple pulse stimulation technique.87

Effectiveness of MEP monitoring
MEP monitoring is less reliable in patients with a pre-existing neurological deficit.65 Furthermore, early hopes of greater sensitivity of MEPs over other monitoring techniques may have been premature. There are recent reports of preserved neurogenic MEPs associated with postoperative motor deficit,76 which suggest the sensitivity of MEPs is less than 100%.

SSEP monitoring has become an accepted standard of care during spinal surgery. It is less affected by the technical difficulties associated with MEP monitoring. MEP monitoring is, however, becoming more widely used and the two methods should be regarded as complementary, with the use of a wake-up test reserved for situations where neurological monitoring is not possible or responses are significantly perturbed during surgery.

Postoperative care
Patients undergoing spinal surgery frequently have significant co-morbidity. Surgery imposes the further stresses of significant blood loss, prolonged anaesthesia, and difficulties in acute postoperative pain management. Surgeons prefer patients to be conscious and able to respond to command immediately after anaesthesia, for early neurological assessment. It is also important that patients are able to expectorate, and to comply with physiotherapy as early as possible in the postoperative period.

Indications for postoperative ventilation
The decision to provide a period of postoperative artificial ventilation should have been made before surgery commences, and explained to the patient. The need for postoperative ventilation is suggested by patient and surgical factors. Patient factors include the presence of a pre-existing neuromuscular disorder, severe restrictive pulmonary dysfunction with a preoperative vital capacity of less than 35% of predicted, a congenital cardiac abnormality, right ventricular failure, and obesity. Surgical factors include a prolonged procedure, surgical invasion of the thoracic cavity,117 and blood loss greater than 30 ml kg⁻¹. Frequently, it is necessary only to provide artificial ventilation for a few hours in the postoperative care unit, until hypothermia and metabolic derangements have been corrected. Chest drains, if present, should be checked regularly to ensure patency; obstruction may lead to a pneumo- or haemothorax.

Postoperative analgesia
Pain management can be a considerable challenge. Patients undergoing spinal surgery, particularly through a thoracic approach, may have a large incision extending over several dermatomes. Many patients have pre-existing chronic pain conditions, may be cognitively impaired (some neuromuscular disorders), or be very young (children). A multimodal approach to analgesia is recommended, using a combination of simple primary analgesics, opioids, and regional anaesthesia techniques where appropriate. For initial postoperative analgesia, it is useful to restart, if possible, all the analgesics the patient was receiving preoperatively. Undoubtedly, the patient’s requirements will be increased postoperatively and additional therapy will be required.

Parenteral opioids
The use of parenteral opioids has been the mainstay of analgesia for all patients undergoing spinal surgery. Opioids can be administered via i.m., i.v. (continuous infusion and patient-controlled analgesia devices with or without background infusions), intrapleural, epidural, and intrathecal routes. Their use, via the i.v. route in particular, is associated with side-effects such as respiratory depression, nausea and vomiting, sedation, and gastrointestinal ileus. The latter may be especially disadvantageous after major spinal surgery, when some degree of paralytic ileus is common.

Patients with cancer may not be naïve to opioid drugs and such individuals must be assumed to have acquired a degree of opioid tolerance. For patients who have received long-term opioids preoperatively by other routes (e.g. enteral, transdermal), these should also be restarted as early as possible postoperatively, and gradually reduced over subsequent days or weeks.

Non-steroidal anti-inflammatory drugs
Simple analgesics alone afford inadequate analgesia even for relatively minor spinal surgery. Non-steroidal anti-inflammatory drugs (NSAIDs), both non-selective cyclooxygenase inhibitors, and selective cyclo-oxygenase 2 (COX 2) inhibitors, have however been used successfully after spinal surgery.75, 93 But the use of a non-selective cyclo-oxygenase inhibitor NSAID cannot be recommended for intraoperative or early postoperative analgesia in such cases. Guidelines on the use of NSAIDs published by The Royal College of Anaesthetists96 do not specify their role for this purpose. The use of NSAIDs may increase bleeding time by 30–35%, cause gastritis, and be associated with acute renal failure, particularly in the presence of hypovoltaemia and hypotension. The safety profile of selective COX 2 inhibitors in major spinal surgery is yet to be fully evaluated. If, however, patients have been taking NSAIDs to
help relieve their pain without complication preoperatively, it is useful to restart this medication in the immediate postoperative period for its opioid-sparing effects.

**Epidural analgesia**
The use of local anaesthetic agents, alone or in combination with opioids, by the epidural route after spinal surgery has been described, the epidural catheter being placed intraoperatively by the surgeon. Two recent studies compared epidural analgesia with parenteral morphine administered via patient controlled analgesia (PCA) devices after major spinal surgery. The retrospective study found time to full diet and hospital stay to be reduced in the epidural group, but the randomized study was unable to find any significant differences in pain scores, side-effects, or resumption of oral intake between the epidural and PCA groups.

Epidural anaesthesia with local anaesthetic agents can make neurological assessment difficult. Concerns over the rare but serious risks of epidural haematoma and infection associated with indwelling catheters have hindered its widespread use. The incidence of local superficial infection after routine epidural catheter placement has been quoted to be as high as 12%. However, the incidence of epidural abscess related to epidural catheter placement, although difficult to determine precisely, is rare. Recent studies suggest the optimum dose of morphine to be 2–5 μg kg⁻¹ h⁻¹, which provides comparable analgesia for 24 h but with fewer side-effects such as respiratory depression, nausea, and pruritus. Doses of this order, in a large retrospective study of 5969 patients, produced respiratory depression in 3% of patients. There were no cases of neurological injury or spinal haematoma.

Significant pain can be expected for up to 4 days postoperatively after major spinal surgery. Intrathecal opioids alone, therefore, will probably be insufficient over this period. Parenteral opioids made available in the immediate postoperative period (as patient-controlled analgesia regimen, for example), in patients who have received intrathecal opioids, provide for a smooth transition from predominately intrathecal opioid-based analgesia to parenteral opioid-based analgesia. The use of such a regimen is advisable in the setting of a postoperative critical care facility; animal data suggest systemic and intrathecal opioids may act synergistically.

**Other techniques**
Intrapleural infusions of local anaesthetic and/or opioids may be considered after a thoracotomy. Intrapleural infusions of local anaesthetic agents have been reported to reduce systemic opioid requirements in such circumstances. A number of studies, however, have found intrathecal analgesia with local anaesthetic agents to offer inferior analgesia to epidural opioids, and there remains concern over the blood levels of local anaesthetic agents achieved, and the risk of local anaesthetic toxicity.

**Late complications**
A retrospective study of 1223 anterior thoracic and lumbar spinal procedures found a respiratory complication rate of 7% (adult respiratory distress syndrome, pneumonitis, atelectasis, infection), pulmonary embolism 0.8%, cerebral vascular accident 0.25%, and death 0.33% (four patients: one died of ARDS on day 31, one myocardial infarction on day 1, and two died of fatal pulmonary emboli on days 3 and 8). Screening studies for thromboembolic complications after spinal surgery have quoted varied incidences between 0.395 and 15.5%. One partially randomized study found an incidence of 0.3% when Doppler ultrasonography was used postoperatively to detect venous thrombosis in patients treated with either mechanical (compression stockings and pneumatic boots), or pharmacological (warfarin) methods of prophylaxis. If, however, no methods of thrombo prophylaxis are used and venography is the screening method, incidences of venous thrombosis of 15.5% have been quoted. In one prospective study, symptomatic pulmonary emboli occurred in 2.2% of all spinal fusions, and these were more common after combined anterior/posterior approach procedures (6%), than posterior approach procedures alone (0.5%).

There has been a paucity of well-conducted randomized controlled trials comparing methods of thromboprophylaxis. Few would argue against the use of compression stockings and pneumatic boots, the use of which is relatively free of complications. However, the use of pharmacological...
methods of thromboprophylaxis (using heparin, for example) is contentious. Their use may be associated with haemorrhagic complications such as increased intraoperative and postoperative blood loss, and epidural haematoma. Further studies are required to adequately ascertain the most appropriate methods of prophylaxis against thromboembolism.

Treatment of thromboembolism produces the risk of major heparin-related complications (44%) such as epidural haematoma, gastrointestinal bleeding, and wound infection. Insertion of an IVC filter may be appropriate in these circumstances.

Conclusions

Spinal surgery presents a number of challenges to the anaesthetist. Patients are now undergoing major spinal surgery for conditions such as malignancy, scoliosis, and trauma, which would not have been contemplated 20 yr ago. Despite this, postoperative neurological morbidity has been reduced by advances in spinal cord monitoring techniques. The anaesthetist has an important role to play in facilitating the use of these new techniques. They must also manage the relief of postoperative pain in these patients, who have frequently been receiving several analgesics preoperatively.

References

30 Goodarzi M, Shier N-H, Grogan DP. Effect of intrathecal opioids
32 Guerit JM. Neuromonitoring in the operating room: why, when, and how to monitor! Electroenceph Clin Neurophysiol 1998; 106: 1–21
42 Hur SR, Huizenga BA, Major M. Acute normovolaemic haemodilution combined with hypotensive anesthesia and other techniques to avoid homologous transfusion in spinal fusion surgery. Spine 1992; 17: 867–73
49 Kafer ER. Respiratory and cardiovascular functions in scoliosis and the principles of anesthetic management. Anesthesiology 1980; 52: 339–51
69 McPherson RW, Sell B, Traysman RJ. Effects of thiopental, fentanyl, and etomidate on upper extremity somatosensory evoked potentials in humans. Anesthesiology 1986; 65: 584–9
Anesthesia for spinal surgery in adults

80 Owen JH, Naito M, Bridwell KH, Oakley DM. Relationship between duration of spinal cord ischaemia and postoperative neurologic deficits in animals. Spine 1990; 15: 846–51
82 Owen JH. The application of intraoperative monitoring during surgery for spinal deformity. Spine 1999; 24: 2649–62
89 Peterson DO, Drummond DC, Todd MM. Effects of halothane, enflurane, isoflurane and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 1986; 65: 35–40
92 Reid JM, Appleton PJ. A case of ventricular fibrillation in the prone position during back stabilisation surgery in a boy with Duchenne's muscular dystrophy. Anaesthesia 1999; 54: 364–7
112 United Kingdom Department Of Health: http://www.doh.gov.uk/thes/free_data/index.html
116 Vauzelle C, Stagnara P, Jouvinoux P. Functional monitoring of


Brain protection by anesthetic agents
Ines P. Koerner and Ansgar M. Brambrink

Purpose of review
Patients at risk for perioperative stroke, or those who have suffered recent cerebral injury, may benefit from neuroprotective properties of anesthetic agents during surgery. This manuscript reviews recent clinical and experimental evidence for neuroprotective effects of common anesthetic agents, and presents potential mechanisms involved in anesthetic neuroprotection.

Recent findings
Although strong experimental data support a neuroprotective potential of several anesthetic agents, specifically isoflurane and xenon, consistent long-term protection by either agent has not been demonstrated. Unfortunately, there is a lack of clinical studies that would support the use of any one anesthetic agent over the others. Mechanisms of neuroprotection by anesthetic agents appear to involve suppression of excitatory neurotransmission, and potentiation of inhibitory activity, which may contribute to the reduction of excitotoxic injury. Activation of intracellular signaling cascades that lead to altered expression of protective genes may also be involved.

Summary
Solid experimental evidence supports neuroprotection by anesthetic agents. It is too early to recommend any specific agent for clinical use as a neuroprotectant, however. Further study is warranted to unravel relevant mechanisms and to appreciate the potential clinical relevance of experimental findings.

Keywords
anesthesia, neuroprotection, neurotoxicity, perioperative cerebral ischemia, posttreatment, preconditioning

Introduction
Anesthesiologists routinely care for patients at risk for intraoperative or perioperative cerebrovascular accidents and cerebral ischemia, due to a combination of preexisting cerebrovascular disease or high-risk surgery, such as clipping of cerebral aneurysms, or open heart surgery on cardio-pulmonary bypass. It is obvious that the anesthesia provider will be greatly interested in any effects that his or her choice of anesthetic agents may have on the functional deficit caused in these patients by ischemic events that take place during anesthesia, or shortly thereafter. In addition, a positive or detrimental influence of anesthetic agents on the still evolving brain damage in patients who have recently suffered cerebral injury, and now require surgery, would clearly affect the anesthesia care provided to these patients. Unfortunately, despite a long history of experimental studies and some highly interesting data from recent experimental research, so far, no anesthetic agent that would render profound neuroprotection in humans has been identified in clinical trials.

Change of paradigm in anesthetic neuroprotection
Neuroprotection by anesthetic agents was first described more than three decades ago, when barbiturates were found to reduce neuronal energy consumption by reducing electrical activity. Accordingly, intraoperative neuroprotection by anesthetic agents for many years relied mainly on the reduction of the cerebral metabolic rate of oxygen (CMRO₂) by suppressing electric activity, as monitored by electroencephalography.

In parallel to our growing understanding of the many facets of and pathways involved in ischemic cell death, evidence has evolved in recent years that anesthetic agents actually act more specifically, and can interfere with detrimental ischemic cascades beyond a simple reduction of metabolic activity. Various potential mechanisms have been described, including inhibition of excitatory activity and potentiation of inhibitory circuits. Most anesthetics have been found to be antagonists of glutamate at N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptors, and to also potentiate inhibitory γ-aminobutyric-acid (GABA)-A receptor activity [1,2]. In addition, they reduce glutamate release [3,4] and increase glutamate reuptake from the synaptic cleft, thereby attenuating excitotoxic death of neurons. Volatile anesthetics as well as xenon can also open K⁺ channels, including the newly described two-pore TREK channel, which causes
neuronal hyperpolarization and contributes to anesthesia as well as to resistance against ischemia [5]. Other important mechanisms potentially involved in neuroprotection by anesthetics include blocking of calcium influx, activation of adenosine A1-receptors [6], activation of intracellular signaling cascades such as MAP kinase and Akt, which may lead to changes in gene expression, as well as a direct scavenging of damaging free radicals [7]. In a change of paradigms, the relevance of these specific effects on ischemic cascades is now thought to by far exceed the benefits derived from a simple suppression of cerebral metabolic activity.

**Relevance of anesthetic neuroprotection**

The degree of protection that can be achieved by anesthetics, as well as the longevity of this effect, remain unclear. Most experimental studies have failed to show a long-term protection by anesthetics, despite impressive short-term protection. In an experimental setup [8] that employs a very mild ischemia regimen, however, protection was still present one month after the insult. This apparent discrepancy may be due to a selective effect of anesthetics on one mode of ischemic cell death only: anesthetic agents may reduce excitotoxic damage by their antagonistic action on NMDA-receptors, suppression of glutamate release, and potentiation of inhibitory activity, thereby decreasing immediate neuronal death. Delayed apoptotic death that takes place long after the anesthetic agent was discontinued may not be affected, however. Alternatively, anesthetics may reduce the severity of the ischemic insult, reducing the number of cells that undergo immediate necrotic death, yet failing to prevent delayed apoptotic suicide of damaged neurons.

Either way, the main clinical relevance of neuroprotection by anesthetic agents may be that time is gained and a window of opportunity arises, in which additional means of protection aiming at other elements of the ischemic cascade, such as caspase inhibitors [9,10], may be applied (multimodal neuroprotection). Beyond a certain threshold of damage severity, however, anesthetics may not be able to protect cells from imminent death [11]. Thus, instead of aiming at complete neuroprotection (reducing the incidence of perioperative stroke), the current approach for anesthetic neuroprotection focuses more on reducing the severity of the insult (reducing morbidity after perioperative stroke).

**Timing of anesthetic neuroprotection**

Another question that remains to be answered is what timing is best for neuroprotection by anesthetics. Post-insult protection by anesthetics was not easily explained according to the old paradigm of reduction of energy needs by anesthetics, and a clinical study of posttreatment with barbiturates in survivors of cardiac arrest failed to prove beneficial effects. The more modern concept of a specific, receptor-mediated protective action, however, can accommodate protection of the brain from evolving damage after the initial insult, and recent in-vitro studies [12,13] of posttreatment with anesthetic agents have accordingly supplied promising results. Lasting beneficial effects of previous exposure to anesthetic agents, namely preconditioning, may additionally contribute to improved outcome after cerebral ischemia in the immediate postoperative period. Potential mechanisms involved in this preconditioning effect are currently studied, and may involve adenosine A1 receptor activation [14] and altered gene transcription secondary to changed activation of intracellular signaling cascades [15*].

**Tolerability of anesthetic neuroprotection**

Reports [16,17] that exposure to anesthetic agents can cause neurodegeneration and cell death, especially in immature brains, have caused new questions about the tolerability of these agents. The discussion focuses on isoflurane, nitrous oxide and ketamine, all of which block the NMDA-glutamate receptor subtype. Interestingly, xenon, also assumed to act via the same receptor system, has not been associated with detrimental effects. Some strongly argue that the reports about anesthetic neurotoxicity in the newborn result from experimental methodology and cannot be easily translated to clinical practice in humans [18**,19,20**]. The relevance of these findings for clinical applications remains uncertain, but further study employing clinically relevant regimens is clearly warranted.

**Chiasm between bench and bedside**

This discussion emphasizes once more the difficulties encountered when clinical situations are to be modeled in experimental paradigms, and the importance of choosing appropriate controls and outcome measures to achieve meaningful results from experimental studies. Long-term outcome is difficult to study after experimental ischemia, as many models do not permit long-term survival. This is especially true for in-vitro preparations. Appropriate control groups are difficult to establish, as effects of the anesthetic agent on cerebral blood flow and energy consumption before or during ischemia may affect the severity of the insult, which complicates group comparison. In addition, the comparison of results across individual studies is not easy, due to a wide array of different experimental setups, outcome measures used, and time-points studied.

The chiasm between the current lack of clinical evidence of neuroprotection by anesthetic agents in humans and the numerous positive experimental studies results from several factors, which need to be addressed to enable translation from bench to bedside: long-term functional outcome is the single relevant endpoint for patients experiencing cerebral ischemia, yet the vast majority of
experimental studies use short-term follow-up, and assess histopathological endpoints, or even apply in-vitro models of ischemia; dose–response studies are rarely conducted; many models do not adequately depict the clinical reality, that is age, co-morbidity, clinical monitoring, postsischemic critical care are not modeled; the pathomechanisms involved in ischemic injury and in neuroprotection by anesthetic agents appear to differ between developing and adult brains, yet many in-vitro models utilize neuronal cells or slices derived from immature animals.

That being said, a number of recent studies on neuroprotection by anesthetics have enhanced our basic understanding of the neuroprotective potential of several anesthetic agents, and of the molecular mechanisms involved in protection.

**Isoflurane**

Isoflurane may be the one anesthetic receiving most experimental attention. Today, there is a large body of evidence supporting a neuroprotective potential of isoflurane in various experimental models, but the longevity of this effect and the mechanisms behind it remain subjects of intense study.

**Acute neuroprotection**

Isoflurane protection may be more pronounced against moderate, rather than severe ischemia. Isoflurane at 1% reduced neuronal death in rat hippocampal slice cultures 48–72 h after 60 min of hypoxia, but the protection was lost when hypoxia was maintained for 75 min. The protection required calcium release from intracellular stores, and subsequent activation of MAP kinase and Akt signaling pathways [11]. These signaling cascades may elicit changes in gene expression, as isoflurane exposure (2% for 30 min) was shown to increase expression of heat-shock protein in neuronal/glia co-cultures, while decreasing genes associated with apoptosis [21].

The neuroprotective effect of isoflurane appears to be age dependent, as it is lost in the aging rat. When hippocampal slices derived from 5-day or 23-month-old rats were exposed to oxygen–glucose deprivation (OGD) for 20 min, neuronal injury was more pronounced in the tissue from the older animals, and 1% isoflurane reduced damage in the young, but not the older animal [22*]. Interestingly, isoflurane without OGD resulted in significant neuronal death in slices from older animals. The loss of protection may be related to the failure of isoflurane to limit intracellular Ca$^{2+}$ increase by OGD, or to elicit MAP kinase and Akt signaling in slices from aging animals [22*].

Isoflurane-mediated neuroprotection may only be transient. Hippocampal CA1 neuronal survival 5 days after 10 min of global cerebral ischemia was increased in rats that were anesthetized with isoflurane as opposed to fentanyl/nitrous oxide during ischemia and 2 h of reperfusion [23]. No difference in cell count between the groups was seen 3 weeks or 3 months after the insult, however [23]. This may be due to failure of isoflurane to prevent postsischemic apoptosis of damaged neurons. Infarct size was only transiently reduced (on days 1 and 4, but not on day 7) following focal ischemia (MCAO) in isoflurane-anesthetized, as opposed to awake, rats, while apoptotic death was more pronounced in the isoflurane group on days 4 and 7 [24].

**Preconditioning**

Isoflurane can also been used as a preemptive treatment to increase the tolerance of neurons against a subsequent lethal insult. In a recent study [15*], hippocampal slices exposed to 2 h of 0.5–1.5% isoflurane 24 h prior to OGD exhibited reduced neuronal death 48 h after the insult. This preconditioning effect was associated with Ca$^{2+}$ release from the endoplasmatic reticulum, and depended on calmodulin and MAP kinase signaling.

Isoflurane pretreatment may also influence experimental traumatic brain injury. Isoflurane 1% compared with fentanyl infusion for 30 min before traumatic brain injury in rats was associated with improved functional and cognitive performance 5 days after trauma, while post-treatment after the trauma had no effect [25].

**Other volatile anesthetics**

Similar to isoflurane, sevoflurane pretreatment recently was shown to induce ischemia tolerance. One MAC of sevoflurane for 30 min applied 15 min before cardiac arrest (acute), or for 30 min on four consecutive days 24 h before arrest (chronic) reduced neuronal death in hippocampal slices harvested 7 days later [26]. The mechanism responsible is unclear, but may involve opening of ATP-dependent potassium channels [26].

Halothane and desflurane have also been shown to possess neuroprotective effects. Both agents reduced infarct size 24 h after 2 h of transient focal cerebral ischemia in rats when applied during ischemia at 1.5 MAC, as compared with the awake state. Infarct reduction by desflurane was more pronounced than by halothane, which was attributed by the authors to a more pronounced decrease in sympathetic tone than can be achieved by desflurane [27].

**Xenon**

Xenon’s anesthetic properties are thought to be mediated in part through NMDA receptor blockade and, accordingly, xenon was shown to have neuroprotective potential [28*]. Seventy percent inhaled xenon during 60 min of focal cerebral ischemia in mice improved neurologic
function and decreased infarct size at 24 h of reperfusion, as compared with 70% nitrous oxide [29]. Xenon can precondition against OGD in vitro and against hypoxia/ischemia in neonatal rats by CREB-mediated alteration of gene expression [30\textsuperscript{*}]. Posttreatment with xenon is also effective in reducing neuronal damage. Three hours of 50% inhaled xenon after 90 min of hypoxia–ischemia reduced damage 1 week after the insult in 7-day-old rats [13\textsuperscript{*}]. Subanesthetic doses of xenon add to the neuroprotective effects of hypothermia and appear to favorably affect the ratio of pro compared with antiapoptotic proteins after OGD in neuronal culture as well as after hypoxia–ischemia in neonatal rats [31\textsuperscript{*}].

**Barbiturates**

While the barbiturates were the first anesthetic agents widely used for perioperative neuroprotection, they became less popular when the focus of the field moved away from protection by reduction of energy consumption to receptor-mediated protection. Although it is now recognized that barbiturates can block glutamate receptors, potentiate GABA-ergic activity and inhibit calcium influx, similarly to other anesthetic agents [32\textsuperscript{**}], there is also strong evidence for a pronounced systemic immunosuppression by barbiturates, which increases the risk of infection [33,34]. This may contribute to the reduced research interest in this group of anesthetics.

**Propofol**

Propofol at doses resulting in burst-suppression reduced the number of dying neurons and positively affected the ratio of apoptosis-associated proteins following incomplete hemispheric [8]. In this model of mild ischemic injury, neuroprotection was sustained until 4 weeks after the insult [8]. While comparable doses in vitro (100 μM) reduced NMDA receptor response in cultured CA1 neurons and hippocampal slices, however, they failed to protect the CA1 region from OGD-induced cell death in a hippocampal slice preparation [35]. The discrepancy between the in-vivo and in-vitro findings is currently best explained by propofol’s potential to scavenge free radicals. While neuronal damage from transient cerebral ischemia is in part mediated by free radicals generated during early reperfusion, this mechanism may be less relevant in slice cultures [35]. In contrast to this, however, propofol could reduce infarct size 24 h after permanent middle artery occlusion in rats [36].

No clinical data exist that establish neuroprotection by propofol in humans. A small study [37] comparing propofol with isoflurane anesthesia during coronary artery bypass grafting (CABG) in 20 patients found no difference in neuropsychological performance early (days 3–6) after the intervention, and even saw a transient increase in serum S100B levels (a surrogate marker for neuronal damage) in the propofol group.

**Ketamine**

The neuroprotective potential of ketamine is attributed to its activity as an NMDA-receptor antagonist. A recent in-vitro study [38] showed that 100 μM ketamine during or after 1 h of OGD protected the cellular integrity (reduced LDH release) in striatal slices cultures, although it did not affect neurotransmitter release from these cells. Neuroprotection by ketamine has been described in a variety of different experimental settings, including transient focal and global, as well as permanent ischemia, traumatic brain injury, and in-vitro hypoxia/ischemia. Clinical studies [39\textsuperscript{**}] comparing ketamine sedation with fentanyl or sufentanil after traumatic brain injury, however, failed to find effects on functional outcome after 6 months. Similarly, the addition of S\textsuperscript{-}-ketamine to propofol/remifentanil anesthesia during open heart surgery in a clinical study [40] including 106 patients had no effects on neurobehavioral outcome tests one and 10 weeks after the intervention.

**Lidocaine**

Neuroprotection by lidocaine has been attributed to S\textsuperscript{-}-channel blockade. A recent in-vitro study [12] found that postinsult administration of lidocaine to hippocampal slice cultures reduces cell death after OGD. Another study [41] identified a reduction in infarct size 24 h after focal ischemia in rats that was associated with reduced early release of cytochrome c release and caspase-3 activation. Protection of hippocampal slices from OGD was associated with preservation of mitochondrial integrity [42].

**Neurotoxic effects of anesthetics**

While several lines of clear evidence suggest a distinct neuroprotective potential for various anesthetics, others have reported neurotoxic effects of the very same drugs. NMDA-receptor blockade during synaptogenesis in the immature brain can induce widespread neuronal degeneration [16], and it was suggested that NMDA-antagonistic anesthetics cause cerebral damage in neonates [17]. A recent study [43] on cultured rat forebrain neurons showed evidence of apoptotic cell death and increased expression of bax and the NR1 NMDA receptor subunit after 48 h of ketamine exposure. Ketamine also increased death in nonhuman primate forebrain cultures, which was associated with increased NFκB translocation [44].

Another recent study [18\textsuperscript{**}] adds new evidence to this discussion. Sixty minutes of isoflurane anesthesia (1.8% in oxygen) was found to induce severe hypoglycemia in 10-day-old mice, which was more pronounced after 60 min of hypoxia/ischemia. Isoflurane induced hypoglycemia in newborn mice is an interesting observation, as it may contribute to the neurodegeneration observed in newborn rodents after long-term (6–h) exposure to
volatile anesthetics [17]. These findings emphasize that complete monitoring and control of physiologic parameters, although technically challenging, is a necessary prerequisite if clinically meaningful results are to be obtained from these kinds of experiments [19,20**].

Recent evidence [45] suggests that lidocaine can also exert neurotoxic effects in animal and human spinal cord. This appears to be unrelated to Na+ channel blockade, but the precise mechanism remains unclear.

Conclusion

Recommending the use of a specific agent for the care of patients at risk for perioperative cerebral ischemia, or in the immediate postinjury period seems premature. Isoflurane appears to be the most promising candidate for a protective agent, but this may be a selection bias, as it is among the most commonly used and studied agents, both clinically and experimentally. Potential negative effects of isoflurane and ketamine in very young and elderly people require more careful study using appropriate, well controlled models. At this point, it seems reasonable to recommend that the anesthesia provider use standard evaluation to choose the anesthetic regimen that is most appropriate for the individual patient, judging by clinical status and co-morbidities. As always, anesthesiologists should strive to provide the best care possible, which may include using techniques they are familiar with, rather than choosing a regimen they are less comfortable with, based on less-than-convincing experimental data.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

** of special interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 579).


3 Winegar BD, Machtet MB. Isoflurane depresses hippocampal CA1 glutamate nerve terminals without inhibiting fiber volleys. BMC Neurosci 2006; 7:5.


Xenon posttreatment after hypoxia/ischemia in neonatal rats decreases neuronal damage 1 week after the insult.


16 Isoflurane preconditioning causes delayed tolerance against oxygen–glucose deprivation in hippocampal slices, which depends on phosphorylation of MAP kinase and activation of calmodulin.


19 Loepke AW, McCann JC, Kurth CD, McAuliffe JJ. The physiologic effects of isofoxane anesthesia in neonatal mice. Anesth Analg 2006; 102:75–80. This excellent study applied comprehensive physiological monitoring to 10-day-old mice undergoing isoflurane anesthesia and hypoxic–ischemic injury. Isoflurane anesthesia induced severe hypoglycemia and metabolic acidosis, and was associated with 100% mortality in spontaneously breathing animals during hypoxia–ischemia.


A recent excellent review that weighs the experimental evidence for neurotoxic effects of anesthetics in immature animals against the clinical evidence for benefits from anesthesia for painful procedures in very immature infants. The methodological shortcomings of several experimental studies are emphasized, and the developmental differences between rodents and humans that complicate translation of the experimental findings are summarized.


Brain protection by anesthetic agents Koerner and Brambrink 485
39 Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? Anesth Analg 2005; 101:524–534. This review emphasizes the tolerability of ketamine for neurologically impaired patients. A neuroprotective effect is likely, but was only found in studies with short-term outcome.
Cerebral protection

S. Fukuda1 and D. S. Warner1–3*

1Department of Anesthesiology, 2Department of Neurobiology and 3Department of Surgery, Duke University Medical Center, Box 3094, Durham, NC 27710, USA

*Corresponding author: Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA. E-mail: david.warner@duke.edu

Ischaemic/hypoxic insults to the brain during surgery and anaesthesia can result in long-term disability or death. Advances in resuscitation science encourage progress in clinical management of these problems. However, current practice remains largely founded on extrapolation from animal studies and limited clinical investigation. A major step was made with demonstration that rapid induction of mild sustained hypothermia in comatose survivors of out-of-hospital ventricular fibrillation cardiac arrest reduces death and neurological morbidity with negligible adverse events. This provides the first irrefutable evidence that outcome can be favourably altered in humans with widely applicable neuroprotection protocols. How far hypothermic protection can be extended to global ischaemia of other aetiologies remains to be determined. All available evidence suggests an adverse response to hyperthermia in ischaemic or post-ischaemic brain. Management of other physiological values can have dramatic effects in experimental injury models and this is largely supported by available clinical data. Hyperoxaemia may be beneficial in transient focal ischaemia but deleterious in global ischaemia. Hyperglycaemia causes exacerbation of most forms of cerebral ischaemia and this can be abated by restoration of normoglycaemia. Studies indicate little, if any, role for hyperventilation. There is little evidence in humans that pharmacological intervention is advantageous. Anaesthetics consistently and meaningfully improve outcome from experimental cerebral ischaemia, but only if present during the ischaemic insult. Emerging experimental data portend clinical breakthroughs in neuroprotection. In the interim, organized large-scale clinical trials could serve to better define limitations and efficacy of already available methods of intervention, aimed primarily at regulation of physiological homeostasis.

Keywords: brain, ischaemia; complications, cerebral ischaemia; recovery, neurological

Cerebral ischaemia/hypoxia can occur in a variety of perioperative circumstances. Outcomes from such events range from sub-clinical neurocognitive deficits to catastrophic neurological morbidity or death. Although certain surgical procedures present greater risk for ischaemic/hypoxic brain injury, most insults are not presaged but instead arise as unintended complications of either the surgical procedure or the anaesthetic.

It has been the investigative interest of surgeons and anaesthesiologists to reduce perioperative brain injury for more than 60 yr.12 Classically, such intervention has been categorized as either neuroprotection or neuroresuscitation. Neuroprotection was defined as treatment initiated before onset of ischaemia, intended to modify intra-ischaemic cellular and vascular biological responses to deprivation of energy supply so as to increase tolerance of tissue to ischaemia resulting in improved outcome. Neuroresuscitation, in contrast, implied treatment begun after the ischaemic insult had occurred with the intent of optimizing reperfusion.

However, it has become increasingly clear that an ischaemic/hypoxic insult does not simply constitute energy failure with consequent interruption of ongoing metabolic events. Indeed this does occur. In addition, though, ischaemia and hypoxia stimulate active responses in the brain, which persist long after substrate delivery has been restored. These responses include activation of transcription factors which up-regulate expression of genes contributing to apoptosis and inflammation, inhibition of protein synthesis, sustained oxidative stress, and neurogenesis. Although some of these responses may have a teleological advantage [e.g. elimination of dead or dysfunctional tissue or increased tolerance to a subsequent insult (preconditioning)], most responses aggravate damage caused by the primary insult. Consequently, the concept that neuroprotection can be extended well into the reperfusion phase seems appropriate, albeit with different targets other than preservation of energy stores. This possibility may, in part, explain the efficacy of various experimental post-ischaemic interventions, which have manifested either as
clinically available therapies (e.g. mild hypothermia) or instead as promising candidates for future clinical use targeting events, such as oxidative stress, apoptosis, and neurogenesis.

The above logic is presented as a taste of where we are going with investigations aimed at ameliorating long-term improvement from an ischaemic/hypoxic insult that may occur in the perioperative period. However, the rest of this article will focus on the opportunities and limitations of currently available interventions (Table 1).

### Anaesthetics

#### Barbiturates

It has been postulated for more than 50 yr that anaesthetics increase the tolerance of brain to an ischaemic insult.28 The logic is simple. Most drugs selected to be anaesthetics suppress neurotransmission. This suppression reduces energy requirement, and reduction in energy requirement should allow tissue better to preserve energy balance during a transient interruption of substrate delivery. Since adenosine triphosphate (ATP) synthesis recovers rapidly after restoration of substrate delivery, anaesthetics would be expected to be protective if present during ischaemia but not if given after restoration of substrate delivery. It would also follow that efficacy of an anaesthetic is dependent upon the severity of the ischaemic insult. If the insult were sufficiently severe to cause loss of all electrical activity, there would be no activity for anaesthetics to suppress and thus no mechanism for such drugs to increase tolerance to ischaemia. In contrast, in less severe insults, suppression of activity by the anaesthetic before onset of ischaemia should delay decay of ATP concentrations and thus also delay loss of ionic gradients and calcium influx.

Many studies have supported this logic. Indeed, during abrupt onset of hypoxaemia, barbiturates and isoflurane slow deterioration of ATP concentrations.43 48 Furthermore, post-ischaemic treatment with either barbiturates or volatile anaesthetics has no effect on outcome.1 59 Surprisingly, irrefutable data supporting efficacy of pre-treatment with anaesthetics have proved difficult to acquire.

Early work testing intra-ischaemic anaesthetic efficacy was confounded by poor physiological control of experimental subjects. It was recognized later in the evolution of anaesthetic efficacy studies that factors such as blood glucose, brain temperature, and perfusion pressure were important determinants of ischaemic outcome and that anaesthetics independently modulated these factors. In addition, early studies typically compared one anaesthetic against another. The assumption was that the ‘control’ anaesthetic was not protective and thus failure to improve outcome by the ‘test’ anaesthetic indicated lack of a protective state. However, little work was done to confirm that the ‘control’ anaesthetic was not protective. Subsequent studies, which became feasible as experimental models evolved, often found considerable protection from the ‘control’ anaesthetic when compared with an awake state.

Thus, the field remained confused for more than a decade and insufficient data were generated to warrant human trials of anaesthetic efficacy when employed intraoperatively. Even then, the early results were mixed. One

| Table 1 Evidence-based status of plausible interventions to reduce perioperative ischaemic brain injury. ++, Repeated physiologically controlled studies in animals/randomized, prospective, adequately powered clinical trials; +, consistent suggestion by case series/retrospective or prospective small sample size trials, or data extrapolated from other paradigms; −/+ , inconsistent findings in clinical trials; may be dependent on characteristics of insult; −, well-defined absence of benefit; −−, absence of evidence in physiologically controlled studies in animals/randomized, prospective, adequately powered clinical trials; −−−, evidence of potential harm; *, out-of-hospital ventricular fibrillation cardiac arrest |
|---|---|---|---|---|---|
| Intervention | Pre-ischaemic efficacy in experimental animals | Post-ischaemic efficacy in experimental animals | Pre-ischaemic efficacy in humans | Post-ischaemic efficacy in humans | Sustained protection in experimental animals | Sustained protection in humans |
| Moderate hypothermia | ++ | ++ | −/+ | ++* | ++ | ++ |
| Mild hyperthermia | | | | | | |
| Hyperventilation | | | | | | |
| Normoglycaemia | ++ | − | + | + | ++ | − |
| Hyperbaric oxygen | ++ | − | − | −/+ | − | − |
| Barbiturates | ++ | − | + | − | − | − |
| Propofol | ++ | − | + | − | − | − |
| Etomidate | | | | | | |
| Nitrous oxide | | | | | | |
| Isoflurane | ++ | − | − | − | ++ | − |
| Sevoflurane | | | | | | |
| Desflurane | ++ | − | − | − | − | − |
| Lidocaine | ++ | − | − | − | − | − |
| Ketamine | ++ | − | − | − | − | − |
| Glucocorticoids | | | | | | |
study found efficacy from thiopental when given in cardiac surgical patients, whereas another did not.\textsuperscript{50, 67} However, only short-term outcomes were assessed, which prevented assessment of the full evolution of the ischaemic injury. Furthermore, surgical procedures and cardiopulmonary bypass conditions were markedly different between the two trials. Numerous other explanations have been offered, but perhaps the overall potency of barbiturates as neuroprotective agents is weak in the face of severe ischaemic insults.\textsuperscript{65}

One problem with barbiturates is their prolonged duration of action. It was believed that optimal protection would be present only when massive doses were administered to abolish electroencephalographic (EEG) activity, thereby eliciting maximal suppression of cerebral metabolic rate (CMR) before onset of the insult. Some practitioners still adhere to this principle when using barbiturates to protect the brain but such large doses can markedly delay anaesthesia emergence, which has limited their clinical application. Although it is unlikely that these massive doses are necessary to obtain maximal efficacy,\textsuperscript{65} recognition that volatile anaesthetics can also produce EEG isoelectricity at doses which still allow rapid anaesthesia emergence was greeted with optimism because such compounds could be more widely applied in clinical settings.

\textbf{Volatile anaesthetics}

The efficacy of volatile anaesthetics as neuroprotective agents has undergone more than 30 yr of scrutiny and still no human outcome trials have been conducted to guide clinical practice. We know the following facts from the laboratory. Volatile anaesthetics provide major improvement in ischaemic outcome. The dose required to obtain this protection is within a clinically relevant range, with higher doses potentially worsening outcome.\textsuperscript{36} Volatile anaesthetics protect against both focal (e.g. obstruction of flow distal to the circle of Willis) and global (e.g. complete cessation of blood flow to the brain or forebrain) ischaemia. However, the improvement in outcome is transient in global ischaemia,\textsuperscript{23} whereas it is persistent in focal ischaemia.\textsuperscript{58} Sevoflurane has also been shown to provide long-term protection in one experimental model.\textsuperscript{51} The mechanism by which volatile anaesthetics protect is, in part, attributable to suppression of energy requirements.\textsuperscript{47} Both inhibition of excitatory neurotransmission and potentiation of inhibitory receptors are likely to be involved.\textsuperscript{15, 22, 30} It is also likely that volatile anaesthetics have other important effects that include regulation of intracellular calcium responses during ischaemia,\textsuperscript{29} and activation of TREK-1 two-pore-domain K\textsuperscript{þ} channels.\textsuperscript{25}

Although a great deal has been learned from the laboratory, in the absence of human outcome data, it cannot be stated that volatile anaesthetics improve outcome from perioperative ischaemic insults. However, if an anaesthetic is required for a surgical procedure, inclusion of volatile anaesthetics can be considered. Isoflurane and sevoflurane carry the largest data set to this decision. Desflurane also offers promise,\textsuperscript{33, 38} but has been insufficiently studied to determine whether it should be equally considered in this class of potential neuroprotective compounds.

\textit{Other anaesthetics}

Other anaesthetics possess properties that suggest potential for intra-ischaemic neuroprotection. These include propofol, etomidate, and lidocaine. Study of these drugs has not been as extensive as for either barbiturates or volatile anaesthetics. The principle feature of propofol and etomidate is suppression of CMR by inhibition of synaptic activity.\textsuperscript{19, 35} Propofol may also have free radical scavenging and anti-inflammatory properties.\textsuperscript{57} Propofol appears unique among anaesthetics in the laboratory setting because it offers efficacy with post-ischaemic therapy onset, although such treatment provides only transient protection.\textsuperscript{9} Propofol appears to offer efficacy similar to barbiturates but a dose-dependent study of its efficacy has not been completed, leaving little guidance for potential clinical use. Furthermore, propofol infused to induce EEG burst suppression failed to improve outcome in cardiac valve surgery patients.\textsuperscript{56} Etomidate, although initially heralded as a substitute for barbiturates,\textsuperscript{4} has never met rigorous evaluation for neuroprotective properties. In fact, some work has indicated that etomidate may paradoxically exacerbate ischaemic injury by inhibiting nitric oxide synthase, thereby intensifying the ischaemic insult.\textsuperscript{21} As a result of this and other studies, the use of etomidate for neuroprotection has fallen out of favour in clinical settings.

Lidocaine also suppresses CMR, but this effect is only meaningful at doses beyond those typically employed in clinical environments. Numerous laboratory studies have found efficacy for lidocaine, with perhaps its principle mechanism of action relating to inhibition of apoptosis.\textsuperscript{39} The efficacy of lidocaine appears dependent on dose, with doses in the range used to manage cardiac dysrhythmias having greatest efficacy.\textsuperscript{61} There have been no long-term outcome studies of lidocaine efficacy in experimental stroke. One small human trial found benefit from low-dose lidocaine infusion during cardiac surgery on long-term neuropsychological impairment.\textsuperscript{44} Lidocaine should be further evaluated for neuroprotective properties since its use is supported by a litany of laboratory successes such as short-duration of action and ease of use. However, because it has not been evaluated in a large-scale clinical trial, efficacy in clinical environments remains speculative.

Ketamine offers potent inhibition of glutamatergic neurotransmission at the N-methyl-D-aspartate (NMDA) receptor. There is a long history of NMDA receptor antagonists as potential neuroprotective agents but, overall, such compounds offer little or no protection against global
insults. Protection against focal insults is substantial, but only if the drug is given before ischaemia onset. Because ketamine is clinically available, it is tempting to argue that it should be considered when a focal ischaemic insult is anticipated. To date, however, there are no human data supporting this practice. Little is also known about dose–response properties, even in animals. Thus, it is difficult to recommend ketamine for the purposes of neuroprotection in the clinical environment at this time.

**Physiological management**

**Temperature**

Hypothermia has been proposed to offer therapeutic benefit for more than 60 yr. Early investigators examined its effects in both neurosurgery and cardiac surgery patients. In the same era, it was also considered to offer benefit in survivors of cardiac arrest and hypoxic insults.

It remains unclear why hypothermia fell out of favour in subsequent decades. One factor may have been its apparent lack of efficacy, which reduced enthusiasm for the logistical issues necessary routinely to cool and re-warm a large patient population. Another factor may have been the influence of mechanistic studies conducted in the laboratory. That work examined effects of hypothermia on brain energy metabolism and found hypothermia to reduce CMR in a temperature-dependent fashion, which became the presumed mechanism of action. The most impressive effects on CMR were at very low temperatures, and those temperatures required use of cardiopulmonary bypass. The effects of mild (32–35°C) hypothermia on CMR were negligible. In contrast, barbiturate rates can reduce CMR by 50–60% without the use of cardiopulmonary bypass and were therefore viewed as having a greater potential benefit. Perhaps for those reasons, the use of perioperative hypothermia persisted only in the context of caring for some cardiac surgical patients.

There is no doubt that deep hypothermia (e.g. 18–22°C) is highly neuroprotective. We know that only a few minutes of complete global ischaemia will cause neuronal death in normothermic brain. This has been best examined in the laboratory, but human evidence is consistent with those findings. In contrast, it is widely observed that induction of deep hypothermia before circulatory arrest routinely allows the brain to tolerate intervals of no-flow exceeding 40 min, and substantially greater intervals of arrest with complete or near-complete neurological recovery are frequently reported. As a result of this *prima facie* evidence, the efficacy of deep hypothermia has not been subjected to randomized controlled trials. However, there is still much to be learned with respect to optimizing cooling and re-warming methods, optimal magnitude of hypothermia, determination of brain temperature using surrogate sites, and defining within individual patients when the duration of circulatory arrest approaches the limits of deep hypothermic neuroprotection.

The story might have ended there had it not been for several laboratory studies that ignored the CMR hypothesis. Those studies re-visited the possibility that mild hypothermia could protect the brain against ischaemia insults. To most people’s surprise, reduction in brain temperature by only a few degree Celsius provided major protection. These findings stimulated numerous clinical trials in both adults and newborns, which have since provided a scientific basis defining the opportunities and limitations of using off-bypass hypothermia to provide meaningful neuroprotection.

The first reported work related to traumatic brain injury (TBI). Three pilot studies provided suggestive evidence that mild hypothermia improved either brain physiology or outcome. However, those studies employed small sample sizes and more definitive evidence was needed. Thus, a large-scale prospective human trial was conducted, but disappointing results were obtained. Cooling TBI patients within the first several hours after injury failed to improve outcome. The design and conduct of this trial have been vigorously debated but what is clear is that induced hypothermia is not a panacea for TBI. If it is proven effective in later trials, it will probably be shown to have efficacy only in certain patient populations and only when conducted with specific protocols. Such work is ongoing.

If the TBI study had been performed in isolation, perhaps off-bypass hypothermia would have been abandoned in the clinic again. However, other studies were already underway, two of which markedly altered the mood of the investigative community. Both studies were reported simultaneously and used similar experimental designs wherein comatose survivors of out-of-hospital cardiac arrest were randomized to normothermia or mild hypothermia, which involved rapid surface cooling as soon as spontaneous circulation was restored. Both studies found significantly more patients with good outcome in the hypothermia group and negligible adverse events. Finally, convincing evidence is available that off-bypass hypothermia can appreciably improve outcome from at least cardiac arrest in humans.

These findings have prompted publication of guidelines recommending that comatose survivors of out-of-hospital cardiac arrest undergo cooling after restoration of spontaneous circulation. The extent to which the efficacy of induced hypothermia can be extrapolated to other conditions of cardiac arrest (loss of airway, asphyxia, and drowning) may never be known given the sporadic and relatively rare nature of those events. However, such intervention may be considered.

In addition, there is an increasing evidence that peripartum neonatal asphyxial brain injury favourably responds to treatment with hypothermia. Two trials have been reported. The first employed selective head cooling and
could only find a beneficial effect of hypothermia in a subset of the study population. The second employed total body cooling. In this study, the benefit of induced mild hypothermia was clear. Despite this, some feel additional trials are required before such intervention can be widely advocated.

In the course of defining hypothermia efficacy, it has also become apparent that hyperthermia has adverse effects on post-ischaemic brain. Spontaneous post-ischaemic hyperthermia is common and, in animals, intra-ischaemic or even delayed post-ischaemic hyperthermia dramatically worsens outcome. Spontaneous hyperthermia has also been associated with poor outcome in humans. These facts provide sufficient evidence to advocate frequent temperature monitoring in patients with cerebral injury (and those at risk for cerebral injury). Aggressive treatment of hyperthermia should be considered.

**Glucose**

Glucose is a fundamental substrate for brain energy metabolism. Deprivation of glucose in the presence of oxygen can result in neuronal necrosis, but the presence of glucose in the absence of oxygen carries a worse fate. The mechanistic basis for this dichotomy remains unclear. The most persistent hypothesis is that glucose, in the absence of oxygen, undergoes anaerobic glycolysis resulting in intracellular acidosis, which amplifies the severity of other deleterious cascades initiated by the ischaemic insult. Many animal studies have demonstrated adverse effects of hyperglycaemia from a wide variety of brain insults. Human studies remain principally correlative in nature, that is, patients having worse outcomes from stroke, TBI, etc. also tend to have higher blood glucose concentrations on hospital admission. For some time, it was unclear whether admission hyperglycaemia simply represented a stress response to the brain insult, or instead was contributing to a worsened injury. The animal data clearly favour the latter interpretation. More importantly, human research has demonstrated more rapid expansion of ischaemic lesions in hyperglycaemic, compared with normoglycaemic patients. In addition, there is accumulating evidence that regulation of blood glucose yields a higher incidence of good outcome in stroke patients. For all of these reasons, it is rational to maintain normoglycaemia in all patients at risk for, or recovering from acute brain injury.

**Arterial carbon dioxide partial pressure (Paco2)**

Because cerebral blood flow and Paco2 are linearly related within physiologically relevant ranges, hyperventilation had become an entrenched practice in cerebral resuscitation. Reduction in Paco2 was presumed to augment cerebral perfusion pressure favourably by reducing the cross-sectional diameter of the arterial circulation and thus cerebral blood volume. This would offset increases in intracranial pressure. Although the logic behind this practice can be appreciated, in fact, it is contradicted by direct examination of cerebral well being. The most salient evidence is derived from TBI investigations. These studies support a different concept, that being worsening of perfusion by hyperventilation-induced vasoconstriction in ischaemic tissue. Indeed, the volume of ischaemic tissue, elegantly assessed with positron emission tomography in TBI patients, was markedly increased when moderate hypocapnia was induced. This is consistent with the only prospective trial of hyperventilation on TBI outcome, which observed a decreased number of patients with good or moderate disability outcomes when chronic hyperventilation was employed. It remains unevaled whether acute hyperventilation improves outcome from pending transtentorial herniation or when rapid surgical decompression of a haematoma (e.g. epidural) is anticipated. Within the context of focal ischaemic stroke, clinical trials have found no benefit from induced hypocapnia, although hyperventilation is sometimes employed in cases of refractory brain oedema. Use of hyperventilation during cardiopulmonary resuscitation may serve to increase mean intrathoracic pressure thereby decreasing perfusion pressure and is not advocated. Consequently, there are few data to support use of hyperventilation in the context of cerebral resuscitation.
delivery after restoration of spontaneous circulation, so as to maintain pulse oximeter values within the range of 94–96, optimized short-term neurological outcome.7 These compelling data should serve as a stimulus for a randomized clinical trial and stimulates re-consideration of the necessity for hyperoxaemia in the early post-resuscitation interval.

Steroids

Steroids such as dexamethasone reduce oedema surrounding brain tumours. Beyond that, evidence for benefit from the use of steroids is weak. Evidence that methylprednisolone improves outcome from acute spinal cord trauma is controversial,13 but some surgeons have extended this observation to intraoperative use in spinal cord surgery. There is insufficient evidence to define the role of glucocorticoids in focal ischaemic stroke.64 A large retrospective analysis found no benefit from glucocorticoid treatment in patients with cardiac arrest.34 In fact, there is animal evidence that such glucocorticoids exacerbate injury from global ischaemia by increasing plasma glucose concentration.66 Given the potential adverse effects of steroids and lack of demonstrable efficacy in ischaemic brain, their use cannot be advocated.

Conclusion

Ischaemic brain injury remains a potentially devastating disorder, although progress is being made in resuscitation science. Two key advances occurred in the past decade. The first was repeated demonstration that induced mild hypothermia reduces neurological morbidity and mortality associated with out-of-hospital ventricular fibrillation cardiac arrest. Beyond the immediate potential to apply this intervention is the larger message that post-ischaemic intervention can favourably influence outcome in humans. The second advance was recognition that efficacy of mild hypothermia depends at least in part upon the type of ischaemic lesion being treated. Trauma and focal ischaemia could not be shown to be amenable to hypothermic intervention, at least within the bounds of the clinical trial protocols employed.

Other than the use of mild hypothermia for ventricular fibrillation cardiac arrest, practice of clinical neuroprotection rests on extrapolation from animal studies and weak clinical trials. Review of these data allows some recommendations to be made (Table 2). Such recommendations are likely to be advanced with increased understanding of cellular responses to ischaemia and appropriately conducted clinical trials.

References

3 Part 7.5: Postresuscitation support. Circulation 2005; 112: IV84–8

Table 2 Considerations when anticipating or managing a perioperative ischaemic insult

| Assurance of absence of hyperthermia |
| Manage blood glucose with insulin to induce normoglycaemia |
| Optimize haemoglobin-oxygen saturation (increasing concern that hyperoxaemia may be adverse in global ischaemia) |
| Establish normocapnia |
| Consider the use of volatile anaesthetics if surgery ongoing (consistent sustained benefit in experimental animal studies, reversible allowing neurological examination, human trials not performed) |
| Resist the use of glucocorticoids (no evidence of efficacy, preclinical evidence of adverse effect in global ischaemia) |
| Consider the use of volatile anaesthetics if surgery ongoing (consistent sustained benefit in experimental animal studies, reversible allowing neurological examination, human trials not performed) |
| but supported by consistent evidence of efficacy when used in out-of-hospital ventricular fibrillation cardiac arrest) |


This talk will outline the roles of the Anesthesiologist in the Interventional Neuroradiology (INR) suite with an emphasis on management strategies to prevent complications and minimize their effects if they occur. We will discuss fundamental management principles of affording "protection," of which direct pharmacological protection is perhaps the least important. Planning the anesthetic and perioperative management is predicated on understanding the goals of the therapeutic intervention and anticipating potential problems. Endovascular neurosurgery / INR is firmly established in the management of cerebrovascular disease, most notably in the management of intracranial aneurysms. For the overall management approach to the patient with cerebrovascular disease, there is accelerating interest and discussion in appropriate management of asymptomatic or unruptured lesions.

There are several anesthetic concerns that are particularly important for INR procedures, including: (1) maintaining immobility during the procedure to facilitate imaging; (2) rapid recovery from anesthesia at the end of the case to facilitate neurological examination and monitoring, or provide for intermittent evaluation of neurological function during the procedure; (3) managing anticoagulation; (4) treating and managing sudden unexpected procedure-specific complications during the procedure, i.e., hemorrhage or vascular occlusion, which may involve manipulating systemic or regional blood pressures; (5) guiding the medical management of critical care patients during transport to and from the radiology suites; (6) self-protection issues related to radiation safety.

PRE-OPERATIVE PLANNING AND PATIENT PREPARATION
Baseline blood pressure and cardiovascular reserve should be assessed carefully. This almost axiomatic statement is particularly important for several reasons. Blood pressure manipulation is commonly required and treatment-related perturbations should be anticipated. Therefore, a clear sense of "where the patient lives" needs to be established. One must keep in mind that "autoregulation" as presented in the textbooks is a description of a population; individual patients are likely to vary considerably, a concept based on the historical observations that underlie our modern notions of autoregulatory behavior. In those cases where intra-arterial catheters are used, the concordance between blood pressure cuff and intra-arterial readings needs to be considered; pre-operative blood pressure range is likely to be known through blood pressure cuff values.

Pre-operative calcium channel blockers for prophylaxis for cerebral ischemia may be used and can affect hemodynamic management. In addition, these agents or trans-dermal nitroglycerin are sometimes used to lessen the incidence of catheter-induced vasospasm.

For cases managed with an unsecured airway, routine evaluation of the potential ease of laryngoscopy in an emergent situation should take into account that direct access to the airway may be limited by table or room logistics. Recent pterional craniotomy can sometimes result in impaired tempomandicular joint mobility.

For i.v. sedation cases, careful padding of pressure points and working with the patient to obtain final comfortable positioning may assist in the patient’s ability to tolerate a long period of lying supine and motionless, decreasing the requirement for sedation, anxiolysis, and analgesia. The possibility of pregnancy in female patients and a history of adverse reactions to radiographic contrast agents should be explored.

Secure intravenous (iv) access should be available with adequate extension tubing to allow drug and fluid administration at maximal distance from the image intensifier during fluoroscopy. Access to intravenous or arterial catheters can be difficult when the patient is draped and the arms are restrained at the sides; connections should be secure. Infusions of anticoagulant, primary anesthetics or vasoactive agents should be through proximal ports with minimal dead space.

In addition to standard monitors, capnography sampling via the sampling port of nasal cannula is useful for i.v. sedation cases. A pulse oximeter probe can be placed on the great toe of the leg that will receive the femoral introducer sheath to provide an early warning of femoral artery obstruction or distal thromboembolism. For intracranial procedures and post-operative care, beat-to-beat arterial pressure monitoring and blood sampling can be facilitated by an arterial line. A side port of the femoral artery introducer sheath can be used, but the sheath is usually removed immediately after the procedure. In a patient who requires continuous blood pressure monitoring post-operatively or frequent blood sampling, it is convenient to have a separate radial arterial blood pressure catheter. Using a co-axial or tri-axial catheter system, arterial pressure at the carotid artery, vertebral artery, and the
distal cerebral circulation can be measured. Pressures in these distal catheters usually underestimate systolic and overestimate diastolic pressure; however, mean pressures are reliable. Bladder catheters assist in fluid management as well as patient comfort. A significant volume of heparinized flush solution and radiographic contrast is used.

Radiation Safety is a critical part of pre-operative planning. It is probably reasonable to assume that the x-ray machine is always on. There are three sources of radiation in the INR suite: direct radiation from the X-ray tube, leakage (through the collimator's protective shielding), and scattered (reflected from the patients and the area surrounding the body part to be imaged). A fundamental knowledge of radiation safety is essential for all staff members working in an INR suite. The amount of exposure decreases proportionally to the inverse of the square of the distance from the source of radiation (inverse square law). Digital subtraction angiography (DSA) delivers considerably more radiation than fluoroscopy.

Optimal protection would dictate that all personnel should wear lead aprons, thyroid shields, and radiation exposure badges. The lead aprons should be periodically evaluated for any cracks in the lead lining that may allow accidental radiation exposure. Movable lead glass screens may provide additional protection for the anesthesia team. Clear communication between the INR and anesthesia teams is also crucial for limiting radiation exposure. With proper precautions the anesthesia team should be exposed to far less than the annual recommended limit for health care workers (see URL http://pdg.lbl.gov/).

ANESTHETIC TECHNIQUE
Choice of Anesthetic Technique
Most centers routinely involved use general endotracheal anesthesia for aneurysm coiling and endovascular treatment of vasospasm. Choice of anesthetic technique varies between centers with no clear superior method.

General Anesthesia
A primary reason for employing general anesthesia is to minimize motion artifacts and to improve the quality of image. Relative normocapnia or modest hypocapnia consistent with the safe conduct of positive pressure ventilation should be maintained unless intracranial pressure is a concern. The specific choice of anesthesia may be guided primarily by other cardio- and cerebrovascular considerations. Total intravenous anesthetic techniques, or combinations of inhalational and intravenous methods, may optimize rapid emergence. To date, pharmacological protection against ischemic injury during neurosurgical procedures has not been proven. A theoretical argument could be made for eschewing the use of N2O because of the possibility of introducing air emboli into the cerebral circulation and reports that it worsens outcome after experimental brain injury.

Intravenous Sedation
Intravenous sedation in aneurysm management is used most often for patients coming for interim follow-up angiography to assess the necessity for retreatment after primary coiling. If further treatment is indicated, the technique can be converted to a general anesthetic. Goals of anesthetic choice for intravenous sedation are to alleviate pain, anxiety, and discomfort, provide patient immobility and allow rapid recovery. There may be a discomfort associated with injection of contrast into the cerebral arteries (burning) and with distention or traction on them (headache). A long period of lying can cause significant discomfort.

A variety of sedation regimens are available, and specific choices are based on the experience of the practitioner and the goals of anesthetic management. Common to all intravenous sedation techniques is the potential for upper airway obstruction. Placement of nasopharyngeal airways may cause troublesome bleeding in anticoagulated patients and is generally avoided.

Dexmetetomidine is a new agent that may have applicability in the setting of INR. It is a potent, selective alpha2-agonist with sedative, anxiolytic, and analgesic properties, with recent regulatory approval for sedation. Dexmedetomidine is especially noteworthy for its ability to produce a state of patient tranquility without depressing respiration. However, there are two caveats to consider. First, there are still unclear effects on cerebral perfusion. More importantly, there is a tendency for patients managed with dexmedetomidine to have relatively low blood pressure in the post-anesthesia recovery period. Because patients with aneurismal subarachnoid hemorrhage may be critically dependent on adequate collateral perfusion pressure, use of regimens that may result in blood pressure decreases should be used with great caution.
ANTICOAGULATION

Heparin:
Careful management of coagulation is required to prevent thromboembolic complications during and after the procedure. Generally, after a baseline activated clotting time (ACT) is obtained, intravenous heparin (70 units/kg) is given to a target prolongation of 2 ~ 3 times of baseline. Then heparin can be given continuously or as an intermittent bolus with hourly monitoring of ACT. Occasionally, a patient may be refractory to attempts to obtain adequate anticoagulation. Switching from bovine to porcine heparin or vice versa should be considered. If antithrombin III deficiency is suspected, administration of fresh frozen plasma may be necessary.

Direct Thrombin Inhibitors:
Heparin-induced thrombocytopenia (HIT) is a potentially devastating prothrombotic syndrome caused by heparin dependent antibodies after exposure. Direct thrombin inhibitors may be used in patients with or at risk of HIT, although they entail their own risks, including a small risk of anaphylaxis. They inhibit thrombin both in the free form or bound to the clot. Monitoring of action is done by measuring the aPTT, or ACT. Lepirudin is FDA-approved for anticoagulation in patients with HIT. The half-life of lepirudin is 40 to 120 minutes, and it undergoes renal elimination. For HIT patients with renal impairment, Argatroban, predominantly metabolized in the liver, may be preferrable. Bivalirudin, a synthetic derivative of lepirudin, has a short half-life of about 25 minutes. Since bivalirudin is partially renally eliminated, dose adjustments may be needed in patients with renal dysfunction. A recent report described bivalirudin as a potential alternative during INR procedures to heparin for intravenous anticoagulation and intra-arterial thrombolysis.10

Antiplatelet agents:
Antiplatelet agents (aspirin, the glycoprotein IIb/IIIa receptor antagonists and the thienopyridine derivatives) are increasingly being used for cerebrovascular disease management, as well as rescue from thromboembolic complications.11,12 Activation of the platelet membrane glycoprotein (GP) IIb/IIIa leads to fibrinogen binding and is a final common pathway for platelet aggregation. Abciximab, eptifibatide and tirofiban are glycoprotein IIb/IIIa receptor antagonists. The long duration and potent effect of Abciximab also increase the likelihood of major bleeding. The smaller molecule agents, eptifibatide and tirofiban, are competitive blockers and have a shorter half-life (about 2 hours). Thienopyridine derivatives (ticlopidine and clopidogrel) bind to the platelet’s ADP receptors and permanently alter the receptor; therefore, the duration of action is the life span of the platelet. The addition of clopidogrel to the antiplatelet regimen is used when stent-assisted coiling is anticipated, and also for management of unruptured aneurysms.

Reversal of Anticoagulation:
At the end of the procedure or at occurrence of hemorrhagic complication, heparin may be reversed with protamine. Since there is no specific antidote for the direct thrombin inhibitors or the antiplatelet agents, the biological half-life is one of the major considerations in drug choice and platelet transfusion is a non-specific therapy, should reversal be indicated. There is no currently available accurate test to measure platelet function in patients taking the newer antiplatelet drugs. Desmopressin (DDAVP) has been reported to shorten the prolonged bleeding time of individuals taking antiplatelet agents such as aspirin and ticlopidine. There are also increasing recent reports on using specific clotting factors, including recombinant factor VIIa and factor IX complex, to rescue severe life-threatening bleeding, including intracranial hemorrhage uncontrolled by standard transfusion therapy. The safety and efficacy of these coagulation factors remain to be investigated.

DELIBERATE HYPERTENSION
During acute arterial occlusion or vasospasm, the only practical way to increase collateral blood flow may be an augmentation of the collateral perfusion pressure by raising the systemic blood pressure. The Circle of Willis is a primary collateral pathway in cerebral circulation. However, in as many as 21% of otherwise normal subjects, the circle may not be complete. There are also secondary collateral channels that bridge adjacent major vascular territories, most importantly for the long circumferential arteries that supply the hemispheric convexities. These pathways are known as the pial-to-pial collateral or leptomeningeal pathways.

The extent to which the blood pressure has to be raised depends on the condition of the patient and the nature of the disease. Typically, during deliberate hypertension the systemic blood pressure is raised by 30-40% above the baseline, in the absence of some direct outcome measure such as resolution of ischemic symptoms or imaging evidence of improved perfusion. Phenylephrine is usually the first line agent for deliberate hypertension and is
titrated to achieve the desired level of blood pressure. The risk of causing hemorrhage into the ischemic area must be weighed against the benefits of improving perfusion, but augmentation of blood pressure in the face of acute cerebral ischemia is probably protective in most settings.

DELIBERATE HYPOTENSION
The two primary indications for induced hypotension are: (1) to test cerebrovascular reserve in patients undergoing carotid occlusion, and (2) to slow flow in a feeding artery of BAVMs before glue injection. The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the patient physiologically stable. The choice of agent should be determined by the experience of the practitioner, the patient's medical condition, and the goals of the blood pressure reduction in a particular clinical setting. Intravenous adenosine has been used to induce transient cardiac pause and may be a viable method of partial flow arrest.13

MANAGEMENT OF NEUROLOGICAL AND PROCEDURAL CRISSES
A well thought-out plan, coupled with rapid and effective communication between the anesthesia and radiology teams, is critical for good outcomes. The primary responsibility of the anesthesia team is to preserve gas exchange and, if indicated, secure the airway. Simultaneous with airway management, the first branch in the decision-making algorithm is for the anesthesiologist to communicate with the INR team and determine whether the problem is hemorrhagic or occlusive.

In the setting of vascular occlusion, the goal is to increase distal perfusion by blood pressure augmentation with or without direct thrombolysis. If the problem is hemorrhagic, immediate cessation of heparin and reversal with protamine is indicated. As an emergency reversal dose, 1 mg protamine can be given for each 100 units of initial heparin dosage that resulted in therapeutic anticoagulation. The ACT can then be used to fine-tune the final protamine dose. Complications of protamine administration include hypotension, true anaphylaxis and pulmonary hypertension. With the advent of new long-acting direct thrombin inhibitors such as bivalirudin, new strategies for emergent reversal of anticoagulation will need to be developed.

Bleeding catastrophes are usually heralded by headache, nausea, vomiting and vascular pain related to the area of perforation. Sudden loss of consciousness is not always due to intracranial hemorrhage. Seizures, as a result of contrast reaction or transient ischemia, and the resulting post-ictal state can also result in an obtunded patient. In the anesthetized or comatose patient, the sudden onset of bradycardia and hypertension (Cushing response) or the endovascular therapist’s diagnosis of extravasation of contrast may be the only clues to a developing hemorrhage. Most cases of vascular rupture can be managed in the angiography suite. The INR team can attempt to seal the rupture site endovascularly and abort the procedure; a ventriculostomy catheter may be placed emergently in the angiography suite. Patients with suspected rupture will require emergent CT scan, but emergent craniotomy is usually not indicated.

SPECIFIC PROCEDURES
Intracranial Aneurysm Ablation
The two basic approaches for INR therapy of cerebral aneurysms are occlusion of proximal parent arteries and obliteration of the aneurysmal sac. With the publication of the ISAT trial,14 coil embolization of intracranial aneurysms has become a routine first choice therapy for many lesions. The anesthesiologist should be prepared for aneurysmal rupture and acute SAH at all times, either from spontaneous rupture of a leaky sac or direct injury of the aneurysm wall by the vascular manipulation. There is great interest in the development of stent-assisted coiling methods. The stent can provide protection of the parent vessel. Stent placement requires a greater degree of instrumentation and manipulation, probably increasing the ever-present intra-procedural risk of parent vessel occlusion, thromboembolism or vascular rupture.

Angioplasty of Cerebral Vasospasm from Aneurysmal SAH
Roughly 1 out of 4 patients with SAH will develop symptomatic vasospasm. Angioplasty, either mechanical (balloon) or pharmacological (intraarterial vasodilators), may be used as a treatment.15 Angioplasty is ideally done in patients that have already had the symptomatic lesion surgically clipped and for patients in the early course of symptomatic ischemia in order to prevent hemorrhagic transformation of an ischemia region. A balloon catheter is guided under fluoroscopy into the spastic segment and inflated to mechanically distend the constricted area. It is also possible to perform a “pharmacologic” angioplasty by direct intra-arterial infusion. There
is the greatest experience with papaverine, but there are potential CNS toxic effects. Other agents such as calcium channel blockers (nicardipine and verapamil) are being used. Intraarterial vasodilators may have systemic effects (bradycardia and hypotension).

Patients who come for angioplasty are often critically ill with a variety of challenging co-morbidities, including neurocardiac injury, volume overload from “triple-H” therapy, hydrocephalus, brain injury from recent craniotomy, and residual effects of the presenting hemorrhage. Procedural complications include arterial rupture, reperfusion hemorrhage, thromboembolism, and arterial dissection.

**Carotid Test Occlusion and Therapeutic Carotid Occlusion**

Large or otherwise unclippable aneurysms may be partly or completely treated by proximal vessel occlusion. In order to assess the consequences of carotid occlusion in anticipation of surgery, the patient may be scheduled for a test occlusion in which cerebrovascular reserve is evaluated in several ways. A multimodal combination of angiographic, clinical, and physiologic tests can be used to arrive at the safest course of action for a given patient’s clinical circumstances. The judicious use of deliberate hypotension can increase the sensitivity of the test. The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the patient physiologically stable. The choice of agent should be determined by the experience of the practitioner, the patient's medical condition and the goals of the blood pressure reduction in a particular clinical setting.

**Brain Arteriovenous Malformations (BAVMs)**

Also called cerebral or pial AVMs, these are typically large, complex lesions made up of a tangle of abnormal vessels (called the nidus) frequently containing several discrete fistulae served by multiple feeding arteries and draining veins. The goal of the therapeutic embolization is to obliterate as many of the fistulae and their respective feeding arteries as possible. BAVM embolization is usually an adjunct for surgery or radiotherapy.

The cyanoacrylate glues offer relatively “permanent” closure of abnormal vessels. Passage of glue into a draining vein can result in acute hemorrhage; in smaller patients, pulmonary embolism of glue can be symptomatic. For these reasons, deliberate hypotension may increase safety of glue delivery. Although less durable, polyvinyl alcohol microsphere embolization is also commonly used. If surgery is planned within days after PVA embolization, the rate of recanalization is low.

**Dural AVMs**

Dural AVM is considered an acquired lesion resulting from venous dural sinus stenosis or occlusion, opening of potential AV shunts, and subsequent recanalization. Symptoms are variable according to which sinus is involved. Venous hypertension of pial veins is a risk factor for intracranial hemorrhage. Dural AVMs may be fed by multiple meningeal vessels, and therefore, multi-staged embolization is often necessary. Dural AV fistulas can induce markedly increased venous pressure and decrease net cerebral perfusion pressure. Therefore, presence of venous hypertension should be factored into management of systemic arterial and cerebral perfusion pressure.

**Angioplasty and Stenting for Atherosclerotic Lesion**

Angioplasty and stenting for atherosclerosis for treatment of atherosclerotic disease involving the cervical and intracranial arteries continue to supplant open surgical management. Risk of distal thromboembolism is a major issue in this procedure. Catheter systems employing some kind of trapping system distal to the angioplasty balloon are being developed. There are multiple ongoing trials to compare the utility of stenting to carotid endarterectomy for extracranial carotid disease. It is likely that use of stenting will continue to increase as favorable data supporting its safety and efficacy emerge.

Preparation for anesthetic management may include placement of transcutaneous pacing leads, in case of severe bradycardia or asystole from carotid body stimulation during angioplasty. Intravenous atropine or glycopyrrolate may be also used in an attempt to mitigate against bradycardia, which almost invariably occurs to some degree with inflation of the balloon. This powerful chronotropic response may be difficult or impossible to prevent or control by conventional means. Adverse effects of increasing myocardial oxygen demand need to be considered in anti-bradycardia interventions.
Potential complications include vessel occlusion, perforation, dissection, spasm, thrombo-emboli, occlusion of adjacent vessels, transient ischemic episodes, and stroke. Similar to carotid endarterectomy, there is about a 5% risk of symptomatic cerebral hemorrhage and/or brain swelling after carotid angioplasty. Although the etiology of this syndrome is unknown, it has been associated with cerebral hyperperfusion, and it may be related to poor post-operative blood pressure control.

**Thrombolysis of Acute Thromboembolic Stroke**

In acute occlusive stroke, it is possible to recanalize the occluded vessel by superselective intra-arterial thrombolytic therapy. Thrombolytic agents can be delivered in high concentration by a microcatheter navigated close to the clot. Neurological deficits may be reversed without additional risk of secondary hemorrhage if treatment is completed within 4-6 hours from the onset of carotid territory ischemia and 24 hours in vertebrobasilar territory. One of the impediments in development in this area has been the fear of increasing the risk of hemorrhagic transformation of the acute infarction patient. Despite an increased frequency of early symptomatic hemorrhagic complications, treatment with intra-arterial pro-urokinase within 6 hours of the onset of acute ischemic stroke with MCA occlusion significantly improved clinical outcome at 90 days. Details of anesthetic management are reviewed elsewhere.

**POST-OPERATIVE MANAGEMENT**

Endovascular surgery patients pass the immediate post-operative period in a monitored setting, to watch for signs of hemodynamic instability or neurologic deterioration. Control of blood pressure may be necessary during transport and post-operative recovery, e.g., induced hypertension, if indicated. Abrupt restoration of normal systemic pressure to a chronically hypotensive (ischemic) vascular bed may overwhelm autoregulatory capacity and result in hemorrhage or swelling (normal perfusion pressure breakthrough, NPPB). In the absence of collateral perfusion pressure inadequacy, fastidious attention to preventing hypertension is warranted. Complicated cases may go first to CT or some other kind of tomographic imaging; critical care management may need to be extended during transport and imaging.

**References:**

Interventional neuroradiology—anesthetic considerations

Tomoki Hashimoto, MD\textsuperscript{a,d}, Dhanesh K. Gupta, MD\textsuperscript{a,d}, William L. Young, MD\textsuperscript{a,b,c,d,*}

\textsuperscript{a}Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94110, USA
\textsuperscript{b}Department of Neurological Surgery, University of California, San Francisco, CA 94110, USA
\textsuperscript{c}Department of Neurology, University of California, San Francisco, CA 94110, USA
\textsuperscript{d}Center for Cerebrovascular Research, University of California, San Francisco General Hospital, 1001 Potrero Avenue, Room 3C-38, San Francisco, CA 94110, USA

Interventional neuroradiology (INR) is a hybrid of traditional neurosurgery and neuroradiology, with certain overlaps with aspects of head-and-neck surgery. It can be broadly defined as treatment of central nervous system (CNS) disease by endovascular access for the purpose of delivering therapeutic agents, including both drugs and devices [1]. Because of a recent advancement in the field of INR [2], more anesthesiologists are involved in care of patients undergoing INR procedures. Anesthesiologists have several important concerns when providing care to patients who undergo INR procedures, including (1) maintenance of patient immobility and physiologic stability; (2) manipulating systemic or regional blood flow; (3) managing anticoagulation; (4) treating and managing sudden unexpected complications during the procedure; (5) guiding the medical management of critical care patients during transport to and from the radiology suites; and (6) rapid recovery from anesthesia and sedation during or immediately after the procedure to facilitate neurologic examination and monitoring [3,4]. To achieve these goals, anesthesiologists should be familiar with specific radiological procedures and their potential complications.
Preanesthetic considerations

The preanesthetic evaluation of a patient undergoing a potentially long diagnostic and therapeutic procedure in the neuroradiology suite expands on the routine preanesthetic examination of the neurosurgical patient. Airway evaluation should include routine evaluation of the potential ease of laryngoscopy in an emergent situation, and also take into the account the fact that, with the head and neck kept in a neutral position, sedation may compromise airway patency. Further, this patient population often includes head-and-neck tumor patients with their associated airway considerations.

Baseline blood pressure and cardiovascular reserve should be assessed carefully, especially when blood pressure manipulation and perturbations are anticipated. A careful neurologic examination should be performed to characterize any deficits that may be present prior to the procedure, and special note should be made of the patient’s sensorium. Furthermore, careful padding of pressure points may assist in the patient’s ability to tolerate a long period of lying supine and motionless and decrease the requirement for sedation, anxiolysis, and analgesia. In addition to the issues normally considered during the preanesthetic evaluation of the neurosurgical patient, the anesthesiologist should review the patient’s previous experiences with angiography, noting if there were adverse reactions to radiographic contrast agents, such as allergy or excessive dehydration. Because of the possibility of significant radiation exposure, the possibility of pregnancy in female patients should be explored.

Prophylaxis for cerebral ischemia is in a state of development. Some centers use a variety of agents such as oral nimodipine for this purpose. The use of calcium channel blockers has been suggested to decrease catheter-induced vaso-spasm as well; transdermal nitroglycerin has also been used for this purpose.

Monitoring and vascular access

Secure intravenous (i.v.) access should be available with adequate extension tubing to allow drug and fluid administration at maximal distance from the image intensifier during fluoroscopy. Access to i.v. or arterial catheters can be difficult when the patient is draped and the arms are restrained at the sides. Stopcocks and nonlocking tubing connections under the drapes should be minimized. Prior to covering the patient, the tightness of connections between segments of tubing should be verified. Infusions of anticoagulant or potent medications, such as nitroprusside and remifentanil, should be through minimal dead space, into ports that are as proximal to the patient as possible (e.g., into a T-connector at an i.v. catheter). This allows the infusion of medications to be relatively independent of the rate of the i.v. carrier fluid.

Standard monitors should be applied, regardless of anesthetic technique. For i.v. sedation, capnography sampling via the sampling port of special nasal cannula is especially useful. A pulse oximeter probe can be placed on the great
The toe of the leg that will receive the femoral introducer sheath. This may give an early warning of femoral artery obstruction or distal thromboembolism.

For intracranial procedures and postoperative care, beat-to-beat arterial pressure monitoring and blood sampling can be facilitated by an arterial line. A side port of the femoral artery introducer sheath can be used, but most radiologists will remove the sheath immediately after the procedure. Using a coaxial or triaxial catheter system, arterial pressure at the carotid artery, vertebral artery, and the distal cerebral circulation can be measured [5]. The presence of a coaxial catheter frequently underestimates the systolic and overestimates the diastolic pressure; however, mean pressures are reliable, and may be used to safely monitor the induction of either hyper- or hypotension. In a patient who requires continuous blood pressure monitoring postoperatively, it is convenient to have a separate radial arterial blood pressure catheter. Bladder catheters are required for most of the procedures; they assist in fluid management as well as patient comfort. A significant volume of heparinized flush solution and radiographic contrast is often used.

Radiation safety

There are three sources of radiation in the INR suite: direct radiation from the x-ray tube, leakage (through the collimators’ protective shielding), and scattered (reflected from the patients and the area surrounding the body part to be imaged). A fundamental knowledge of radiation safety is essential for all staff members working in an INR suite. It must be realized that the amount of exposure decreases proportionally to the square of the distance from the source of radiation (inverse square law). It should also be realized that digital subtraction angiography delivers considerably more radiation than fluoroscopy.

Optimal protection would dictate that all personnel should wear lead aprons, thyroid shields, and radiation exposure badges. The lead aprons should be periodically evaluated for any cracks in the lead lining that may allow accidental radiation exposure. Movable lead glass screens may provide additional protection for the anesthesia team. Clear communication between the INR and anesthesia teams is crucial for limiting radiation exposure. With proper precautions, the anesthesia team should be exposed to less than the annual recommended limit for health care workers (see http://pdg.lbl.gov/).

Anesthetic technique

Choice of anesthetic technique is a controversial area, and varies between centers. There are no data that support improved outcome with one technique or another. There appears to be a trend to move more towards general endotracheal anesthesia, but it is highly dependent on local practice and training.
Intravenous sedation

Primary goals of anesthetic choice for i.v. sedation are to alleviate pain, anxiety and discomfort, and to provide patient immobility. A rapid recovery from sedation is often required for neurologic testing.

Many neuroangiographic procedures, while not painful per se, can be psychologically stressful. This is especially true when there is a risk of serious stroke or death, particularly patients who have already suffered a preoperative hemorrhage or stroke. There may be an element of pain associated with injection of contrast into the cerebral arteries (burning) and with distention or traction on them (headache). A long period of lying can cause significant pain and discomfort.

A variety of sedation regimens are available, and specific choices are based on the experience of the practitioner and the aforementioned goals of anesthetic management. Common to all i.v. sedation techniques is the potential for upper airway obstruction. Placement of nasopharyngeal airways may cause troublesome bleeding in anticoagulated patients, and is generally avoided. Laryngeal Mask Airways may be useful in rare emergencies in patients with difficult airway. Endotracheal intubation, however, remains a mainstay for securing the airway during neurological crises.

General anesthesia

The primary reason for employing general anesthesia is to reduce motion artifacts and to improve the quality of images, especially in small children and uncooperative adult patients. This is especially pertinent to INR treatment of spinal pathology, in which extensive multilevel angiography may be performed. The specific choice of anesthesia may be guided primarily by other cardio- and cerebrovascular considerations. Total i.v. anesthetic techniques, or combinations of inhalational and i.v. methods, may optimize rapid emergence [6]. To date, pharmacologic protection against ischemic injury during neurosurgical procedures has not been proven. A theoretical argument could be made for eschewing the use of N₂O because of the possibility of introducing air emboli into the cerebral circulation, but there are no data to support this.

Anticoagulation

Careful management of coagulation is required to prevent thromboembolic complications during and after the procedures. Whether heparinization should be used for every case of intracranial catheterization is not clear to date. Generally, after a baseline activated clotting time (ACT) is obtained, i.v. heparin (70 units/kg) is given to a target prolongation of two to three times baseline. Heparin can then be given continuously or as an intermittent bolus with hourly monitoring of ACT. Occasionally, a patient may be refractory to attempts to obtain adequate anticoagulation. Switching from bovine to porcine heparin or vice versa should be
considered. If antithrombin III deficiency is suspected, administration of fresh-frozen plasma may be necessary. At the end of the procedure, heparin may need to be reversed with protamine.

Antiplatelet agents (aspirin, ticlopidine, and the glycoprotein IIb/IIIa receptor antagonists) are used quite extensively in patients with coronary stents, and may have great relevance for patients undergoing INR procedures. Activation of the glycoprotein IIb/IIIa receptor is a final common pathway for platelet aggregation. Abciximab (ReoPro), a chimeric murine–human monoclonal antibody that directly binds to the receptor, has been shown to decrease mortality and morbidity after coronary stenting [7]. Other agents in this class include the peptide receptor antagonists, Eptifibatide (Integrilin) and Tirofiban (Aggrastat).

These agents have various pharmacokinetic and pharmacodynamic properties. Based on experiences in coronary stenting, several basic observations on their use become clear. First, the effects of these agents on platelet aggregation are difficult to monitor clinically because there is no accurate bedside test of platelet aggregation. Second, the duration of the effects is approximately 12–24 hours. Rapid reversal of antiplatelet activity can only be achieved by platelet transfusion. Finally, use of these agents along with heparin may result in unexpected hemorrhage. Therefore, reducing procedural heparin dosage and early removal of vascular access sheaths should be carefully considered to decrease bleeding complications. The sustained long-term reduction in morbidity and mortality of coronary thrombosis patients (undergoing angioplasty/stenting or thrombolysis) by an antiplatelet agent has led to great interest for use in endovascular procedures of the CNS, but their use is not clearly defined in the setting of cerebrovascular disease.

**Superselective anesthesia functional examination (SAFE)**

SAFE is carried out to determine, prior to therapeutic embolization, if the tip of the catheter has been inadvertently placed proximal to the origin of nutritive vessels to eloquent regions, either in the brain or spinal cord [8]. Such testing is an extension of the Wada and Rasmussen test in which amobarbital is injected into the internal carotid artery to determine hemispheric dominance and language function. Its primary application is in the setting of brain arteriovenous malformation (BA VM) treatment, but it may also be used for tumor or other vascular malformation work. Prior to the testing, the patient should be fully awake from sedation or general anesthesia. Careful selection of motivated patients and preoperative teaching may decrease the anxiolytic requirements of these patients and ensure ideal testing conditions. This topic is reviewed elsewhere [4].

**Deliberate hypotension**

The two primary indications for induced hypotension are (1) to test cerebrovascular reserve in patients undergoing carotid occlusion, and (2) to slow flow in a feeding artery of BAVMs before glue injection.
The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the physiological stability of the patients. The choice of agent should be determined by the experience of the practitioner, the patient’s medical condition, and the goals of the blood pressure reduction in a particular clinical setting.

Intravenous adenosine has been used to induce transient cardiac pause, and may be a viable method of partial flow arrest [9,10]. Further study for its safety and efficacy is needed.

**Deliberate hypertension**

During acute arterial occlusion or vasospasm, the only practical way to increase collateral blood flow may be an augmentation of the collateral perfusion pressure by raising the systemic blood pressure. The Circle of Willis is a primary collateral pathway in cerebral circulation. However, in as many as 21% of otherwise normal subjects, the circle may not be complete. There are also secondary collateral channels that bridge adjacent major vascular territories, most importantly for the long circumferential arteries that supply the hemispheric convexities. These pathways are known as the pial-to-pial collateral or leptomeningeal pathways.

The extent to which the blood pressure has to be raised depends on the condition of the patient and the nature of the disease. Typically, during deliberate hypertension the systemic blood pressure is raised by 30–40% above the baseline or until ischemic symptoms resolve. Phenylephrine is usually the first line agent for deliberate hypertension, and is titrated to achieve the desired level of blood pressure.

**Management of neurologic and procedural crises**

Complications during endovascular instrumentation of the cerebral vasculature can be rapid and life threatening, and require a multidisciplinary collaboration. Having a well thought-out plan for dealing with intracranial catastrophe may make the difference between an uneventful outcome and death. Rapid and effective communication between the anesthesia and radiology teams is critical.

The primary responsibility of the anesthesia team is to preserve gas exchange and, if indicated, secure the airway. Simultaneous with airway management, the first branch in the decision-making algorithm is for the anesthesiologist to communicate with the INR team and determine whether the problem is hemorrhagic or occlusive. In the setting of vascular occlusion, the goal is to increase distal perfusion by blood pressure augmentation with or without direct thrombolysis. If the problem is hemorrhagic, immediate cessation of heparin and reversal with protamine is indicated. As an emergency reversal dose, 1 mg protamine can be given for each 100 units heparin total dosage during the case. The ACT can then be used to fine tune the final protamine dose.

Bleeding catastrophes are usually heralded by headache, nausea, vomiting, and vascular pain related to the area of perforation. Sudden loss of consciousness
is not always due to intracranial hemorrhage. Seizures, as a result of contrast reaction or transient ischemia, and the resulting post-ictal state can also result in an obtunded patient. In the anesthetized patient, the sudden onset of bradycardia or the radiologist’s diagnosis of extravasation of contrast may be the only clues to a developing hemorrhage.

**Postoperative management**

After INR procedures, patients spend the immediate postoperative period in a monitored setting to watch for signs of hemodynamic instability or neurologic deterioration. Blood pressure control, either induced hypotension or induced hypertension, may be continued during the postoperative period. Complicated cases may go first to CT or some kind of physiologic imaging such as single photon emission computed tomography (SPECT) scanning; only rarely is an emergent craniotomy indicated.

**Specific procedures**

*Brain arteriovenous malformations (BAVMs).*

BAVMs are typically large, complex lesions made up of a table of abnormal vessels (called the nidus) frequently containing several discrete fistulae [5]. They are often called cerebral or pial arterio-venous malformations. There are usually multiple feeding arteries and draining veins. The goal of the therapeutic embolization is to obliterate as many of the fistulae and their respective feeding arteries as possible. BAVM embolization is usually an adjunct for surgery or radiotherapy [11]. In rare cases, embolization treatment is aimed for total obliteration. SAFE is frequently used during BAVM embolization.

There are generally two schools of thought on how to manage anesthesia in the patient undergoing endovascular therapy, especially with permanent agents such as cyanoacrylate glues. One must rely on the knowledge of neuroanatomy and vascular architecture to ascertain the likelihood of neurologic damage after deposition of the embolic agents. The “anatomy” school, therefore, will prefer to embolize under general anesthesia. Arguments for this approach include improved visualization of structures with the absence of patient movement, especially if temporary apnea is used. Further, it is argued that if the glue is placed “intranidal,” then, by definition, no normal brain is threatened. There are two major concerns for this approach. A considerable variation in the normal localization of function exists, and cerebral pathology may cause neurologic function to shift from its native location to another one. The other school, which we might call the “physiologic” school, trades off the potential for patient movement for the increased knowledge of the true functional anatomy of a given patient. Localization of cerebral function may not always follow textbook descriptions, as described in
the section on SAFE. Furthermore, the BAVM nidus or a previous hemorrhage may result in a shift or relocalization of function. The “physiologic” approach demands, at the present, careful titration of sedation to wake the patient for SAFE before injection of embolic material.

The cyanoacrylate glues offer relatively “permanent” closure of abnormal vessels. Although less durable, polyvinyl alcohol microsphere embolization is also commonly used. If surgery is planned within days after PVA embolization, the rate of recanalization is low and PVA is felt to be easier and safer to work with. Advances in polymer development may obviate some of the risks of glue therapy.

**Dural arterio-venous malformations**

Dural AVM is currently considered an acquired lesion resulting from venous dural sinus stenosis or occlusion, opening of potential arterio-venous shunts, and subsequent recanalization. Symptoms are variable according to which sinus is involved. Dural AVMs may be fed by multiple meningeal vessels, and therefore, multistaged embolization is usually performed. SAFE is performed in certain vessels such as the middle meningeal artery and the ascending pharyngeal artery to evaluate the blood supply to peripheral cranial nerves and the possible existence of dangerous extra- to intracranial anastomosis. Complete obliteration is not always necessary considering the purpose of treatment, which is to reduce risk of bleeding or to alleviate symptoms. Subsequent spontaneous thrombosis can be expected in view of pathogenesis of this disease.

It is important to bear in mind that dural AV fistulas can induce increased venous pressure. Venous hypertension of pial veins is a risk factor for intracranial hemorrhage. Additionally, the venous hypertension should be factored into estimating safe levels of reductions in systemic arterial, and therefore, cerebral perfusion pressure.

**Carotid cavernous and vertebral fistulae**

Carotid cavernous fistulae (CCF) are direct fistulae usually caused by trauma to the cavernous carotid artery leading to communication with the cavernous sinus, usually associated with basal skull fracture. Treatment of CCF, a challenging surgical procedure, has become relatively easier with the development of detachable balloons [12]. Vertebral artery fistulae are connections to surrounding paravertebral veins, usually as a result of penetrating trauma, but may be congenital, associated with neurofibromatosis, or result from blunt trauma. In addition to cerebral involvement, spinal cord function may also be impaired.

**Vein of Galen malformations**

These are relatively uncommon but complicated lesions that present in infants and require a multidisciplinary approach including an anesthesiologist skilled in
the care of critically ill neonates. The patients may have intractable congestive heart failure, myocardial lesions, intractable seizures, hydrocephalus, and mental retardation [13].

**Spinal cord lesions**

Embolization may be used for intramedullary spinal AVMs, dural fistulae, or tumors invading the spinal canal. Often, general endotracheal anesthesia with controlled ventilation is used to provide temporary apnea that may increase the ability to see small spinal cord arteries at the limits of angiography imaging resolution and exquisitely sensitive to motion artifact. For selected lesions, intraoperative somatosensory and motor-evoked potentials may be helpful in both anesthetized and sedated patients. Intraoperative wake-up tests may be requested to test neurologic function during embolization.

In cases where wake-up tests might be needed, preoperative discussion of the logistics of the wake-up procedure and the testing process may facilitate the intraoperative management of this part of the procedure.

**Carotid test occlusion and therapeutic carotid occlusion**

Carotid occlusion, both permanent and temporary, may be used in several circumstances. Skull base tumors frequently involve the intracranial or petrous portion of the carotid artery or its proximal Willisian branches. Large or otherwise unclippable aneurysms may be partly or completely treated by proximal vessel occlusion. To assess the consequences of carotid occlusion in anticipation of surgery, the patient may be scheduled for a test occlusion in which cerebrovascular reserve is evaluated in several ways. A multimodal combination of angiographic, clinical, and physiologic tests can be used to arrive at the safest course of action for a given patient’s clinical circumstances. The judicious use of deliberate hypotension can increase the sensitivity of the test [14,15].

**Intracranial aneurysm ablation**

The two basic approaches for INR therapy of cerebral aneurysms are occlusion of proximal parent arteries and obliteration of the aneurysmal sac. The aneurysmal sac may be obliterated by use of coils and balloons. However, obliterating the aneurysmal sac while sparing the parent vessel is still challenging [16]. Manipulation of the sac may cause distal thromboembolism and rupture. Incomplete obliteration may result in recurrence and hemorrhage. The anesthesiologist should be prepared for aneurysmal rupture and acute SAH at all times, either from spontaneous rupture of a leaky sac or direct injury of the aneurysm wall by the vascular manipulation. It should be noted after coil ablation of aneurysms, that at the present time, there is not the same degree of certainty that
the lesion has been completely removed from the circulation as with application of a surgical clip. There may be areas of the aneurysmal wall that are still in contact with the arterial blood flow and pressure. Therefore, attention to postoperative blood pressure control is warranted.

**Balloon angioplasty of cerebral vasospasm from aneurysmal SAH**

Angioplasty may be used to treat symptomatic vasospasm with correlating angiographic stenosis refractory to maximal medical therapy [17]. Angioplasty is usually reserved for patients that have already had the symptomatic lesion surgically clipped (for fear of rerupture), or for patients in the early course of symptomatic ischemia to prevent transformation of a bland infarct into a hemorrhagic one. A balloon catheter is guided under fluoroscopy into the spastic segment and inflated to mechanically distend the constricted area.

It is also possible to perform a “pharmacologic” angioplasty. There is the greatest experience with papaverine, but there are potential CNS toxic effects (see ref. [18] for a review), but other agents such as calcium channel blockers may find a place for this purpose.

**Sclerotherapy of venous angiomas**

Craniofacial venous malformations are congenital disorders causing significant cosmetic deformities, that may impinge on the upper airway and interfere with swallowing. Absolute alcohol (95% ethanol) opacified with contrast is injected percutaneously into the lesion, resulting in a chemical burn to the lesion and eventually shrinking it. The procedures are short (30–60 minutes) but painful, and general endotracheal anesthesia is used. Complex airway involvement may require endotracheal intubation with fiberoptic techniques [19]. Because marked swelling often occurs immediately after alcohol injection, the ability of the patient to maintain a patent airway must be carefully assessed in discussion with the radiologist before extubation. Alcohol has several noteworthy side effects. First, upon injection it can cause changes in the pulmonary vasculature and create a short-lived shunt or a ventilation-perfusion mismatch. Desaturation on the pulse oximeter is frequently noted after injection. Absolute alcohol may also cause hypoglycemia, especially in younger children. Finally, the predictable intoxication and other side effects of ethanol may be evident after emergence from anesthesia.

**Angioplasty and stenting for atherosclerotic lesion**

Angioplasty with or without stenting for atherosclerosis has been tried in cervical and intracranial arteries with favorable results [20,21]. Risk of distal thromboembolism is the major issue to be resolved in this procedure and methods. A catheter system that employs an occluding balloon distal to the angioplasty
balloon has been proposed [22]. Carotid angioplasty and stenting may provide a therapeutic option for patients particularly at risk of surgery. However, efficacy and indications in relation to carotid endarterectomy remain to be determined.

Preparation for anesthetic management include, in addition to the usual monitors and considerations already discussed, placement of transcutaneous pacing leads in case of severe bradycardia or asystole from carotid body stimulation during angioplasty. Intravenous atropine or glycopyrrolate may be used in an attempt to mitigate against bradycardia, which almost invariably occurs to some degree with inflation of the balloon. This powerful chronotropic response may be difficult or impossible to prevent or control by conventional means. If indicated by hemodynamic instability, the anesthesiologist must have the ability to immediately administer advanced cardiac life support, including catecholamine and temporary cardiac pacing therapy.

Potential complications include vessel occlusion, perforation, dissection, spasm, thromboemboli, occlusion of adjacent vessels, transient ischemic episodes, and stroke. Furthermore, compared to carotid endarterectomy, there appears to be an increased incidence of cerebral hemorrhage and/or brain swelling after carotid angioplasty [23]. Although the etiology of this syndrome is unknown, it has been associated with cerebral hyperperfusion, and it may be related to poor postoperative blood pressure control.

**Thrombolysis of acute thromboembolic stroke**

In acute occlusive stroke, it is possible to recanalize the occluded vessel by superselective intra-arterial thrombolytic therapy. Thrombolytic agents can be delivered in high concentration by a microcatheter navigated close to the clot. Neurologic deficits may be reversed without additional risk of secondary hemorrhage if treatment is completed within 6 hours from the onset of carotid territory ischemia and 24 hours in vertebrobasilar territory. One of the impediments in development in this area has been the fear of increasing the risk of hemorrhagic transformation of the acute infarction patient. Despite an increased frequency of early symptomatic hemorrhagic complications, treatment with intra-arterial pro-urokinase within 6 hours of the onset of acute ischemic stroke with middle cerebral artery (MCA) occlusion significantly improved clinical outcome at 90 days [24].

**Important points and objectives**

There is a rapidly expanding list of application of INR procedures in the field of the treatment of CNS disease. Anesthesiologists should be familiar with specific procedures and their potential complications. Constant and effective communication between the anesthesia and radiology teams is critical to safely carry out INR procedures and to deal with intracranial catastrophe.
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References

Methylprednisolone for acute spinal cord injury: not a standard of care

Herman Hugenholtz

It is time to clear the confusion about the utility of steroids in cases of acute spinal cord injury. A committee of Canadian neurosurgical and orthopedic spine specialists, emergency physicians and physiatrists (listed at the end of the article) has reviewed the evidence and concluded that high-dose methylprednisolone infusion is not an evidence-based standard of care for patients with such an injury.1

The consequences of a spinal cord injury are often devastating, and any possibility of mitigating neurologic loss is attractive. To this end, management of acute spinal cord injuries has included the use of steroids for the past 30 years, based in large part on physiological hypotheses with limited clinical support.2,3 Mechanical injury to the spinal cord initiates a cascade of secondary events that include ischemia, inflammation and calcium-mediated cell injury. Animal experiments have shown that methylprednisolone exhibits potential neuroprotective effects through its inhibition of lipid peroxidation and calcium influx and through its anti-inflammatory effects.4,5 Three well-designed, large, randomized clinical trials (the National Acute Spinal Cord Injury Studies [NASCIS I, II and III]) examined the effect of steroid administration in patients with acute spinal cord injury.6–11

NASCIS I examined the change in motor function in specific muscles and changes in light touch and pinprick sensation from baseline.6,7 The study detected no benefit from methylprednisolone, but the dose was considered to be below the therapeutic threshold determined from animal experiments. Therefore, NASCIS II used a much higher dose, and patients were randomly assigned to receive a 24-hour infusion of methylprednisolone, naloxone or placebo within 12 hours after acute spinal cord injury.8,9 Again, there was no benefit overall in the methylprednisolone group; however, post hoc analyses detected a small gain in the total motor and sensory score in a subgroup of patients who had received the drug within 8 hours after their injury. As a result, this 24-hour, high-dose methylprednisolone infusion, if started within 8 hours after injury, quickly became an implied standard of care despite considerable criticism of the validity of such a post hoc analysis.

Subsequent clinical trials have provided conflicting evidence about steroid treatment in acute spinal cord injury. A Japanese study attempted to replicate the results seen in the 8-hour subgroup from NASCIS II and reported improved function at 6 months in a larger number of muscles and sensory dermatomes among subjects who received high-dose methylprednisolone infusion than among those who received only low doses of the drug or no drug.12 However, the study lacked detail about randomization and outcome measures, and it included only 74% of the enrolled subjects in the outcome analysis. Conversely, an underpowered prospective randomized trial that used a methylprednisolone regimen similar to that used in NASCIS II found no improvement in motor and sensory scores at 1 year.13,14 NASCIS III compared a 48-hour infusion of methylprednisolone with a 24-hour infusion started within 8 hours after injury and found no benefit from extending the infusion beyond 24 hours. Again, only post hoc analysis showed a benefit from extending the infusion to 48 hours when treatment was started between 3 and 8 hours after injury. No other study has verified the primary outcome of 48 hours versus 24 hours or the post hoc conclusion of benefit from starting treatment between 3 and 8 hours after injury.

A meta-analysis of all of the trials concluded, on the basis of the controversial subgroup post hoc analyses in NASCIS II and III and the data from the Japanese study, that a 24-hour high-dose methylprednisolone infusion within 8 hours after injury is efficacious.15 Despite this meta-analysis, the efficacy of such a regimen remains uncertain and will require further study. The controversy about the post hoc analyses of NASCIS data continues,16–23 and unfortunately the studies that could have clarified the efficacy of such a regimen have lacked the rigour to do so.

Steroid therapy is not without risk. Most patients with acute spinal cord injury are treated in intensive care units, have polytrauma, have impaired lung capacity and are vulnerable to sepsis. In all 3 NASCIS studies and other, smaller studies, the incidence of sepsis and pneumonia was higher in the high-dose methylprednisolone groups than in the placebo or other treatment groups;6–11,24–26 the differences were not significant except in NASCIS III. Hyperglycemia and gastrointestinal complications were also reported following high-dose methylprednisolone treatment.11,24 Therefore, it has been proposed that, without compelling evidence for its efficacy, methylprednisolone should be used with caution and may even be harmful, particularly if infusion goes beyond 24 hours.17

The cost of a 24-hour methylprednisolone infusion is not prohibitive, and a gain of antigravity strength in one or more muscles below a spinal segment can provide an impor-

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tant functional gain, especially for patients with cervical spinal cord injuries. Therefore, even the small improvement observed in the NASCIS subgroups could be viewed as a benefit in cases of complete or incomplete cervical cord injury. Despite the risk of complications and as long as the outcomes in the NASCIS subgroups remain a possibility, physicians may still opt to administer a high-dose methylprednisolone infusion within 8 hours after injury. However, they should no longer feel compelled to do so. Physicians who conduct the initial triage and resuscitation of patients with acute spinal cord injury should consult their specialist colleagues who will be continuing the care of these patients regarding their preference for methylprednisolone infusion.

The Canadian Neurosurgical Society, the Canadian Spine Society and the Canadian Association of Emergency Physicians have adopted the committee’s recommendation that a high-dose, 24-hour infusion of methylprednisolone started within 8 hours after an acute closed spinal cord injury is not a standard treatment nor a guideline for treatment but, rather, a treatment option, for which there is very weak level II and III evidence.27

This article has been peer reviewed.

Dr. Hugenholtz is with the Division of Neurosurgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS.

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References


Correspondence to: Dr. Herman Hugenholtz, New Halifax Infirmary, Rm. 3808, 1796 Summer St., Halifax NS B3H 3A7; fax 902 473-8912

Members of the Committee of the Canadian Spine Society and the Canadian Neurosurgical Society to Review the Role of Methylprednisolone in Acute Spinal Cord Injury: Herman Hugenholtz (chair), Division of Neurosurgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS; Nirmala D. Bharatwal, Toronto Rehabilitation Institute, Toronto, Ont.; Dan E. Cass, Director of Emergency Services, St. Michael’s Hospital, Toronto, Ont.; Marcel F. Dvorak, Medical Director, Combined Spine Program, Vancouver Hospital and Health Sciences Centre, Vancouver, BC; Derek Fewer, Section of Neurosurgery, Health Sciences Centre, Winnipeg, Man.; Richard J. Fox, Department of Neurosurgery, Walter C. Mackenzie Health Science Centre, University Hospital, Edmonton, Alta.; Dennis M.S. Izukawa, Department of Neurosurgery, Trillium Health Centre, Mississauga, Ont.; Joel Lexchin, Emergency Department, University Health Network, Toronto, Ont.; Christine Short, Nova Scotia Rehabilitation Centre, Halifax, NS; and Sagun Tuli, Department of Neurosurgery, Brigham and Women’s Hospital, Boston, Mass.
Purpose of review
Translating the efficacy of neuroprotective agents in experimental traumatic brain injury to clinical benefit has proven an extremely complex and, to date, unsuccessful undertaking. The focus of this review is on neuroprotective agents that have recently been evaluated in clinical trials and are currently under clinical evaluation, as well as on those that appear promising and are likely to undergo clinical evaluation in the near future.

Recent findings
Excitatory neurotransmitter blockage and magnesium have recently been evaluated in phase III clinical trials, but showed no neuroprotective efficacy. Cyclosporin A, erythropoietin, progesterone and bradykinin antagonists are currently under clinical investigation, and appear promising.

Summary
Traumatic brain injury is a complex disease, and development of clinically effective neuroprotective agents is a difficult task. Experimental traumatic brain injury has provided numerous promising compounds, but to date these have not been translated into successful clinical trials. Continued research efforts are required to identify and test new neuroprotective agents, to develop a better understanding of the sequential activity of pathophysiologic mechanisms, and to improve the design and analysis of clinical trials, thereby optimizing chances for showing benefit in future clinical trials.

Keywords
clinical trial, head injury, neuroprotection, neurotrauma, traumatic brain injury

Introduction
Traumatic brain injury (TBI) is a major cause of death and disability worldwide, leading to immense personal suffering to victims and relatives, and high costs to society. Injuries are the leading cause of death between the ages of 15 and 44, and head trauma accounts for the majority of all trauma deaths. Today, at least 11.5 million people live with TBI-related disability, impairment, complaint or handicap in Europe (6.2 million) and the USA (5.3 million) alone [1,2].

Depending on the severity of injury, the medical management of brain-injured patients currently includes specialized prehospital care, clinical (intensive) care, and, for some, long-term rehabilitation, but lacks clinically proven effective management with neuroprotective agents to limit pathophysiologic cascades or enhance repair. The enormous burden of TBI, however, clearly supports the need for such neuroprotective agents. Translating promising experimental results into clinical benefit has proven an extremely complex issue. First, although many pathophysiologic cascades inducing secondary damage have been identified, it remains uncertain which of these are active in individual patients and at what time after injury. Moreover, many pathways may initially have detrimental effects, but at later stages can be protective. Second, clinical trials have suffered from inadequacy in their design and analysis, not in the least part due to heterogeneity of the population and variability in treatment approaches [3].

Rationale for treatment: primary and secondary injury
Brain trauma results in brain damage and dysfunction from both primary injury (due to biomechanical effects) and subsequent secondary damage due to activation of pathophysiologic cascades. These are further aggravated by secondary insults. Early detection of such secondary insults, including intracranial insults (e.g. mass lesions, increased intracranial pressure) and systemic insults (e.g. hypoxia, hypotension), followed by appropriate intervention currently forms the basis of clinical management [4].

Secondary damage consists of seemingly innumerable complex biochemical and cellular pathways that influence progression of the primary injury. The primary goal of neuroprotection is to prevent and/or reduce secondary...
damage and to enhance repair [5]. Over the past decades our understanding of the pathophysiology of TBI has greatly increased and based on this understanding numerous pharmacological therapies have been developed, tested and proven effective in the treatment of experimental TBI. To date, however, promising experimental results have not been translated into successful clinical trials, and hence the cornerstone of management of TBI patients remains the prevention of initial injury and the minimization or reversal of secondary insults. The excitement about the new knowledge of the neurobiology and neuropharmacology of TBI should not detract from the absolute importance of correcting hypoxia, hypotension, raised intracranial pressure and other causes of secondary ischemic insult [6,7]. On the other hand, we should not be discouraged by negative results and difficulties in previous clinical trials, but continue our search for effective neuroprotective drugs for TBI patients in order to further improve outcome of this devastating disease.

Neuroprotective strategies

The complex pathobiology of TBI offers numerous targets for potential neuroprotective agents. Many of these have been or will be investigated in experimental models of TBI (Table 1 [8**,9–13]). The few that made it into clinical trials join a growing list of neuroprotective agents without proven clinical benefit (Table 2 [14–24]). The focus of this review is on neuroprotective agents that have recently been evaluated in clinical trials and are currently under clinical evaluation, as well as on those that appear promising and are likely to undergo clinical evaluation in the near future.

**Excitatory neurotransmitter antagonism**

Disturbances in neurotransmitter concentration occur frequently following TBI. Excitotoxicity refers to an excessive release of excitatory neurotransmitters (primarily glutamate) initiating various pathophysiologic processes including excessive calcium influx in neurons, resulting in neuronal cell death [10]. High concentrations of extracellular glutamate have been demonstrated in both experimental models and clinical patients with TBI. Experimental research has elucidated many aspects of excitotoxicity and identified a number of glutamate antagonists acting either pre- or postsynaptically on N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolly-propionic acid (AMPA)/kainate or metabotropic receptors, in a competitive, noncompetitive or modulating way. However, glutamate receptors are of utmost importance to normal functioning, so antagonism of excessive excitotoxic activity must be achieved

<table>
<thead>
<tr>
<th>Pharmacological target</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excitatory amino acids</strong></td>
<td>Numerous compounds have been evaluated and reviewed elsewhere [8**,10]. New compounds with different pharmacological profiles (e.g. memantine) require further experimental evaluation.</td>
</tr>
<tr>
<td><strong>Calcium channels</strong></td>
<td>Extensively studied, also in clinical TBI (Nimodipine and SNX-111); the short time frame following injury seems to limit further clinical use.</td>
</tr>
<tr>
<td><strong>Scavenging oxygen radicals</strong></td>
<td>Tirilazad Mesylate, PEG-SOD and Lubeluzole have been clinically evaluated; many new compounds are at least promising in experimental TBI.</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>A double-edged sword in TBI, both detrimental and beneficial. The massive inflammatory response is a high potential target for neuroprotection, with special attention for NO inhibitors, nitrates and nitrooxides.</td>
</tr>
<tr>
<td><strong>Caspases</strong></td>
<td>Caspases are important enzymes in apoptotic cell death known to occur following TBI. It is however still a matter of debate whether apoptosis is a good or bad thing compared to necrosis following TBI.</td>
</tr>
<tr>
<td><strong>Calpains</strong></td>
<td>Calcium-dependent proteases involved in cytoskeletal remodeling. Calpain inhibitors in experimental TBI reduce damage to fiber tracts, and therefore are of major interest in axonal injury.</td>
</tr>
<tr>
<td><strong>Hormonal treatment</strong></td>
<td>Progesterone is currently being evaluated in a clinical trial. Steroids have been extensively studied in the past. Experimental compounds attracting a lot of attention are dehydroepiandrosterone, thyrotropin-releasing hormone and their analogs.</td>
</tr>
<tr>
<td><strong>Neurotransmission</strong></td>
<td>Widespread changes in neurotransmitters occur following TBI. All compounds interfering in catecholamine, serotonin, histamine, γ-aminobutyric acid (GABA) and acetylcholine metabolism are therefore of potential interest following TBI. Cognitive problems and depression frequently present following TBI, which might benefit from this approach, although a rationale for more acute administration exists.</td>
</tr>
<tr>
<td><strong>Neurotrophic factors</strong></td>
<td>These growth/survival factors effectively reduce apoptosis and improve functional outcome in experimental TBI. Many questions about dosage, time-window and route of administration remain to be answered.</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td>Recombinant human factor VII has been evaluated in a clinical trial. Coagulation disorders are common following TBI, relate to outcome, and will be a hot topic for future research. Controversies regarding treatment of microvascular thrombosis and progressive hemorrhagic contusions require attention [11].</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td>Seizures occur frequently following TBI, and anticonvulsants may reduce early seizures. In addition, acute administration can be neuroprotective [12,13].</td>
</tr>
<tr>
<td><strong>Immunoophilin ligands</strong></td>
<td>Cyclosporin A is currently being evaluated in a clinical trial, other compounds are under experimental investigation.</td>
</tr>
<tr>
<td><strong>Minocycline</strong></td>
<td>Minocycline is a broad-spectrum antibiotic, shown to be neuroprotective in experimental studies.</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>In experimental research additional hot topics far from translation into clinical trials are neurogenesis, improvement of axonal outgrowth and stem-cell transplantation, although for the latter a small clinical trial in pediatric TBI has been initiated.</td>
</tr>
</tbody>
</table>

TBI, traumatic brain injury. Neuroprotective strategies are discussed more extensively in [8**,9].

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## Table 2 Disappointing results of trials on neuroprotective agents in traumatic brain injury

<table>
<thead>
<tr>
<th>Study and agent</th>
<th>Study population</th>
<th>No. of patients</th>
<th>Start of treatment</th>
<th>Year of study</th>
<th>Status</th>
<th>Published</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin inhibition</td>
<td>Bradycor/CP-0127&lt;sup&gt;7&lt;/sup&gt;</td>
<td>GCS 3–8</td>
<td>≤ 12 h</td>
<td>1996</td>
<td>Completed</td>
<td>[14]</td>
<td>12% improvement in favorable outcome ($P = 0.26$)</td>
</tr>
<tr>
<td>Calcium-mediated</td>
<td>HIT I Nimodipine&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Not obeying commands</td>
<td>351</td>
<td>1987–1989</td>
<td>Completed</td>
<td>[15]</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Neuropeptide damage</td>
<td>HIT II Nimodipine&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Not obeying commands</td>
<td>852</td>
<td>1989–1991</td>
<td>Completed</td>
<td>[16]</td>
<td>No significant effect overall population</td>
</tr>
<tr>
<td>Calcium-mediated</td>
<td>HIT III Nimodipine</td>
<td>Traumatic subarachnoid hemorrhage</td>
<td>123</td>
<td>1994</td>
<td>Completed</td>
<td>[17]</td>
<td>Significant reduction in unfavorable outcome</td>
</tr>
<tr>
<td>Glutamate excitotoxicity</td>
<td>Parke Davis/SNX-111</td>
<td>GCS &lt;15 + traumatic subarachnoid hemorrhage</td>
<td>592</td>
<td>1997–1999</td>
<td>Completed</td>
<td>No</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>Eliprodil study</td>
<td>GCS 4–8</td>
<td>≤ 12 h</td>
<td>1993–1995</td>
<td>Completed</td>
<td>No</td>
<td>Higher mortality</td>
</tr>
<tr>
<td></td>
<td>Selfotel&lt;sup&gt;8&lt;/sup&gt;</td>
<td>GCS 4–8</td>
<td>≤ 8 h and within 4 h of admission</td>
<td>1994–1996</td>
<td>Terminated</td>
<td>[18]</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>Cerestat/Aptiganel&lt;sup&gt;9&lt;/sup&gt;</td>
<td>GCS 4–8, GCS 3 if pupils reactive</td>
<td>532</td>
<td>1996–1997</td>
<td>Terminated</td>
<td>No</td>
<td>No significant effect reported</td>
</tr>
<tr>
<td></td>
<td>Saphir/&lt;sup&gt;D&lt;/sup&gt;CPP-ene</td>
<td>Not obeying commands, 1 reactive pupil</td>
<td>924</td>
<td>1995–1997</td>
<td>Completed</td>
<td>No</td>
<td>No significant effect reported</td>
</tr>
<tr>
<td>Lipid peroxidation/free radical damage</td>
<td>Pfizer/CP-101606</td>
<td>GCS 4–8</td>
<td>≤ 8 h</td>
<td>1997–2000</td>
<td>Completed</td>
<td>No</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>PEG-SOD&lt;sup&gt;10&lt;/sup&gt;</td>
<td>GCS &lt;8</td>
<td>Within 8 h</td>
<td>1993–1995</td>
<td>Completed</td>
<td>[19], in part</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Tirilazad domestic trial&lt;sup&gt;11&lt;/sup&gt;</td>
<td>GCS &lt;8, 70%; GCS 9–12, 30%</td>
<td>1155</td>
<td>1991–1994</td>
<td>Terminated</td>
<td>No</td>
<td>No significant effect reported</td>
</tr>
<tr>
<td></td>
<td>Tirilazad international trial&lt;sup&gt;12&lt;/sup&gt;</td>
<td>GCS &lt;8, 85%; GCS 9–12, 15%</td>
<td>1120</td>
<td>1992–1994</td>
<td>Completed</td>
<td>[20]</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Steroids</td>
<td>Triamcinolone steroid trial&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Severe head injury, not further defined</td>
<td>396</td>
<td>1985–1990</td>
<td>Completed</td>
<td>[21]</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>Dexethamsone mega dose trial&lt;sup&gt;14&lt;/sup&gt;</td>
<td>GCS &lt;13</td>
<td>≤ 3 h</td>
<td>1986–1989</td>
<td>Completed</td>
<td>[22]</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>CRASH/steroid trial&lt;sup&gt;15&lt;/sup&gt;</td>
<td>GCS &lt;15</td>
<td>≤ 8 h</td>
<td>2000–2004</td>
<td>Terminated</td>
<td>[23,24]</td>
<td>Higher mortality</td>
</tr>
<tr>
<td>Multiple actions</td>
<td>Pharmos/dexanabinol&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Motor score 2–5 + CT abnormalities</td>
<td>10 008</td>
<td>2000–2004</td>
<td>Completed</td>
<td>[27&lt;sup&gt;*&lt;/sup&gt;]</td>
<td>No significant effect</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>GCS 3–12 and/or intracranial surgery</td>
<td>499</td>
<td>1998–2004</td>
<td>Completed</td>
<td>[32&lt;sup&gt;*&lt;/sup&gt;]</td>
<td>Poorer outcome at low dose; higher mortality at high dose</td>
</tr>
</tbody>
</table>

CT, computed tomography; GCS, Glasgow Coma Score.

<sup>*</sup> Currently included in the IMPACT database.

<sup>†</sup> Planned for inclusion in the IMPACT database.
without interference in normal function [25]. Some highly neuroprotective NMDA antagonists have not been evaluated in clinical trials because of concerns of psychotropic side effects whereas for other compounds trials were terminated prematurely due to excess mortality in concomitant stroke trials. Recently, Traxoprodil, a second-generation NMDA antagonist that selectively targets NMDA receptors containing the NR2B subunit, has been evaluated in a clinical trial. Traxoprodil treatment was well tolerated and, although not statistically significant, resulted in increased favorable outcome and reduced mortality, which was more pronounced in the more severe subset of patients [26]. Dexanabinol is a synthetic cannabinoid devoid of psychotropic activity, but with strong neuroprotective potential due to antioxidant, anti-inflammatory and antieexcitotoxic properties. This compound was recently evaluated in a phase III trial and found safe, but not efficacious in the treatment of TBI [27*]. Efficacy of blocking excitotoxic responses following TBI as well as other insults to the central nervous system, to date, remains unproven [28,29]. Termination of trials before definitive evidence could be obtained, incomplete publication of data and underpowered studies limit definitive conclusions for this group of neuroprotective drugs. New drugs with different pharmacological profiles are currently under investigation in experimental TBI and show promising results. Translation into clinical trials should only occur in well designed trials based on what we have learned from previous trials.

**Magnesium**

Magnesium plays an important role in normal cellular functioning, and has demonstrated neuroprotective properties in experimental studies in models of cerebral ischemia as well as TBI. Magnesium treatment results in reduction of cerebral edema and neuronal cell death, and attenuated motor impairment and cognitive dysfunction following experimental TBI [30,31]. One of the seemingly great advantages of magnesium, besides being inexpensive and widely available, is its multidirectional effect. Where other neuroprotective compounds usually interfere with just one pathophysiological mechanism, magnesium exerts its neuroprotective effects among others by noncompetitive NMDA receptor blockade, inhibition of presynaptic excitatory neurotransmitter release, suppression of cortical spreading depression, and blockade of voltage-gated calcium channels. Despite the solid amount of experimental evidence concerning the neuroprotective effects of magnesium, a recently completed randomized double-blind trial evaluating the efficacy of a 5-day continuous magnesium administration in 499 patients with moderate or severe TBI was unable to show neuroprotective effects and even indicated a possibility of harm [32*]. The absence of efficacy is consistent with a recently reported stroke trial [33]. Possible statistical and methodological causes (e.g. lack of power to detect differences) of these negative results have not been identified. Even though magnesium administration (dose, start time, duration, concentration) in these studies was based on positive preclinical data, and targeted serum levels of magnesium were achieved, availability of magnesium in cerebrospinal fluid (CSF) or cerebral extracellular fluid might be a concern [34–36]. Further studies to elucidate the relationships between total and ionized concentrations of magnesium in serum and CSF at different times following clinical TBI may hopefully provide an explanation for the negative results of recent clinical trials.

**Mitochondrial dysfunction**

Mitochondria, as the centers of aerobic metabolism, show marked dysfunction following experimental and clinical TBI, contributing to cell death through several mechanisms. Increased mitochondrial calcium results in decreased ATP production and generation of reactive oxygen species as well as increased permeability of the inner mitochondrial membrane. The opening of the mitochondrial permeability transition pore is responsible for mitochondrial swelling and membrane rupture, resulting in cell death. Mitochondrial dysfunction can be attenuated by inhibitors of mitochondrial permeability transition such as cyclosporin A and its derivatives [37]. Based on preclinical data cyclosporin A has been evaluated in two phase II clinical trials, and was found to improve cerebral perfusion pressure and cerebral metabolism, as evaluated with microdialysis. Cyclosporin A is considered safe in TBI patients, and its CSF pharmacokinetics in the injured central nervous system have been elucidated, supporting the initiative for a phase III clinical trial, which is currently being designed [38*,39,40].

In experimental research, blockage of N-type voltage-gated calcium channels by ziconotide (SNX-111) has been shown to induce partial restoration of mitochondrial function, but a clinical trial was terminated prematurely because of increased mortality in the treatment group. Newly developed, more selective N-type voltage-gated calcium-channel blockers like SNX-185 have better bioavailability, and appear neuroprotective in experimental models, but will need additional preclinical evaluation [41].

**Erythropoietin**

Erythropoietin is a kidney-derived cytokine regulating hematopoiesis, and has recently been recognized as being neuroprotective. Abundant expression of erythropoietin and its receptor in most of the cell types in the central nervous system exists, and in response to hypoxia or excitotoxicity this expression is increased, suggesting a central role in endogenous protection from deleterious stimuli [42]. Erythropoietin has been shown to be
neuroprotective in experimental models of stroke, and following experimental TBI treatment with erythropoietin leads to decreased lesion volume and improved functional outcome, possibly by limiting the inflammatory reaction [43]. Based on these experimental data clinical trials were initiated and the safety of erythropoietin administration in stroke patients was confirmed. A double-blind proof-of-concept trial showed no adverse events, and suggested improved functional outcome in erythropoietin-treated patients [44]. These results prompted further clinical research, which is currently being conducted as a multicenter phase II/III trial in stroke patients, as well as an additional pharmacokinetic study evaluating CSF erythropoietin following systemic administration [45]. In TBI, a randomized phase II clinical trial is currently ongoing in Wisconsin, USA. This trial focuses primarily on moderate TBI patients, and instead of using the Glasgow Outcome Score evaluates neuronal cell-death markers as a primary outcome measure.

Hormones
There has been considerable debate about sex differences in outcome following TBI, but a large meta-analysis suggests that no differences in outcome between men and women exist in outcome following TBI [46]. This debate, however, together with gender difference in treatment response and outcome in experimental TBI, stimulated research directed at the role of sex steroids following TBI. Both progesterone and estrogen may exert neuroprotective effects [47]. Based on experimental research, progesterone is thought to exert its neuroprotective effects through a variety of mechanisms including a decrease of edema formation due to changes in the blood–brain barrier and modulation of γ-aminobutyric acid (GABA)-ergic neurotransmission resulting in decreased excitotoxicity. In addition progesterone inhibits apoptosis and reduces gliosis and the postraumatic inflammatory response [48,49]. Allopregnanolone, a metabolite of progesterone, has also been shown to be neuroprotective, and might even be more effective than progesterone [50]. Both progesterone and allopregnanolone improve neuronal survival and functional recovery following experimental TBI [51].

In experimental TBI estrogen has shown to possess antioxidant and antiapoptotic properties, and improves cerebral blood flow. However, estrogen supplementation in females increased mortality following experimental brain injury [47], and most studies evaluating estrogen used pretreatment paradigms, raising questions about the value of estrogen in clinical TBI.

The wealth of experimental data on neuroprotective effects of progesterone together with adequate pharmacokinetic studies [52] resulted in a phase II clinical trial which concluded that no serious adverse events occurred due to progesterone administration in TBI patients. Even more interesting was the observation that, in moderate TBI survivors treated with progesterone, the outcome was better than in those treated with placebo [53]. A large multicenter study to prove what this study suggests has been initiated by the authors.

Bradykinin antagonists
Increased production of kinins has been reported following brain trauma, and their interaction with the constitutive B2-bradykinin receptor has been shown to be important in the development of postinjury inflammation-induced secondary damage. Specific inhibition of the B2-bradykinin receptor is considered a promising strategy for neuroprotection. Experimental data support this strategy, and recently a phase I clinical trial to investigate the pharmacokinetics of Anatibant, a selective potent bradykinin receptor antagonist, was conducted and published [54]. Currently a phase II safety study is being conducted on 500 patients with TBI.

Nitric oxide and inhibitors of nitric oxide synthases
Nitric oxide is a key factor in the development of secondary injury, regulating the dilation of blood vessels and acting as chemotoxin during inflammatory processes. Nitric oxide is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS), of which four isoforms have been identified. Three of these are constitutive and one inducible [55]. The three constitutive isoforms are neuronal NOS, endothelial NOS and mitochondrial NOS. The fourth isoform is the inducible NOS (iNOS), which is induced under pathological conditions [55–57].

In excess, nitric oxide is potentially neurotoxic because it contributes to excitotoxic neuronal death, generates cytotoxic peroxynitrites, damages DNA directly, inhibits DNA synthesis, inhibits mitochondrial respiration, and has been associated with apoptotic cell death [58]. In addition to producing nitric oxide, NOSs are also known to produce considerable amounts of the free radicals superoxide and hydrogen peroxide. This occurs particularly when substrate levels fall below those required to saturate the enzyme. This mechanism is called uncoupling of NOS [59,60]. Following TBI, nitric oxide synthesis is also activated by inflammation, which is initiated by both primary and secondary injuries. Proinflammatory cytokines can induce iNOS, thereby promoting persistent iNOS over-activation for several days after injury [61]. iNOS is mainly expressed in macrophages, microglia and infiltrating neutrophils recruited from the blood and thus has a substantially greater capacity to synthesize nitric oxide than endothelial NOS [58,61]. During the course of the pathophysiological process triggered by TBI, nitric oxide accumulates in the brain immediately after injury, as well as several hours or days later.
Various studies have shown that nitric oxide and the NOS pathways are involved, both positively and negatively, in the secondary injury cascade following injury. These pathways, and the recognition of the importance of nitric oxide in modulating regional cerebral blood flow, indicate a promising treatment target. Overall, experimental studies with inhibitors of NOS have shown beneficial effects, in particular with inhibitors of neuronal NOS and iNOS\(^{[8**]}\). Other studies, however, failed to show benefit and a few even show deleterious effects (see \(^{[8**]}\) for references). These differences may reflect differential effects of agents investigated on the different isoforms of NOS as well as time-dependent influences. A new drug currently under investigation is the compound VAS203, a structural analog of 5678-tetrahydro-1-bioperin (BH4), the endogenous cofactor of NOS, and one of the most potent inhibitors of NOs discovered so far. This compound competitively displaces BH4 from NOS and thus inhibits the formation of nitric oxide, but does not interact with the binding site of the substrate (L-arginine) \(^{[62]}\). Further, VAS203 is capable of reducing uncoupling of NOS, with an additional effect, the inhibition of increased superoxide production.

**Translational neuroprotection: neuroprotection from bench to bedside**

The neuroprotective agents that fail in clinical trials have all been proven effective in experimental models. One could question whether the current models of TBI adequately mimic human TBI. Many aspects of human TBI, either focal or diffuse, are reflected by the different experimental models, but experimental models cannot reproduce the entire heterogeneous spectrum of clinical TBI \(^{[63]}\). Additional concerns exist about the severity of experimental injuries as well as ultra-early or even pretreatment paradigms in experimental TBI. Extrapolation of results obtained in animals to clinical setting will remain problematic.

In ‘early’ TBI trials patient inclusion was primarily based on Glasgow Coma Score on admission (Table 2). The actual presence of the pathophysiological mechanism that was targeted with the neuroprotective compound that was studied, however, has hardly or never been confirmed. The presence of certain pathophysiological mechanisms in patients should be the basis of inclusion in a clinical trial evaluating the compound that interferes with this mechanism in a hopefully beneficial manner. In other words: diffuse axonal injury patients and subdural hematoma patients should not be included in the same trial even though their Glasgow Coma Scores on admission are identical. We should select and include patients in trials that are likely to benefit from the evaluated treatment \(^{[64]}\).

Similarly, mild and moderate TBI may be considered completely different diseases than severe TBI. Unsuccessful clinical trials in which the subpopulation of moderately injured patients responded to therapy (e.g. \(^{[53]}\)) raise the question of whether trials should not focus more on moderate or even mild TBI patients whose brains actually are ‘salvageable’. This population remains poorly represented in clinical trials, but constitutes the majority of all TBI worldwide.

To date, both clinical trials and experimental research have focused on the evaluation of a single potential neuroprotective compound at a time when it is considered unlikely that one ‘magic bullet’ will improve outcome in all subtypes of TBI. Serious consideration should be given to the possibility of combination therapies in which multiple compounds are administered sequentially, each in their own appropriate therapeutic time window.

Another major concern in clinical trials is the uncertainty about pharmacokinetics in the TBI patient, which are considerably different from the normal physiological situation. In recent phase III trials drug administration was based on specifically designed phase II trials \(^{[32,40]}\). More detailed pharmacokinetic studies are advocated by some, in which, in addition to the target, serum concentrations in CSF or cerebral extracellular fluid should be monitored \(^{[34,57]}\). In this development, cerebral microdialysis is likely to become an increasingly important monitoring tool for diagnosis (presence of a pathophysiological mechanism in a patient), drug monitoring (measurement of drug concentration in the target organ) and outcome (surrogate outcome markers) in clinical TBI \(^{[65]}\).

**Outcome**

Pharmaceutical clinical trials in TBI, to date, have been largely unsuccessful \(^{[66**]}\). To improve the quality of future clinical trials it is imperative that all data, including negative data, are published. Unfortunately, studies with negative results have not always been published (Table 2). In addition, trials have been prematurely terminated by sponsors because of interim analysis or (primarily psychomimetic) adverse effects in concurrent stroke trials. The question remains whether adverse effects leading to termination of clinical trials in stroke should have the same consequence in TBI trials because the average TBI patient, in contrast to the average stroke patient, is younger and – more importantly – comatose and fully sedated at the time of drug administration.

The primary end point in most TBI trials to date has been the dichotomized Glasgow Outcome Score (favorable/unfavorable). The use of this scale, together with the hypothesis of most trials that a 10% increase in favorable outcome is considered a positive result, has led to negative trial results. Although reported as negative, many trials showed some improvement in outcome.
but this was not statistically significant, indicating that neither efficacy nor inefficacy of the tested compound was proven.

In the recently published Dexanabinol trial, a new statistical method to reduce the effect of differences in initial prognostic risk factors on outcome analysis has been introduced. This so-called sliding dichotomy reduces the effect of differences in initial prognostic risk on outcome analysis, and thereby improves statistical power [27,67]. Somewhat similar, an improved outcome measure was introduced in the recently published magnesium trial. A composite outcome measure consisting of mortality, seizures, functional measures and neuropsychological tests was used as a primary outcome in this study, and is suggested to be more sensitive for the detection of a treatment effect [32]. The value of such composite outcomes, however, remains to be further evaluated in additional clinical trials.

In addition to clinical outcome markers there is an argument that surrogate outcome markers, like intracranial pressure, improved lactate/pyruvate ratio, or other biochemical markers, can be used to reflect therapeutic efficacy. Such surrogate outcome markers, however, would have to correlate with outcome, and this has not been proven to date, even for the most studied surrogate outcome marker, intracranial pressure.

A further complicating factor in clinical trials to date has been the limited standardization of treatment. Analysis of multicenter trials has shown heterogeneities in the patient population and treatment approaches, which have not been corrected for by covariate adjustment [68,69]. In contrast, generalization of results from single-center trials is not necessarily valid, as a result of differences in treatment. Adherence to treatment protocols using evidence-based guidelines is likely to reduce heterogeneity in multicenter clinical trials [4].

Conclusion

TBI is a major central-nervous-system disorder, with enormous burden to individual patients and society. Although extensive preclinical research has identified numerous effective neuroprotective agents, none of these agents has been proven to be effective in clinical trials. Before translation into clinical trial, experimental evidence should be strong, based on multiple experiments, preferably in multiple models, and include pharmacokinetic analysis. Successful translation of compounds into clinical trials will probably require a more mechanistic approach, in which only patients with the proven presence of a certain pathophysiological mechanism are included in trials evaluating a compound that interferes with this particular mechanism. Extensive pharmacokinetic evaluation of the potential neuroprotective agent in the injured brain should be required, ensuring adequate tissue penetration once the agent is studied in efficacy trials. A more sensitive analysis of outcome in new types of clinical trials is advocated, with an important role for surrogate outcome measures as well as new types of outcome analysis. Further standardization in treatment is likely to benefit from further development of evidence-based treatment guidelines. Implementation of these suggestions, even though a complex challenge, is likely to improve the chance that experimentally effective agents will show positive results in future clinical trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 226–227).


This paper summarizes the current knowledge on the epidemiology of TBI in Europe and serves to highlight the lack of standardized data.


This is an excellent and extensive review of almost all preclinical research in TBI research.


Neuroprotection in traumatic brain injury


29 Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006; 97:1611 – 1626.


35 Chen HS, Lipton SA. The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem 2006; 97:1611 – 1626.

This is a brief review with the same topic as the current review. There is some overlap in the drugs discussed, some points of view are different.
Cervical spinal injury occurs in 2% of victims of blunt trauma; the incidence is increased if the Glasgow Coma Scale score is less than 8 or if there is a focal neurologic deficit. Immobilization of the spine after trauma is advocated as a standard of care. A three-view x-ray series supplemented with computed tomography imaging is an effective imaging strategy to rule out cervical spinal injury. Secondary neurologic injury occurs in 2–10% of patients after cervical spinal injury; it seems to be an inevitable consequence of the primary injury in a subpopulation of patients. All airway interventions cause spinal movement; immobilization may have a modest effect in limiting spinal movement during airway maneuvers. Many anesthesiologists state a preference for the fiberoptic bronchoscope to facilitate airway management, although there is considerable, favorable experience with the direct laryngoscope in cervical spinal injury patients. There are no outcome data that would support a recommendation for a particular practice option for airway management; a number of options seem appropriate and acceptable.

THE provision of acute medical care to patients with cervical spinal injuries (CSIs) is a complex, challenging, and rewarding task. It is also an anxiety-provoking endeavor because care is provided in a milieu where there is constant concern about medical interventions resulting in the conversion of a spinal injury without neurologic sequelae to one in which the two are now concurrent. It is also a topic of continuous debate because care providers struggle in an environment of limited data and incomplete answers to try to craft clinical care paradigms designed to optimize preservation and return of neurologic function, while minimizing the risk of creating additional injury and neurologic compromise. Many questions regarding the initial care of these patients, particularly as they relate to airway management, remain unresolved, but there has been great effort, energy, and enthusiasm expended during the past two decades searching for these answers. This article reviews the literature that has been generated on the topic of airway management after CSI, particularly that published in the past 10 yr, identifying new areas of knowledge and evolving practice patterns. It also attempts to address and resolve controversy surrounding areas of care that have proven more contentious, most particularly the use of the direct laryngoscope to facilitate direct tracheal intubation in these patients.

The Adult Cervical Spine: Stability, Injury, and Instability

Movement and Stability of the Upper Cervical Spine

Flexion–extension occurs in the upper cervical spine at both the atlanto-occipital and atlantoaxial articulations, and a combined 24° of motion may be achieved. Flexion is limited by contact between the odontoid process and the anterior border of the foramen magnum at the atlanto-occipital articulation and by the tectorial membrane and posterior elements at the Cl–C2 level. Extension is limited by the contact of the posterior arch of the atlas with the occiput superiorly and with the arch of the axis inferiorly. The distance from the posterior arch of the atlas to the occiput is termed the atlantooccipital gap, and a narrow atlanto-occipital gap has been cited as being a cause of difficult intubation. Nichol and Zuck suggested that attempts to extend the head in patients with a narrow atlanto-occipital gap results in anterior bowing of the cervical spine, forward displacement of the larynx, and a poor view during laryngoscopy. This concept, although offering an elegant anatomical explanation for the clinical experience of difficult laryngoscopy, has yet to be validated, and the truth may be simpler. Calder et al. have reported that limited separation of the occiput from the atlas and the atlas from the axis yields an immobile upper spine and reduces both cervical spine extension and mouth opening, resulting in difficult direct laryngoscopy.

The ligaments contributing to the stability of the upper complex are the transverse, apical, and alar ligaments as well as the superior terminations of the anterior and posterior longitudinal ligaments (fig. 1). In adults, the transverse ligament normally allows no more than 3 mm of anteroposterior translation between the dens and...
the anterior arch of the atlas. This may be measured on lateral radiographs of the neck and is termed the atlas-dens interval. If the transverse ligament alone is disrupted and the alar and apical ligaments remain intact, up to 5 mm of movement may be seen. If all the ligaments have been disrupted, 10 mm or more of displacement may be seen. Destruction of these ligaments is a common consequence of severe and long-standing rheumatoid arthritis.4

Significant posterior displacement of the dens reduces the space available for the spinal cord (SAC) in the vertebral column. The SAC is defined as the diameter of the spinal canal measured in the anteroposterior plane, at the Cl level, that is not occupied by the odontoid process. The SAC represents the area composed of both cord and space. The area of the spinal canal at Cl may be divided into one third odontoid, one third cord, and one third “space.” The one third space allows for some encroachment of the spinal lumen without cord compromise. However, when this margin of safety has been exhausted, compression of neural elements will occur; persistent compression will eventually lead to myelopathy and neurologic deficit. The cord occupies a greater proportion of the available SAC in the subaxial spine; at the C6 level, approximately 75% of the SAC is occupied by the cord.5

**Movement and Stability of the Lower Cervical Spine**

A further 66° of flexion–extension may be achieved in the lower cervical spine, with the C5–C7 segments contributing the largest component. There is an inverse relation between age and range of motion, i.e., as age increases, mobility decreases. However, most of the decrease occurs at the C5–C7 motion segments, and this usually does not have a significant impact on the ease of direct laryngoscopy. With the head in the standard sniffing position, the cervical spine below C5 is relatively straight; there is increasing flexion from C4 to C2, and the occipitoatlantoaxial complex is at or near full extension.

In the lower cervical spine, the structures contributing to stability include, from anterior to posterior, the anterior longitudinal ligament, the intervertebral discs, the posterior longitudinal ligament, the facet joints with their capsular ligaments and the intertransverse ligaments, the interspinous ligament, and the supraspinous ligaments (fig. 2). The posterior longitudinal ligament and the structures anterior to it are grouped as the anterior elements or anterior column (fig. 3). The posterior elements or posterior column are those grouped behind the posterior ligament. Motion segments are defined as two adjacent vertebrae and the intervening soft tissue elements.
Cervical Spinal Instability after Injury: Mechanisms and Consequences

White et al.6 have defined stability as “the ability of the spine to limit its pattern of displacement under physiologic loads so as not to allow damage or irritation of the spinal cord or nerve roots.” Instability occurs when physiologic loading causes patterns of vertebral displacement that jeopardize the spinal cord or nerve roots.7 Instability may result from congenital anomalies, acquired conditions related to chronic disease, and acutely after trauma. The following discussion will primarily relate to traumatic instability.

One element in the injured column must be preserved to achieve spinal stability. Clinically, to ensure a margin of safety, preservation of elements in the injured column cannot be assumed, and the spine must be considered to be potentially unstable until proven otherwise. The anterior column contributes more to the stability of the spine in extension, and the posterior column exerts its major forces in flexion. Therefore, the anterior elements tend to be disrupted in hyperextension injuries, and the posterior elements tend to be disrupted in hyperflexion injuries. With extreme flexion or extension or if either a compressive or rotational force is added, both columns may be disrupted.

Flexion injuries usually cause compression of the anterior column and distraction of the posterior column (fig. 4).5 Pure flexion trauma may result in wedge fracture of the vertebral body without ligamentous injuries. These injuries are stable and are rarely associated with neurologic injuries. With more extreme trauma, elements of the posterior column are disrupted as well, and facet joint dislocation may result. These injuries are unstable and are associated with a high incidence of cord damage. Flexion–rotation injuries also commonly disrupt the posterior ligamentous complex and may also produce facet joint dislocation. They tend to be stable and are not usually associated with spinal cord injury, although cervical root injury is common. Hyperextension injuries cause compression of the posterior column and distraction of the anterior column (fig. 4). Hyperextension combined with compressive forces (e.g., diving injury) may result in injury to the lateral vertebral masses, pedicles, and laminae. Because both anterior and posterior columns are disrupted, this injury is unstable and is associated with a high incidence of cord injury. Violent hyperextension, with fracture of the pedicles of C2 and forward movement of C2 on C3, produces a traumatic spondylolisthesis of the axis, or hangman’s fracture. The fracture is unstable, but the degree of neurologic compromise is highly variable, because the bilateral pedicular fractures serve to decompress the spinal cord at the site of injury.

Burst fractures are caused by compressive loading of the vertex of the skull in the neutral position and are not as common as flexion–extension injuries. Compression forces in the lower cervical spine result in the explosion of intervertebral disc material into the vertebral body. Depending on the magnitude of the compression loading and associated angulating forces, the resulting injury ranges from loss of vertebral body height with relatively intact margins, to complete disruption of the vertebral body. Posterior displacement (retropulsion) of comminuted fragments may result, producing cord injury; the spine is usually stable. Pure distraction injuries are uncommon but, if severe, may result in ligamentous disruption causing both cord trauma and an unstable spine.

Determining Stability of the Cervical Spine after Injury

Because spinal instability usually results in vertebral displacement, it may be detected in many instances by radiography. White and Panjabi6 identified the upper limit of vertebral displacement and that which is beyond the physiologic range. They concluded that a normal adult spine would not permit horizontal motion greater than 2.7 mm between vertebrae. Therefore, if horizontal displacement exceeding 3.5 mm (corrected for x-ray magnification) or 20% of the vertebral body width was
found on lateral radiographs of the neck (or with flexion-extension views or dynamic fluoroscopy), this motion was deemed abnormal and the spine was considered unstable. With respect to angular displacement, the upper limit of physiologic angular displacement of a vertebral body compared with adjacent vertebrae was 11°. If there is greater angulation of the vertebra in question demonstrated on imaging studies, the spine is deemed unstable at the site of the excessively rotated vertebra.

The ligamentous structures, intervertebral discs, and osseous articulations have been extensively studied, and their major role in determining clinical stability has been demonstrated. Although the muscles in the neck exert some stabilizing forces, the contribution that they make toward clinical stability has not been studied. The repeated observation that secondary neurologic injuries occur frequently in spine-injured patients who are not immobilized suggests that muscle splinting is not highly protective after injury.

Not all cervical spine injuries result in clinical instability. Generally, fractures are considered to be clinically insignificant if failing to identify them would be unlikely to result in harm to the patient or, alternatively, recognizing the injury would prompt no specific treatment. Two groups have categorized, by expert consensus, a number of injuries as not clinically important. The National Emergency X-Radiography Utilization Study (NEXUS) group identified the following injuries as not clinically significant: spinous process fractures, wedge compression fractures with loss of 25% or less of body height, isolated avulsion fractures without ligament injury, type 1 odontoid fractures, end-plate fractures, isolated osteophyte fractures, trabecular fractures, and isolated transverse process fractures. Similarly, the Canadian CT Head and Cervical Spine Study group identified the following injuries as not significant: simple osteophyte fractures, transverse process fractures, spinous process fractures, and compression fractures with loss of less than 25% of body height.

Mechanisms of Spinal Cord Injury

There are a number of mechanisms implicated in primary spinal cord injuries. Immediate neural damage may result from shear, compressive, ballistic, or distracting forces, which primarily avulse and devitalize tissues. Persistent cord compression from fracture–dislocation may lead to ischemia. The cord may be injured by bone fragment or missile injury with resultant laceration, contusion or concussion. Secondary and progressive injury may also result from local perfusion deficits due to vascular compression by deranged anatomy (e.g., tissue damage or edema) or from global perfusion compromise caused by systemic hypotension. In addition, tissue hypoxemia leading to secondary injury may also occur as a result of hypoventilation caused by head or cord injury or by primary lung trauma. Finally, there are multiple mechanisms at the cellular and subcellular level that may result in exacerbation of the injury resulting in an extension of the clinical deficit.

The impact of persistent cord compression and the benefits of urgent decompression of injured cord have been assessed by a number of authors. Carlson et al. determined the relation between the duration of sustained spinal cord compression and the extent of spinal cord injury and the capacity for functional recovery after immediate decompression. Sixteen dogs underwent spinal cord compression for 30 or 180 min. Sustained cord compression was associated with a gradual decline in the amplitude of evoked potentials. Within 1 h of decompression, dogs that had experienced 30 min of compression had recovery of the evoked potentials, but no animal that had been subjected to 180 min of compression had similar recovery. Motor tests demonstrated rapid recovery of hind-limb function in the 30-min group, but there was considerable impairment in the 180-min group, and this impairment was persistent. In a similar model, Delamarter et al. demonstrated that neurologic recovery after 1 h of cord compression occurred after immediate decompression but not when cord compression persisted for 6 h or more.

Despite the basic science support for early decompression after spinal cord injury, two recent reviews have concluded that the evidence supports decompression as a practice option only. The authors of these reviews concluded that the data assessing the impact of early decompression on neurologic outcomes was limited, consisted of primarily class III (case series, retrospective reviews, and opinion) and limited class II (prospective cohort studies or controlled studies with comparison cohorts) evidence, and demonstrated a possible benefit to patients with incomplete injury only. Both early decompression and conservative management were associated with neurologic improvement in some patients and deterioration in others. Both groups of authors acknowledged the need for randomized, controlled trials to better delineate the role of surgery in the management of acute spinal cord injury.
Fig. 5. The Poisson effect: schematic representation. The axis of rotation is indicated by the small squares superimposed on the vertebral bodies. In the neutral position (A), the gentle arc of the normal lordotic curve is transcribed. In extension (B), the elements posterior to the bodies, including the canal, transcribe the arc of a smaller circle than that of the vertebral bodies, indicated by the small circles. In flexion (C), the opposite effect is seen, and the arc of a larger circle is transcribed by the posterior elements. The Poisson effect dictates that as the extension increases (the arc is of a larger circle), the cross-sectional area (lumen) of the column will decrease.

The functional size of the spinal canal may be further reduced with movement. The spinal canal is a column of relatively fixed volume. As it lengthens, its cross-sectional area will be reduced, and as it is shortened, its area will be increased; this behavior is termed the Poisson effect. With flexion, the canal length is increased and its area is reduced; the cord is stretched. This occurs because the axis of rotation of the spine is centered in the vertebral body. As the spine flexes, the rotation points will transcribe an arc; posterior spinal elements, including the canal, will also transcribe an arc, but that of a larger circle and will axially lengthen (fig. 5). The Poisson effect dictates that both the lumen of the canal and the spinal cord will narrow as they lengthen. The cord will tolerate a degree of elastic deformation while maintaining normal neurologic function. It may be further stretched and deformed if there is a local anomaly such as an osteophyte, prolapsed disc, or subluxed vertebral body projecting into the canal. These deformations may, over time, result in the application of strain and shear forces to the cord and ultimately result in axonal injury and myelopathy.

With extension, the canal length is decreased and its area is increased; the cord is shortened. Again, this is an effect of the axis of rotation being centered in the vertebral bodies and the posterior spinal elements including the canal now transcribing the arc of a smaller circle; the Poisson effect will dictate canal widening. However, the shortening and folding of the cord when the spine is in extension may result in a relative increase in the ratio of cord size to canal lumen, despite the potential increase in the lumen. As well, there is posterior protrusion of the disc annulus and buckling of the ligamentum flavum in extension, which may further reduce canal dimensions and the space available for the cord at any given vertebral level. A number of age-related pathologic processes, including osteophyte formation and ossification of the posterior longitudinal ligament, may lead to further impingement on the canal lumen; these typically manifest a greater impact during spinal extension.

Ching et al. measured the impact of different positioning on canal occlusion in a cervical spine burst fracture model. Extension increased the canal occlusion to levels normally associated with the onset of neurologic injury. Flexion did not result in a significant increase in canal occlusion. These observations run counterintuitive to what might be expected on the basis of the Poisson effect and are likely manifestations of both the soft tissue buckling and bone fragment retropulsion which occur during extension. Prone positioning is also often associated with modest degrees of extension, and there is evidence that canal stenosis is increased with patients with cervical myelopathy who are positioned prone compared with supine positioning. Again, this is likely a manifestation of the soft tissue encroachment on the spinal canal with extension and aggravated by the preexistent canal compromise. The clinical relevance of these findings is that a persistent malposition of an abnormal neck may result in a degree of cord compression. If the abnormality is modest, it is likely that the malposition will need to be of greater magnitude and more prolonged to cause harm; as the anatomical derangement is increased, the duration of positional stress required to cause harm is shortened. Prone positioning is also associated with increases in vena caval pressures that may further reduce cord blood flow already compromised by cord compression.

Dominguez et al. reported the occurrence of irreversible tetraplegia in a 21-yr-old woman without cervical pathology whose neck was maintained in extreme flexion after tracheal reconstruction; a magnetic resonance imaging (MRI) study was consistent with cord infarction. Deem et al. reported the occurrence of quadriplegia in a 60-yr-old man with severe cervical stenosis after thoracolumbar surgery in the prone position. The patient’s trachea was intubated, and he was positioned prone while still awake; anesthesia was in-
duced after his cervical spinal positioning was ascertained to be near neutral, and neurologic examination results were deemed normal. When he awoke from anesthesia after 6 h of surgery, there was evidence of a central cord syndrome. The authors acknowledge the possibility that, even though extreme degrees of flexion and extension were avoided, more subtle degrees of malpositioning may have been present. Unfortunately, cord injury may occur when positions detrimental to canal architecture are persistent; the greater the degree of underlying spinal pathology is, the lesser the magnitude of malpositioning required to cause harm is. The prone position may be especially threatening in these instances for the reasons already outlined.

Patients with severe cervical spondylosis may manifest such severe positional intolerance that they develop symptoms of cord compromise with degrees of malposition that may be imperceptible to the caregivers. Miller et al. described exacerbation of neurologic symptoms in a 74-yr-old woman with an osseous bar at C3–C4 who presented with signs of cord compression and was booked for cervical laminectomy. On the first surgical occasion, after awake tracheal intubation accomplished with sedation, she was considerably weaker than before intubation. Surgery was cancelled, and her trachea was extubated; her neurologic condition returned to baseline within 2 h. Four days later, she presented for surgery in halo traction, and after sedation with intravenous diazepam, her neurologic condition deteriorated. A joint decision was made to induce anesthesia and proceed with tracheal intubation and surgical laminectomy at the C3–C5 spinal levels. Although she awoke with signs of neurologic deterioration, she recovered to her baseline condition by the fourth hour. The authors of this report postulated that the increased neurologic symptoms were an effect of the medications administered to facilitate awake intubation. Whether the drugs actually caused deterioration in the patient’s neurologic status or made the neurologic assessment less reliable is not certain. Equally unknown is whether, in general, patients might be more likely to overlook or underreport neurologic changes that occur if they were sedated during awake intubation. The reliability of a neurologic assessment in a sedated patient might be questioned, especially if one is seeking evidence of subtle changes.

Bejjani et al. reported the case of a 54-yr-old woman with cervical spondylosis and canal stenosis from C4 to C7 who developed signs of cord compression while her head was restrained in a plastic head-holder for the purpose of cerebral angiography. Approximately 45 min after the procedure had begun, she reported neck pain and upper extremity weakness; her symptoms were attributed to anxiety, and she was sedated. At the termination of the procedure, she was hemiparetic on the left side; an MRI study revealed a high-signal lesion consistent with edema. She recovered completely over the next 6 weeks. The potential for general anesthesia to permit positioning for MRI in postures not tolerated by awake patients with resultant neurologic injury has also been reported.

Magnaes measured cerebral spinal fluid pressure with the neck in the extended position for tracheal intubation, in eight patients with a compromised spinal canal due to cervical spondylosis. Pressures up to approximately 140 cm H2O were recorded. Longitudinal skeletal traction with the tong placed frontally significantly reduced the pressure on the spinal cord in all patients. This finding would suggest that there is likely a benefit, in terms of decreased intracanal pressures, in maintaining the compromised cervical spine in as close to the neutral position as possible at all times after injury. As has already been noted, it may be very difficult to determine neutral position in some patients.

Persistent severe malpositioning at the extremes of the spinal range of motion has the potential to cause harm even in the normal spine–cord complex. In patients with disease processes that result in spinal canal compromise, minor degrees of malpositioning may also result in severe stress to the cord. If these positions are enforced, especially for prolonged periods, neurologic injury may result. As well, the use of sedation or anesthesia to allow patients to be maintained in positions that are neurologically intolerable to them while awake may also result in neurologic injury.

Cervical Spine Trauma: Epidemiology and Clinical Characteristics

The Incidence of Cervical Spinal Injury after Blunt Trauma

The incidence of CSI in victims of blunt trauma is estimated to be 0.9–3%, with a weighted average of 1.8%. Many of these previously published studies evaluating CSI after blunt trauma involved data from individual institutions or limited populations of trauma victims; there have been few data available regarding injury patterns at a national level. A substudy of NEXUS was designed to provide such data regarding the prevalence, spectrum, and distribution of CSI after blunt trauma. A total of 34,069 patients with blunt trauma undergoing cervical spine radiography at 21 US institutions were enrolled. Consistent with past reports, 818 (2.4%) of trauma victims had a total of 1,496 distinct CSIs. The second cervical vertebra (C2) was the most common level of injury (24.0% of all fractures), and 39.3% of fractures occurred in the two lowest cervical vertebrae (C6, C7). The vertebral body was the most frequent anatomical site of fracture; nearly one third of all injuries (29.3%) were considered clinically insignificant.
Cervical Spine Injury and Associated Craniocerebral Trauma

Although it has been reported that patients with craniocerebral trauma had an incidence of CSI similar to that of the general trauma population, review of the large databases evolving at major trauma centers now dispute this finding. Holly et al. 36 reviewed a large computerized database to assess the association between CSI and facial injuries in 3,083 patients with facial injuries. Two hundred and sixty (6.7%) of these patients had experienced a concomitant CSI, an incidence substantially higher than would be expected after blunt trauma. Blackmore et al. 39 reviewed their institutional experience with 472 patients with trauma (168 with cervical fractures, 302 without fractures) to delineate the characteristics of trauma patients with cervical fracture. The clinical predictors of cervical spine injury included severe head injury (odds ratio, 8.5; 95% confidence interval [CI], 4–17) and focal neurologic deficit (odds ratio, 58; 95% CI, 12–283). In patients with head injury, those who were persistently unconscious had an even higher likelihood of spinal injury (odds ratio, 14; 95% CI, 6–35) than those with head injury who were not unconscious. Therefore, new evidence has emerged that consistently suggests a higher incidence of cervical injury in patients who have experienced craniocerebral trauma, especially among those with increasing severity of craniocerebral injury as determined by low GCS score and unconsciousness. The finding of a focal neurologic deficit has been identified as a highly important clinical finding predicting spinal injury. 59

Systemic Injuries Associated with Cervical Spine Injury

The majority of patients with CSI also have other injuries; in only 20% of instances are traumatic injuries restricted to the cervical spine. 40 Although 2–10% of patients with craniocerebral trauma have CSI, 25–50% of patients with CSI have an associated head injury. Patients with additional injuries are more likely to experience hypoxia and hypotension, both of which may not only prompt urgent airway intervention, but may also predispose to secondary neurologic injury. There is data to suggest reduced neurologic recovery and increased mortality in cord-injured patients who have concurrent injury. It is not clear whether these patients experienced more severe primary injury or whether they are more likely to experience secondary injury leading to the poorer outcome.

Defining the Low-risk Trauma Patient

The National Emergency X-Radiography Utilization Study. The majority of patients who have experienced a blunt traumatic injury do not have a CSI. Enormous resources are currently expended to clear the spine (determine the absence of injury when injury does not exist) in these patients. The NEXUS project attempted to derive a set of clinical criteria to identify blunt trauma victims at low risk for CSI. 41 The decision instrument required patients to meet five criteria to be classified as having a low probability of injury: (1) no midline cervical tenderness; (2) no focal neurologic deficit; (3) normal alertness; (4) no intoxication; and (5) no painful, distracting injury. Distracting injuries were defined as including long bone fractures; visceral injuries requiring surgical consultation; large lacerations; burns; degloving or crush injuries; or any injury that might impair the patient’s ability to participate in a general physical, mental, or neurologic examination. The decision instrument was applied to 34,069 patients and identified as high risk all but 8 of the 818 patients who had a CSI (sensitivity, 99%; 95% CI, 98–99.6%). The negative predictive value was 99.8% (95% CI, 99.6–100%), the specificity was 12.9%, and the positive predictive value was 2.7%. Only two of the eight patients missed by the screening protocol had a clinically significant injury. In the NEXUS study, plain radiographs alone revealed 932 injuries in 498 patients but missed 564 injuries in 320 patients. 42 The majority of missed injuries (436 injuries in 237 patients) occurred in cases in which plain radiographs were interpreted as abnormal (but not diagnostic of injury) or inadequate. However, 23 patients had 35 injuries (including three potentially unstable injuries) that were not visualized on adequate plain film imaging. In the absence of all five clinical risk factors identified by the NEXUS study as predicting an increased risk of CSI, the likelihood of a significant injury is low. The practice of withholding imaging for patients who meet these exclusionary criteria has been endorsed by recent neurosurgical guidelines. 43

The Canadian C-Spine Rule for Radiography after Trauma. The Canadian CT Head and Cervical Spine Study Group attempted to derive an optimally sensitive clinical decision rule to allow for selectivity in the use of radiography in alert and stable trauma patients. 44 A prospective cohort study was conducted in 10 large Canadian hospitals and included 8,924 consecutive adult patients presenting to emergency departments after...
sustaining acute blunt trauma to the head or neck. Patients were eligible for enrollment if they were alert (GCS of 15), if they had stable vitals signs, and if they had either neck pain after injury or had no neck pain but visible injury above the clavicles after a dangerous mechanism of injury. The patients were assessed using 20 standardized clinical findings from the history, general physical examination, and an assessment of neurologic status. Patients then underwent diagnostic imaging at the discretion of the treating physician; this imaging consisted of a minimum of three views of the cervical spine.

Among the study sample, 151 patients (1.7%) had an important cervical injury. The resultant rule that was derived comprises three questions: (1) Is there any high-risk factor present that mandates radiography? (2) Are there low-risk factors that would allow a safe assessment of a range of motion? and (3) Is the patient able to actively rotate the neck 45° to the left and to the right? When applied to the study population, the derived rule had 100% sensitivity and 42.5% specificity for identifying patients with clinically important injuries. The rule also identified 27 of 28 patients with clinically unimportant cervical injuries (primarily avulsion fractures), defined as those not requiring stabilization or follow-up.

The NEXUS Low-Risk Criteria were compared prospectively with the Canadian C-Spine Rule in 8,283 patients presenting to Canadian hospital emergency departments after trauma.44 Two percent of patients had clinically important cervical injuries, and the C-Spine Rule was both more sensitive than the NEXUS criteria (99.4% vs. 90.7%) and more specific (45.1% vs. 36.8%) for injury. The C-Spine Rule would have missed one patient, and the NEXUS criteria would have missed 16 patients with important injuries.

Strategies to define a low-risk clinical population continue to evolve. It must be emphasized that the primary focus and utility of these strategies is to allow for selective use of diagnostic imaging in patients who have a low-risk of injury, thus reducing imaging use and patient exposure, conserving resources, and allowing for expedited and simplified care for this patient group. A criticism leveled at the NEXUS protocol is that application would have a limited impact in reducing imaging because only 12.9% of patients presenting after trauma would be deferred; most would not meet at least one deferral criteria.45 Application of the C-Spine Rule would allow for the exclusion of 42.5% of trauma patients from radiographic imaging. The original rationale for the derivation of the protocols, to provide more efficient care and conserve imaging resources, is satisfied to a very limited degree by the NEXUS protocol but to a greater degree by the C-Spine Rule. Application of either protocol will still demand imaging in a large portion of the trauma patient population at low risk for CSI.

There will be a small population of patients presenting for urgent surgical intervention after minor injury who are fully evaluable using either the NEXUS criteria (12.9%) or the C-Spine Rule (42.5%); it is likely not necessary to delay surgery to clear the cervical spine of these patients with detailed imaging. Unfortunately, many patients presenting for urgent operative interventions after trauma will manifest more severe injuries; it will not be possible to clinically rule out injury in this patient cohort, and they will still require diagnostic imaging. As well, application of these protocols is complicated by the fact that there is a lack of agreement on the definitions of both distracting injury and intoxication. Failure to appreciate the degree of both distraction and intoxication may reduce the clinical index of suspicion for injury, resulting in missed diagnosis.

Patterns of Practice in Evaluating and Clearing the Cervical Spine after Trauma

Two authors have recently reported descriptions of patterns of practice in the United States and the United Kingdom obtained through postal surveys regarding evaluation and clearance of the cervical spine after trauma.46,47 Grossmann et al.46 surveyed 165 US trauma centers and reported that between 26 and 73% had written protocols for cervical spine clearance after trauma. It was more common for level I and academic centers to have protocols. In most instances where a protocol existed, it also described the radiographic approach to clearance; most centers did not consider that either computerized tomography (CT) or MRI was the standard of care in this setting. The use of a five-view series was moderately prevalent in response to specific scenarios, and the problem of visualizing the cervicothoracic junction was dealt with in most centers (68%) using an axillary/swimmer’s radiographic view. For patients with a head injury who are comatose or who have altered mental status and who have normal plain films, 21% of level II and 10% of level I centers advocated removal of the cervical collar without further testing beyond a five-view series.

Jones et al.47 surveyed 27 United Kingdom neurosurgical and spine injury units to determine the methods of cervical spine clearance used in unconscious, adult trauma patients and the point at which immobilization was discontinued. Most centers did not have either a written protocol to perform clearance or one regarding discontinuing cervical immobilization (78%). All units relied to some degree on plain radiography for clearance; 10 units (37%) performed only a single lateral view as the initial evaluation, and the remainder performed two more views. Five units routinely used CT imaging, and 17 units (63%) made no use of CT to screen for cervical injury. If the initial investigations were normal, 12 units (44%) would discontinue immobilization, and 10 units continued it until the patient could be evaluated.
clinically irregardless as to the results of the screening imaging.

The Eastern Association for the Surgery of Trauma recently reported the results of a survey of 31 large American and Canadian trauma centers.† Centers were asked to identify their routine practice for determining cervical spinal stability in obtunded or comatose patients. Twenty-four centers (77%) reported using three views of the cervical spine (lateral, odontoid, and antero-posterior views) supplemented by CT through suspicious or poorly visualized areas. Three centers (9.7%) relied on three views only, and three centers (9.7%) added a swimmer’s view to visualize the lower cervical spine and the cervicothoracic junction.

There is considerable variation in the approach that different centers take in the performance of radiographic evaluation of at-risk patients, making the determination that the spine has been cleared, and reaching the decision that immobilizing devices can be safely removed. The most common pattern of practice in North American centers is to rely on multiple (at least three views) plain radiographs; the use of supplementary CT is also common.

Radiographic Assessment after Blunt Trauma: Evolving a Best Practice

An evaluative approach that would provide timely and accurate assessment of cervical stability in patients who may not be reliably examined clinically so that immobilizing devices can be safely removed is desirable. This would minimize the potential for sequelae related to prolonged immobilization. The reader is referred to three excellent reviews on the topic of evaluating and clearing the cervical spine in high-risk patients; these reviews form the basis of the subsequent discussion.45,48,49

The cross-table lateral radiograph, of acceptable quality and interpreted by an expert, will disclose the majority of injuries. However, the sensitivity of the cross-table view is such that up to 20% of patients with cervical injury will have a normal study. Half of cross-table views are deemed inadequate to properly assess the entire cervical anatomy; injuries at both the cranio-cervical and the cervicothoracic junctions are often not well visualized in the cross-table view. Too many injuries are missed when only a cross-table view is used for it to be considered an acceptable study to rule out injury in a high-risk patient. The sensitivity of three views (cervical series) approximates 90%; the cervical series was long regarded as an acceptable radiologic evaluation in patients deemed at risk for CSI. Similar technical concerns apply to the cervical series as to the cross-table lateral view with respect to both anatomical limitations at the cervical junctions and inadequate studies being issues. It is estimated that 1% of clinically important injuries will be missed even with a technically adequate cervical series.

A three-view cervical series supplemented by CT through areas that are either difficult to visualize or suspicious on plain radiography will detect most spinal injuries. The negative predictive value of this combination of studies is reported to be 99–100% in several class II and III evidence studies.45,48,49 In the obtunded patient with a normal cervical series and appropriate supplemental CT of the cervical spine, the incidence of significant spine injury is less than 1%. High-resolution CT scanning with sagittal reconstruction of the entire cervical spine rather than directed scanning of only at-risk areas may be even more effective in capturing virtually all injuries.

The use of MRI in addition to plain radiography and supplemental CT has been advocated to perform spinal clearance; the significance of a positive MRI study in the setting of negative CT imaging is currently unclear because many false-positive findings are reported with MRI. As well, MRI is less sensitive than CT for injuries in the upper and posterior cervical spine. Shuster et al.50 studied the role of MRI in assessing the spines of patients with persistent cervical pain and no motor deficits after trauma when the CT imaging was negative for injury. Ninety-three patients (3.4%) had a normal admission motor examination, a CT result negative for trauma, and persistent cervical spine pain; they underwent MRI examination. All MRI examinations were negative for clinically significant injury, and no patient subsequently experienced a neurologic deterioration. Hogan et al.51 assessed the role of magnetic resonance imaging in 366 obtunded or unreliable patients who had normal CT imaging after trauma. Magnetic resonance images were negative for acute injury in 354 of 366 patients; the most common injury seen was a cervical cord contusion, identified in 7 patients. Magnetic resonance images were also negative for spinal ligament injuries in 362 of 366 patients; 4 patients had ligament injuries, but in all cases, the injury was limited to the ligaments of a single column. CT had negative predictive values of 98.9% for ligament injury and 100% predictive value for unstable cervical injury; MRI identified a small number of patients with ligament injuries not diagnosed with CT, but none of these were deemed to be unstable injuries.

In summary, in a patient at high risk for cervical injury, who cannot be evaluated clinically, a three-view cervical series supplemented by high-resolution CT scanning with sagittal reconstruction will reduce the likelihood of an occult fracture to less than 1%. After a technically adequate imaging series has been reviewed and cleared by a radiologist, it is prudent to remove cervical immo-

Spinal Ligament Injuries and Spinal Cord Injury without Radiographic Abnormality

Spinal ligament injuries are of particular concern because of the high incidence of resultant spinal instability, the potential for cord injury, and the hemodynamic instability common at presentation in this subpopulation. In Demetriades' study of CSI patients admitted during 5 yr to a major trauma center, 31 patients (10.6%) had a ligament injury (subluxation without fracture), and 11 patients (3.8%) had an isolated spinal cord injury without fracture or subluxation (spinal cord injury without radiographic abnormality [SCIWORA]). Of the 31 patients with ligament injury, one third required tracheal intubation before clinical evaluation of the spine was completed. Of the 11 patients with spinal cord injury without radiographic abnormality, 27.3% required intubation before spinal evaluation occurred. The diagnosis of cord injury was made on admission in only 5 patients (45.5%) with spinal cord injury without radiographic abnormality. In 3 patients, the neurologic examination on admission was normal, and neurologic deficits appeared a few hours later. In the remaining 3 patients (2 intubated, 1 intoxicated), the diagnosis was missed initially. Patients who required urgent airway intervention were less likely to have had a complete neurologic evaluation and were more likely to have neurologic injury than those who did not require urgent interventions. Chiu et al. also investigated the incidence of cervical spinal ligament injury in 14,577 blunt trauma victims. Six hundred fourteen patients (4.2%) had CSI, and 87 (14% of CSI) had dislocation without evidence of fracture. There were 2,605 (18%) patients who could not be assessed for symptoms, and 143 (5.5%) of these unreliable patients had a CSI; 129 (90%) had a fracture, and 14 had no fracture.

Trauma patients with greater severity of injury are more likely to have had a CSI; clinical evaluation is more difficult in these patients, typically because of depressed consciousness. Patients with ligament injury of the cervical spine without fractures frequently require urgent intubation, and not uncommonly, clinical evaluation is either not possible or not complete at the time that intervention is required; delay in the diagnosis of injury is common in these patients.

Failure to Diagnose Cervical Spine Injury at Initial Assessment: Factors and Consequences

Patients with decreased mental status from trauma, alcohol, or drugs and patients with other painful or distracting injuries have an unreliable history and physical examination for CSI; patients with these characteristics have spinal injuries that are also more likely to be missed on initial presentation. The commonest reasons for missed diagnosis are failure to obtain radiographs, poor quality of the imaging study, or misinterpretation of the radiographs. Inadequate radiographic studies are more likely in patients with hemodynamic compromise on admission or in those patients urgently requiring intervention for operative treatment of associated injuries. Unfortunately, missed injuries are often unstable, and secondary neurologic lesions occur in 10–29% of patients whose injuries are not diagnosed at initial evaluation. Failure to immobilize the spine in patients whose injuries are missed at the initial assessment is considered to be a leading cause of secondary injury.

Poonnoose et al. conducted a detailed review of the experience of a specialty spinal cord injury unit to determine both the incidence of missed injury and the clinical mismanagement that occurred in the setting of missed injury. The medical records of 569 patients with neurologic deficits secondary to traumatic spinal cord injury were reviewed. In 52 instances (9.1%), the diagnosis was initially missed, and 26 of these patients (50%) had evidence of neurologic deterioration after admission. The median time to recognition of the injury was 4 days. Therapeutic interventions were performed in 34 patients that were deemed inappropriate to their condition before the diagnosis was made. In 19 patients, there were significant neurologic findings present on initial assessment, and in 7, the initial neurologic deficit was minimal. Nine patients eventually developed paralysis, and 6 died with the deaths attributed to the delay in diagnosis. Again, the major cause for delayed diagnosis was related to radiographic assessments: In 18 cases, the initial images were of poor quality; in 11 patients, the area of concern was not adequately visualized; in 10 cases, an obvious fracture was missed; in 11 cases, facet joint malalignment was not recognized; and in 10 cases, prevertebral hematoma went undetected. It was common for the clinicians to consider the spine cleared when the radiographs “failed” to reveal injury and to attribute neurologic findings to either preexistent conditions (e.g., ankylosing spondylitis) or peripheral traumatic injuries. As well, 7 patients with evidence of neurologic deficits were initially labeled as “hysterical” and not managed as at-risk.

It is unfortunately the case that patients with CSI are frequently not correctly diagnosed at the time of initial presentation. This may occur in a small percentage of CSI patients because the injury is a ligamentous one and the screening imaging seems on initial review to be negative. However, it more commonly occurs because there is a low index of suspicion for injury despite high-risk mechanisms, inadequate radiographic studies are deemed acceptable, and neurologic signs or symptoms are either attributed to other causes or ig-
Secondary Neurologic Injury after Cervical Spine Injury

Secondary injury may be precipitated in CSI victims when management is suboptimal, and in particular when the injured spine is not immobilized. However, there is also evidence that neurologic deterioration occurs after acute injury despite appropriate management paradigms; the reported incidence of neurologic deterioration in this setting ranges from 2 to 10%. Frankel reported the occurrence of an ascending myelopathy 2–18 days after spinal cord injury despite appropriate clinical management. Only patients with ascension of injury level of at least four levels were included in this analysis; despite the high threshold for inclusion, this magnitude of secondary injury occurred in 1% of 808 patients admitted to the center. Frankel attributed the deterioration to either vascular catastrophes (arterial insufficiency or venous thrombosis) or inflammation; this report predated MRI, so no imaging is available in these patients to support the clinical conjecture. Marshall et al. reported a prospective study assessing neurologic deterioration in cord-injured patients conducted in five US trauma centers. Deterioration occurred in 4.9% of patients and was consistent across the five centers. Although the deterioration was often associated with a specific intervention (surgery in 4 patients, traction application in 3, halo vest application in 2, Stryker frame rotation in 2, and rotobed rotation in 1), there was no evidence that these procedures were performed poorly or that they could have been performed in an altered fashion to prevent the deterioration. There were 375 such interventions recorded among the 283 patients. The authors concluded that deterioration is an inevitable consequence of providing care to cord-injured patients and will occur in some patients despite acceptable care practices.

Farmer et al. reported the experience of a US regional spinal cord center regarding neurologic deterioration after cervical cord injury. Deterioration was evident in 1.84% of 1,031 patients assessed. The average time from injury to deterioration was 3.95 days, and deteriorations were associated with early surgery (<5 days after injury), sepsis, ankylosing spondylitis, and tracheal intubation. Tracheal intubation was associated with two minor and two major deteriorations, but no further details were offered regarding this cohort; it is possible that the intubation was necessitated by the neurologic deterioration and not the cause of it. In the patients who experienced deterioration and survived, 92% of patients eventually had improvement in their neurologic status. Harrop et al. analyzed the cases of 12 of 186 patients (6%) with acute traumatic cord injuries who demonstrated neurologic ascension within 30 days after injury. Three subgroups were defined: an early deterioration group who worsened within 24 h, a delayed deterioration group (1–7 days), and a late (beyond 7 days) deterioration group. Two patients in the late group had vertebral artery injury; vertebral artery injury is common after midcervical injury, and its clinical significance is uncertain.

Yablon et al. described 14 cases of ascending myelopathy (involving 1–4 levels) that occurred in the first 4 weeks after injury. These cases were attributed to spinal cord edema; MRI studies demonstrated evidence of this as well as diffuse intrathecal hemorrhage. Be
defined a similar occurrence of ascending myelopathy, which they labeled as subacute post-traumatic ascending myelopathy, occurring within the first 2 weeks after injury. This syndrome occurred in three patients who experienced neurologic deterioration with a secondary injury ascending six or more levels (6, 9, and 17 levels) from the initial level after an eventful early course. No etiologic factors could be identified. In all three patients, T2-weighted MRI studies revealed a high signal intensity located centrally within the cord and extending rostrally from the site of injury. T2-weighted images are sensitive to the presence of edema and effectively distinguish pathologic from normal tissue; the high signal intensity identified indicates injury and edema.

The above reports suggest that there is a progressive postinjury course in some patients leading to a secondary neurologic injury and ascension of injury level, sometimes to a striking degree. In some instances, this deterioration has been associated with clinical interventions, including immobilization, traction, surgery, intubation, and sepsis. In other instances, no clear factors are associated, and in particular, both extrinsic cord compression and vascular interruptions have been excluded. This syndrome, when witnessed early in the course after injury, has usually been attributed to vascular perturbations or cord edema and inflammation; MRI studies have been consistent with this attribution. More recent work has also suggested a role for apoptosis in the causation and progression of ascending myelopathy. A diagnosis of ascending myelopathy must be considered when a secondary injury has occurred; there is natural temptation to attribute the deterioration to temporally related clinical interventions but, in fact, these interventions are rarely associated with neurologic sequelae. Progressive neurologic injury after CSI may be inevitable in some patients because of pathophysiologic processes initiated at the time of the application of the injuring forces and may occur despite the provision of appropriate management paradigms and interventions.
Clinical Care of the Spine-injured Patient

Spinal Immobilization in Trauma Patients: The Overview

During the past 30 yr, the neurologic status of spinal cord-injured patients arriving in emergency departments has dramatically improved, and the odds of dying during the first year after injury have been significantly reduced.64,65 The improvement in the neurologic status of patients has been attributed to improved initial care and retrieval systems, recognition of the importance of instituting prehospital spinal immobilization, maintaining immobilization until clearance is obtained or definitive therapy is applied, and hospital practices designed to prevent secondary injury. The routine use of spine immobilization for all trauma patients, particularly those with a low likelihood of spinal injury, has been challenged on the basis that it is unlikely that all patients rescued from the scene of an accident or site of traumatic injury require spine immobilization.66 A Cochrane systematic review also concluded that the impact of immobilization on mortality, neurologic injury, and spinal stability was uncertain and that direct evidence linking immobilization to improved outcomes was lacking.67 The Cochrane review further concluded that the potential for immobilization to actually increase morbidity or mortality could not be excluded based on a review of the literature. However, the current consensus among experts remains that all patients with the potential for a CSI after trauma should be treated with spinal column immobilization until injury has been excluded or definitive management for CSI has been initiated.64

The benefits, consequences, and sequelae of spinal immobilization in at-risk patients have been recently analyzed, and the reader is referred to these reviews for more detailed discussions.64,68,69 The chief concern during the initial management of patients with potential CSI is that neurologic function may be further compromised by pathologic motion of the injured vertebrae. Management of the potentially traumatized spine emphasizes three principles: (1) restoration and maintenance of spinal alignment, (2) protection of the cord with preservation of intact pathways, and (3) establishment of spinal stability. To achieve these principles, immobilization of the cervical spine before radiographic assessment and clearance is the accepted standard of care. The rationale behind early immobilization is the prevention of neurologic injury in the patient with an unstable spine. Institution of a clinical care paradigm that features immobilization as a core element has resulted in improved neurologic outcomes in spine-injured patients during the past three decades.64,65 Failure to immobilize in the context of missed or delayed diagnosis is also associated with an increased incidence of neurologic injury.9,10,55 Lack of immobilization has been cited as a cause of neurologic deterioration among acutely injured trauma patients being transported to medical facilities for definitive care.70

A number of complications to prolonged immobilization have been identified.64,68,69 Cutaneous ulcerations (pressure sores) are common, and the incidence increases when immobilization is prolonged beyond 48–72 h. Airway management, central venous access and line care, provision of oral care, enteral nutrition, and physiotherapy regimes are all made more difficult when immobilization must be maintained. The need for multiple staff to allow for safe positioning and transfer of immobilized patients makes barrier nursing more difficult and may result in higher rates of cross-contamination and infection in high-dependency units.

The application of cervical collars has also been associated with increased intracranial pressure (ICP) in both injured patients and healthy volunteers. Davies71 prospectively analyzed ICP in a series of injured patients treated with a rigid collar. The ICP increased a mean of 4.5 mmHg when the collar was firmly in place. Kollb72 also examined changes in ICP after the application of a rigid Philadelphia collar in 20 adult patients. ICP averaged 17.68 cm H2O initially and increased to an average of 20.15 cm H2O after collar placement. Although the difference in ICP of 2.47 mm H2O was statistically significant, it remains uncertain that it has clinical relevance. Nonetheless, this modest increase in pressure may be magnified in patients who already have increased ICP and poor intracranial compliance. The potential for complications should not discourage the use of immobilization where indicated. Rather, because many of the complications are time dependent, they should encourage attempts to promptly assess the patient for cervical injury to expedite the discontinuance of immobilization in those patients whose spines can be cleared.

Techniques and Devices for Preadmission Spinal Immobilization

The position in which the injured spine should be placed and held immobile, the “neutral position,” is poorly defined. De Lorenzo et al.,73 in an MRI study of 19 adults, found that 2 cm of occiput elevation produced a favorable increase in spinal canal/spinal cord ratio at the C5 and C6 levels, a region of frequent unstable cervical spine injuries. Podolsky et al.74 evaluated the efficacy of cervical spine immobilization techniques. Hard foam and hard plastic collars were better at limiting cervical spine motion than soft foam collars, although the use of collars alone did not effectively restrict spinal motion. The use of sandbag-tape immobilization was more effective at reducing spinal movement than any of the other individual methods tested. Adding a Philadelphia collar to the sandbag-tape construct reduced neck extension but had no effect on any other motion of the cervical spine. These authors found that sandbags and tape combined with a rigid cervical collar was the most effective con-
struct of those evaluated to limit cervical spine motion, restricting movement to approximately 5% of the normal range. The sandbag–tape–backboard–collar and variations thereof have become the most commonly used extrication and transport assembly in prehospital trauma care to provide spinal immobilization.

Bednar assessed the efficacy of soft, semirigid, and hard collars to immobilize the neck in a destabilized elderly cadaver model. Bednar’s experiment involved creation of unstable motion segments at the C3–C4, C4–C5, or C5–C6 levels; isolated posterior column, combined column, and then anterior column injuries were sequentially assessed. Soft, semirigid, and rigid collars were used in an attempt to restrict neck movements, and then the spines were subjected to unrestrained gravitational forces with flexion, lateral side-bending, and extension. The collars were not effective in reducing spinal movement; in fact, there was evidence for increased spinal movement. Bednar hypothesized that the increased movement resulted from the levering of the mobile head and proximal cadaver neck over the collar edge. The model described allowed for the application of forces that would rarely be applied or permitted in clinical settings but did emphasize the very limited role that collars would play in limiting spinal movement if the spine were subjected to very hostile forces.

Goutcher and Lochhead measured maximal mouth opening (interincisor distance) in 52 volunteers, before and after the application of a semirigid cervical collar. Three collars were assessed: the Stifneck (Laerdal Medical Corp., Wappinger’s Falls, NY), the Miami J (Jerome Medical, Moorestown, NJ) and the Philadelphia (Philadelphia Cervical Collar Co., Thorofare, NJ). Application of a collar significantly reduced interincisor distance from a mean of 41 ± 7 mm in the control state to 26 ± 8 mm with the Stifneck, 29 ± 9 mm with the Miami J, and 29 ± 9 mm with the Philadelphia. There was a wide variation between subjects, and a significant proportion had an interincisor distance reduced to less than 20 mm after application of the collar (Stifneck, 25%; Miami J, 21%; Philadelphia, 21%). Goutcher and Lochhead concluded that the presence of a semirigid collar significantly reduced mouth opening and would likely often interfere with airway management; removal of the anterior portion of the collar before attempts at tracheal intubation was encouraged by these authors.

Manual In-line Immobilization

The goal of manual in-line immobilization (MILI) is to apply sufficient forces to the head and neck to limit the movement which might result during medical interventions, most notably, airway management. MILI is typically provided by an assistant positioned either at the head of the bed or, alternatively, at the side of the stretcher facing the head of the bed. The patient is positioned supine with the head and the neck in neutral position. Assistants either grasp the mastoid processed with their fingertips and cradle the occiput in the palms of their hands (head-of-bed assistant) or cradle the mastoids and grasp the occiput (side-of-bed assistant). When MILI is in place, the anterior portion of the cervical collar can be removed to allow for greater mouth opening, facilitating airway interventions. During laryngoscopy, the assistant ideally applies forces that are equal in force and opposite in direction to those being generated by the laryngoscopist to keep the head and neck in the neutral position.

Avoiding traction forces during the application of MILI may be particularly important when there is a serious ligamentous injury resulting in gross spinal instability. Lennarson et al. noted excess distraction at the site of a complete ligamentous injury when traction forces were applied for the purposes of spinal stabilization during direct laryngoscopy. Similarly, Kaufmann demonstrated that in-line traction applied for the purposes of radiographic evaluation resulted in spinal column lengthening and distraction at the site of injury in four patients with ligamentous disruptions. Bivins et al. reported that traction applied during orotracheal intubation in four victims of blunt traumatic arrest with unstable spinal injuries resulted in both distraction and posterior subluxation at the fracture site. It is possible that the fracture site distraction that was observed resulted from application of traction forces not appropriately axially aligned.

Majernick et al. demonstrated that MILI reduced total spinal movement during the process of laryngoscopy and tracheal intubation; movement was not reduced to a similar degree by collars. Similarly, Watts et al. measured a reduction of spinal movement with the application of MILI during tracheal intubation in patients with normal spines during general anesthesia. However, Lennarson et al. were unable to demonstrate that application of MILI resulted in any significant reduction in movement during intubation in a cadaver model with a posterior column injury. In a cadaver model with complete ligamentous instability, Lennarson et al. reported that application of MILI minimized distraction and angulation at the injured level but had no effect on subluxation at the site of injury.

Manual in-line immobilization may be effective in reducing overall spinal movements recorded during airway maneuvers but may have lesser restraining effects at the actual point of injury. This may be because spinal movement is restricted by the weight of the torso at the caudal end and the MILI forces at the cephalad end but is unrestricted by any force at its cervical midpoint. It is possible that application of traction forces during MILI would also reduce midcervical movement in some patients, but traction forces may also result in distraction at the site of injury; the use of such forces during applica-
tion of in-line immobilization continues to be discour-
aged.

Impact of MILI on the View Obtained at
Laryngoscopy

The application of MILI during airway maneuvers may
result in decreases in overall spinal movement, but the
evidence also suggests modest, if any, effect at individual
motion segments. However, the use of MILI may have
lesser impact on the view obtained during direct
laryngoscopy than relying on other immobilization tech-
niques, such as axial traction or a cervical collar, tape,
and sandbags. Heath examined the effect on laryngos-
copy of two different immobilization techniques in 50
patients. A grade 3 or 4 laryngoscopic view (partial or no
view of the glottic structures) was obtained in 64% of
patients immobilized with a collar, tape, and sandbags
compared with 22% of patients stabilized with MILI. The
laryngeal view improved by one grade in 56% of patients
compared with 22% of patients stabilized with MILI. The
view of the glottic structures was obtained in 64% of
patients. A grade 3 or 4 laryngoscopic view (partial or no
view of the glottis) was obtained in 64% of patients
immobilized with a collar, tape, and sandbags. The main factor contrib-
uting to the increased difficulty of laryngoscopy when
patients were wearing cervical collars was reduced
mouth opening. Gerling et al. reported the findings of
an analogous study using a cadaver model with a C5–C6
destabilization and arrived at similar findings. MILI al-
lowed less spinal movement than did cervical collar
immobilization during laryngoscopy and intubation and
and was associated with improved laryngeal visualization.

Hastings and Wood measured the degree of head
extension required to expose the arytenoid cartilages
and glottis and determined the impact of applied MILI.
The subjects were 31 anesthetized patients (24 study, 7
control) with normal cervical spines and Mallampati 1
views on preoperative airway assessment. Two methods
of immobilization were assessed. Either axial traction
was applied, wherein the assistant pulled the head in a
caudal to cephalad direction as strongly as he or she
thought was necessary to immobilize the neck, or force
was applied to the head in a downward direction to hold
the head onto the table. Without stabilization, the best
view of the glottis was achieved with 10°–15° of head
extension. Head immobilization reduced extension an-
gles of 4°–5° compared with no stabilization, and it was
more effective than axial traction immobilization in lim-
iting extension. In 4 of the 24 study patients (17%), 2 in
each immobilization group, the laryngoscopic view de-
teriorated from grade I or II to grade III with the appli-
cation of immobilizing forces. Therefore, the use of MILI
reduced the amount of head extension that was neces-
sary for laryngoscopy but resulted in a poorer view in a
portion of the patients studied.

Although MILI seems to have the least impact of all
immobilization techniques on airway management, it
may make direct laryngoscopy more difficult in some
patients than if no immobilizing forces are being applied.

Nolan and Wilson assessed the impact of MILI with
cricoid pressure on the view obtained at laryngoscopy in
157 normal patients and compared it with the view
obtained in the same patients while in the sniffing posi-
tion. With application of MILI and cricoid pressure, the
view remained the same in 86 patients (54.8%), was
worse by one grade in 56 (35.6%), and was worse by two
grades in 15 (9.5%). A grade 3 view (partial glottic view)
was obtained in 34 restrained patients (21.6%) compared
with 2 (1.3%) in the sniffing position. Wood et al. also
studied the effect of cervical stabilization maneuvers on
the view obtained at laryngoscopy in 78 uninjured, elec-
tive surgical patients and concluded that cervical immo-
bilization commonly worsened laryngoscopic view. The
effects of MILI on laryngeal view were in a similar direc-
tion to those reported by Hastings but occurred more
commonly in Wood’s study. Anterior laryngeal or cricoid
pressure often improved the view of the larynx when
the neck was immobilized. Concern has been expressed
in the past regarding the use of anterior cervical pressure
in patients at risk for CSI, but Donaldson et al. reported
that application of cricoid pressure did not result in
movement in an injured upper cervical spine in a ca-
daver model.

Manual in-line immobilization may have lesser impact
on airway interventions than do other forms of immobi-
lization. The experience supports routinely removing at
least the anterior portion of collars to facilitate airway
interventions provided that cervical spinal immobiliza-
tion is maintained by MILI. Removal of the anterior
portion of the collar improves mouth opening and facil-
itates airway management; reapplication of the mechan-
ical immobilization should occur promptly when airway
interventions are complete. MILI may increase laryngo-
scopic grade in some patients; this may be countered
with anterior laryngeal or cricoid pressure.

Spinal Movement during Airway Interventions

The early biomechanical analyses of spinal motion typ-
ically used static radiography to determine the relations
between the vertebral elements of the cervical spine and
to quantify spinal movements. Unfortunately, no stan-
dardized technique of measurement has been used in the
works since published, which have evaluated spinal
movement during airway interventions. Both static radi-
ography and dynamic fluoroscopy have been used; study
findings have been reported movement as absolute dis-
tances, relative distances (typically a percentage of ver-
tebra body width), and degrees of motion and have
further been categorized relative to individual motion
segments or upper and lower cervical spinal divisions or
summed across the entire cervical spine. There is also
little guidance available as to the clinical importance of
the movements recorded, especially as they relate to the
injured spine. Those spinal movements that fall within
physiologic ranges have usually been considered to be
nonthreatening to the cord; whether they are in fact and remain so in a spine with a canal lumen already compromised by an acute, a chronic, or an acute superimposed on chronic anatomical derangement is by no means certain. Unfortunately, as we analyze the published works, we typically find ourselves in the position of comparing the recorded results with physiologic norms and then drawing an empiric conclusion as to the potential risk of such movements.

The Effects of Basic Airway Maneuvers on the Injured Neck. Aprahamian studied the effect of both airway maneuvers on a human cadaver, unstable spine model. The anterior and most of the posterior column were surgically disrupted; the interspinous and supraspinous ligaments were spared. Lateral cervical spine radiographs were taken during both basic and advanced airway maneuvers. Basic maneuvers included chin lift, jaw thrust, head tilt, and placement of both oral and esophageal airways. Advanced maneuvers included placement of the following: an esophageal obturator airway; an orotracheal tube placed with both a straight and a curved laryngoscopic blade; and a nasotracheal tube, blindly placed. Chin lift and jaw thrust resulted in expansion of the disc space more than 5 mm at the site of injury. When blind nasotracheal intubation was facilitated by anterior pressure to stabilize the airway, 5 mm of posterior subluxation occurred at the site of injury. The other advanced airway maneuvers produced 3–4 mm of disc space enlargement. The study was repeated after the application of both soft and semirigid cervical collars; collars did not effectively immobilize the neck for either basic or advanced airway maneuvers.

Hauswald also determined the impact of basic airway maneuvers on cervical spine movement. Eight human traumatic arrest victims were studied within 40 min of death. All subjects were ventilated by mask, and their tracheas were intubated orally with a direct laryngoscope, over a lighted oral stylet and using a flexible laryngoscope blade to achieve laryngeal visualization during laryngoscope blade insertion; elevation of the laryngoscope blade to achieve laryngeal visualization caused superior rotation of the occiput and Cl and mild inferior rotation of C3–C5. The largest magnitude motions were at the atlanto-occipital and atlantoaxial joints, but there was extension at each motion segment assessed. Tracheal intubation created slight additional superior rotation at the craniocervical junction but caused little alteration in the postures of C3–C5. Horton et al. conducted a similar experiment in volunteers during topical anesthesia only. Subjects in a supine, sniffing position underwent direct laryngoscopy, and at full glottic exposure, a lateral radiograph of the head and neck was performed. The radiographs indicated that extension at the craniocervical junction was near maximal and that there was progressively increasing extension from C4 to the base of the skull, but that the position of the lower cervical spine remained static during laryngoscopy. Both Sawin et al. and Horton et al. agreed that, during laryngoscopy, in both awake and unconscious subjects, most cervical motion occurs at the craniocervical junction; the subaxial cervical segments subjacent to and including C4 are minimally displaced (fig. 6).

Cervical Spinal Movement during Direct Laryngoscopy in Normal Patients. Sawin et al. determined the nature, extent, and distribution of segmental cervical motion produced by direct laryngoscopy and orotracheal intubation in normal human subjects. Ten patients underwent laryngoscopy while paralyzed and during general anesthesia. Minimal displacement of the skull base and cervical vertebral bodies was observed during laryngoscopy blade insertion; elevation of the laryngoscope blade to achieve laryngeal visualization caused superior rotation of the occiput and Cl and mild inferior rotation of C3–C5. The largest magnitude motions were at the atlanto-occipital and atlantoaxial joints, but there was extension at each motion segment assessed. Tracheal intubation created slight additional superior rotation at the craniocervical junction but caused little alteration in the postures of C3–C5. Horton et al. conducted a similar experiment in volunteers during topical anesthesia only. Subjects in a supine, sniffing position underwent direct laryngoscopy, and at full glottic exposure, a lateral radiograph of the head and neck was performed. The radiographs indicated that extension at the craniocervical junction was near maximal and that there was progressively increasing extension from C4 to the base of the skull, but that the position of the lower cervical spine remained static during laryngoscopy. Both Sawin et al. and Horton et al. agreed that, during laryngoscopy, in both awake and unconscious subjects, most cervical motion occurs at the craniocervical junction; the subaxial cervical segments subjacent to and including C4 are minimally displaced (fig. 6).

Spinal Movement during Laryngoscopy in Injured Spine Models. Donaldson et al. studied the motion that occurred during intubation in a cadaver model with an unstable C1–C2 segment. The following were measured in the intact specimen and then again after creation of the unstable segment: angulation, distraction, and the space available for the cord (SAC). With maximum flexion and extension, the SAC was narrowed...
1.49 mm in the intact cervical spine but 6.06 mm in the unstable spine. Chin lift and jaw thrust reduced the SAC by 1 mm and 2.5 mm, respectively; oral intubation and nasal intubation created a similar (1.6 mm) reduction of SAC. Distraction at the unstable injured level was similar for chin lift, jaw thrust, and crush intubation (1–2 mm); distraction during gentle oral intubation and nasal intubation was less than 1 mm. Chin lift and jaw thrust created similar angulations (4°–5°) to those of the oral intubation techniques, but nasal intubation caused less (2.5°). Cricoid pressure resulted in no significant movements when it was applied in either the stable or unstable model. Donaldson et al. concluded that (1) the SAC was narrowed to a greater degree by preintubation maneuvers than it was by intubation techniques, (2) nasal and oral intubation techniques resulted in similar amounts of SAC narrowing, and (3) application of cricoid pressure produced no significant movement at the craniovertebral junction.

**Stabilization during Airway Interventions in Cadaver Models of an Injured Spine.** Lennarson et al. evaluated the impact of commonly used immobilization techniques in limiting spinal motion in an injured-spine model; the model involved the creation of a posterior ligamentous injury at the C5 level and compared the effects of MILI and Gardner-Wells traction. The predominant motion measured at all spinal levels during laryngoscopy and intubation in the intact spine was extension; this was consistent with the findings of Donaldson et al., Sawin et al., and Horton et al. Subluxation in the anterior–posterior dimension remained less than 1 mm in both the intact and the partially destabilized spine; rotatory or angular movements were the only significant movement recorded. Application of Gardner-Wells traction limited rotatory motion at the craniovertebral junction after destabilization; MILI did not have a similar effect.

Lennarson et al. conducted a similar experiment assessing the efficacy of immobilization maneuvers in a model of complete C4–C5 segmental instability. Movement was measured at the injured level during the application of traction, during MILI, and without stabilization. Traction resulted in distraction at the site of injury when instability was complete; the magnitude of these movements was not reduced by MILI, although they remained within physiologic limits. Gerling et al. also evaluated the effect of both MILI and cervical collar immobilization on spinal movement during direct laryngoscopy in an unstable C5–C6 cadaver model. Although there was less displacement (2 mm) measured with application of MILI compared with collars, the magnitude of movement was small overall and within physiologic ranges.

Brimacombe et al. assessed spinal movement in a cadaver model with a posterior injury at C3, with MILI applied as various airway interventions (facemask ventilation, direct laryngoscopy and tracheal intubation, fiberoptic nasal intubation, laryngeal mask insertion, intubating laryngeal mask airway insertion followed by fiberoptic intubation, and insertion of a Combitube) were performed. Posterior displacement was less when intubation was performed nasally with a flexible scope (0.1 ± 0.7 mm) than for any other maneuver; most maneuvers caused 2–3 mm of displacement.

**Influence of Laryngoscope Blade Type on Spinal Movement during Direct Laryngoscopy.** Three authors have assessed the influence of the type of laryngoscope blade on the spinal movements generated during direct laryngoscopy. MacIntyre et al. compared the Macintosh and McCoy blades in patients with normal spines during general anesthesia with cervical collars applied. There were no significant differences between the two blades with respect to the amount of spinal movement generated during intubation. Hastings et al. compared head movement occurring during laryngoscopy in patients with normal spines using Macintosh and Miller laryngoscopes, and again, there were no differences in the amount of movement measured. Finally, Gerling et al. compared spine movement in a cadaver model with a C5–C6 transactional injury while performing laryngoscopy with Miller, Macintosh, and McCoy-type blades. There was no difference in the movements recorded with the different blades with regard to either anteroposterior displacement or angular rotation. Less axial distraction was measured with the Miller blade compared with the other two blade types; in absolute terms, the differences was 1.7 mm. Overall, there seems to be little difference in the spinal movement resulting from direct laryngoscopy relative to the type of blade used during laryngoscopy.

**Cervical Spinal Movement with Indirect Rigid Fiberoptic Laryngoscopes.** Watts et al. compared cervical spine extension and time to intubation with the Bullard (ACMI Corp., Southborough, MA) and Macintosh laryngoscopes during a simulated emergency with cervical spine precautions taken. Twenty-nine patients were placed on a rigid board, and anesthesia was induced. Laryngoscopy was performed on four occasions, twice each with the Bullard and Macintosh laryngoscopes, both with and without MILI applied (MILI was applied with cricoid pressure). Cervical spine extension (from the occiput to C5) was greatest with the Macintosh and was reduced both when the Macintosh was used with MILI and when the Bullard was used with or without stabilization. Times to intubation were similar for the Macintosh with MILI and for the Bullard without MILI. MILI applied during laryngoscopy with the Bullard resulted in further reduction in cervical spine extension but a prolonged the time to intubation, although it still was achieved in less than a minute. In a study design similar to that of Watts et al., Hastings et al. found that cervical spine extension from the occiput to C4 was...
decreased when comparing the Bullard with both the Macintosh and the Miller laryngoscope blades.

The times to achieve intubation using the Bullard laryngoscope, in the study of Watts et al.,81 are similar to others reported in the literature. Twenty-two of 29 patients (76%) were intubated in less than 30 s when using the Bullard under standard conditions.81 In a study using the dedicated intubating stylet, Cooper et al.86 found 70% of patients were intubated in less than 30 s. There was also better exposure of the larynx during laryngoscopy with the Bullard than with the direct laryngoscope. Application of MILI resulted in deterioration in the grade view of the larynx when using the Macintosh in 19 of 29 patients (65%). In contrast, only 2 patients (7%) presented an inferior view of the larynx after application of MILI and cricoid pressure when using the Bullard laryngoscope.

Rudolph et al.97 compared movement in the upper cervical spine in 20 patients scheduled to undergo elective surgery, when laryngoscopy was performed with the Bonfils intubation fiberscope (Karl Storz Endoscopy Ltd., Tuttingen, Germany) and the Macintosh laryngoscope. With the patient’s head in neutral position on the table and no pillow used, a baseline lateral radiograph was taken. The head was extended, laryngoscopy was performed using the Macintosh, a second radiograph was taken, and the head was returned to the neutral position. Laryngoscopy was then performed with the Bonfils fiberscope, and the trachea was intubated. With the Macintosh, views at laryngoscopy were class I in 8 patients, II in 5, and III in 7; all views obtained with the Bonfils fiberscope were class I. The time between insertion of the instrument and achievement of optimum view was similar for both instruments. Laryngoscopy with the Macintosh resulted in spinal movement that was greater in magnitude than that measured during Bonfils fiberscopy.

The Glidescope (Saturn Biomedical Systems, Burnaby, British Columbia, Canada) is a new video laryngoscope that incorporates a high resolution digital camera in the blade tip; the image is transmitted to a liquid crystal display monitor via a dedicated video cable. Agro et al.98 compared the laryngeal view obtained initially with a Macintosh and then with the Glidescope in 15 normal patients presenting for general anesthesia who were wearing cervical collars. The laryngeal view was reduced by one Cormack grade in 14 of the 15 patients (93%) studied when the Glidescope was used compared with the Macintosh; the average time to intubation with the Glidescope was 38 s. Turkstra et al.99 compared cervical spine movement, measured fluoroscopically, during intubation with a Macintosh, a light wand, and the Glidescope. In-line immobilization was achieved by taping the patients’ heads into a Mayfield-type headrest; movement was measured at the Oc–C1, C1–C2, C2–C5, and C5–Th levels. The largest amount of motion measured was at the Oc–C1 complex with all devices. Cervical spinal movement was reduced 57% overall (all segments combined) comparing the light wand with the Macintosh; reduced movement was apparent at each level. Spinal movement was reduced only at the C2–C5 segment when the Glidescope was compared with the Macintosh; 6.9° ± 5.2° of flexion was measured during Macintosh laryngoscopy, and this was reduced by 50% using the Glidescope. Motion was not significantly altered at the three other segments studied. The time to intubation was longest with the Glidescope (27 ± 12 s) but similar with the light wand (14 ± 9 s) and the Macintosh (16 ± 7 s).

Cervical spine movements are generally less when rigid indirect laryngoscopes are used compared with the MI direct laryngoscope. Visualization of the glottis is also improved with the use of the rigid laryngoscopes, but the time to achieve the best view is somewhat longer; these trends tend to be short, and the difference compared with the direct laryngoscope is likely to be of little clinical relevance.

Cervical Spinal Movement and Laryngeal Mask Airways. Kihara et al.100 measured cervical movement produced by the intubating laryngeal mask airway during MILI in 20 anesthetized patients with cervical pathology undergoing cervical spine surgery. During the insertion of the intubating laryngeal mask airway, C5 and superior segmental levels were flexed by less than 2°. During intubation, C4 and superior segmental levels were flexed by 3° or less, and C3 and levels above were flexed by an average of 1° during removal. There was some posterior displacement at the C2–C5 levels during insertion and intubation but not during removal.

Keller et al.101 implanted microchip sensors into the pharyngeal surfaces of C2 and C3 in 20 cadavers to determine the pressures exerted against the cervical vertebrae by both the standard laryngeal mask airway and the intubating laryngeal mask airway during insertion and manipulation. The impact of these pressures on cervical spine movement was also determined. Keller et al. concluded that laryngeal mask devices exert high pressures against the upper cervical vertebrae during insertion, during inflation, and while in situ; these pressures could produce posterior displacement of the upper cervical C-spine. The clinical relevance of these findings as they relate to CSI has yet to be clarified.

Cervical Spinal Movement during Surgical Cricothyrotomy. Surgical cricothyrotomy was initially advocated as a preferred airway intervention in patients at risk for CSI compared with orotracheal intubation and now is deemed to be an appropriate alternative if oral or nasal routes cannot be used or are unsuccessful. Although long considered safe in the presence of a CSI, its application in this scenario has not been well studied with respect to either spinal movements or neurologic outcomes. Gerling et al.102 used a cadaver model to
quantify movement during cricothyrotomy. Standard
crcothyrotomy was performed in 13 cadavers with
complete C5–C6 transection injuries, and cervical spine
images were recorded fluoroscopically during the pro-
cedure. Peak axial distraction was measured at 4.5% of
the C5 width, amounting to 1–2 mm of axial compres-
sion; peak antero-posterior displacement was measured
at 6.3% of the C5 width, equivalent to 1–2 mm of dis-
placement. Although these values were statistically sig-
nificant, there clinical relevance has yet to be deter-
m

The Clinical Practice of Airway Management in
Patients with Cervical Spine Injury

Surveys of Patterns of Clinical Practice Regarding
Airway Management after Cervical Spine Injury.
Four authors have surveyed North American anesthesi-
ologists as to their preferred methods of airway manage-
ment in patients with cervical spine trauma or disease. Lord et al. compared practice preferences among
surgical members of the Eastern Association for the Sur-
gery of Trauma with anesthesiologists in US anesthesiol-
gy training programs. In the elective situation (CSI but
breathing spontaneously with stable vital signs), anesthe-
siologists stated that they were less likely to use nasotra-
cheal intubation (53% vs. 69%), equally likely to use
otracheal intubation, and more likely to use the fiber-
optic bronchoscope than were trauma surgeons. In the
urgent scenario (patient with unstable vital signs), anes-
thesiologists tended to use both nasotracheal and orotrach-
eal intubation in a manner similar to that of the sur-
geons but more frequently (16%) preferred the bronchoscope. In an emergency situation (apneic pa-
tient with unstable vital signs), anesthesiologists tend to
use both nasotracheal and orotracheal intubation in a manner similar to that of the sur-
geons but more frequently (16%) preferred the bronchoscope. In an emergency situation (apneic pa-
tient with unstable vital signs), both anesthesiologists
and surgeons relied extensively on the direct laryngo-
scope (78% and 81%); anesthesiologists were more likely
to use the bronchoscope (15%) than were surgeons but
used a surgical airway less frequently than did the sur-
geons (7% vs. 19%).

Rosenblatt et al. received 472 responses from 1,000
active members of the American Society of Anesthesi-
ologists who were surveyed as to their preferences for
management methods for the difficult airway in coopera-
tive adult patients. With respect to patients with CSI, 78% of respondents expressed a preference for an awake intubation and the use of bronchoscope; the bulk of the remainder induced general anesthesia and used a direct
laryngoscope. Rosenblatt et al. did not request informa-
tion regarding the levels of experience attained with the
devices preferred but did ascertain that they were avail-
able to the practitioners who stated that they would use
them. Jenkins et al. collected 833 responses from
1,702 members of the Canadian Anesthesiologists’ Soci-
ety surveyed regarding their management choices for
the difficult airway in Canada. When faced with a patient
with a cervical cord compression and neurologic deficit
presenting for discectomy, 67% expressed a preference
for awake intubation, and most (63%) stated that they
would use a bronchoscope. Thirty-one percent would
induce general anesthesia before airway intervention,
and slightly more would use a direct laryngoscope than
preferred a lighted stylet in this setting. Jenkins et al. did
not solicit information regarding the level of experience
with the methods identified as being preferred by the
survey respondents.

Ezri et al. surveyed 452 American-trained American
Society of Anesthesiologists members attending the 1999
Annual Meeting. When faced with a cooperative adult
patient with cervical spine disease (rheumatoid arthritis
or ankylosing spondylitis) presenting for elective sur-
gery, awake fiberoptic intubation was preferred by most.
Although 75% stated that they would use it in some of
the scenarios outlined, only 59% or respondents re-
ported skill in the use of the bronchoscope.

The surveys are consistent in revealing that many
North American anesthesiologists express a preference
for the use of a fiberoptic bronchoscope during airway
management in patients with cervical spine disease or
injury including in apneic trauma scenarios. This prefer-
ence persists despite the fact that some who state this
preference also acknowledge that they are not confident
regarding their skill levels with the bronchoscope. De-
pending on the setting and the perceived urgency of the
situation, direct laryngoscopy is still commonly used,
and use of the lightwand is preferred by a significant
minority of anesthesiologists, at least in Canada.

Airway Management of Cervical Spine–injured
Patients: The Experience and Outcomes Reported.
Meschino et al. reviewed their experience with 454
patients with critical cervical cord or spine injuries or
both. One hundred sixty-five patients underwent awake
tracheal intubation within 2 months of injury; 289 did
not require intubation during the same period. The di-
rect laryngoscope was used in 36 patients (22%), the
fiberoptic bronchoscope was used in 76 (46%), and 51
patients (32%) underwent blind nasal intubation. Pa-
tients undergoing intubation were more severely im-
paired than those who did not require intubation. De-
spite this, there was no difference in the incidence of
neurologic deterioration over time between the two
groups, and tracheal intubation was not associated with
neurologic deterioration in any patient. Holley and Jor-
dan conducted a retrospective analysis of traumatic,
unstable cervical spine fractures requiring operative
management to determine both the airway management

techniques used and the incidence of neurologic com-
plications. One hundred thirty-three patients with 140
fractures were reviewed. Ninety-four patients under-
went nasal intubation in the operating room, and 29
were intubated with direct laryngoscopy and in-line sta-
bilization. No neurologic complications were recognized
in any patient.
Rhee et al. analyzed their experience with 21 patients with cervical cord or spine injury who underwent tracheal intubation in the emergency room. Orotracheal intubation was used in 81% of CSI patients; neuromuscular blockers were used in 82% of these intubations. The authors concluded that no injury was recognized to be caused or exacerbated by airway maneuvers. However, one patient with a C7-T1 dislocation and a C7 cord transection was noted to have absent sensation below the nipples before intubation (T4 level) and motor and sensory examination results consistent with a C7 cord transection after intubation. Whether this disparity reflects an ascension in the level of injury from T4 to C7 or the difference in findings between an emergency room screening neurologic exam and a more precise examination performed later is not certain; the authors’ conclusions seem to prefer the latter explanation. Scanell et al. reviewed their experience with 81 patients with CSI, including 58 with unstable fractures, who received emergency orotracheal intubations performed by experienced anesthesiologists. Neurologic assessment was documented before and after intubation, and in no instance was there a recognized deterioration of neurologic functions after tracheal intubation. Shatney et al. reviewed their experience with 81 patients with CSI, including 58 with unstable fractures, who received emergency orotracheal intubations performed by experienced anesthesiologists. Neurologic assessment was documented before and after intubation, and in no instance was there a recognized deterioration of neurologic functions after tracheal intubation. Shatney et al. reviewed their experience with 81 patients with 98 fractures who were neurologically intact on initial presentations. Orotracheal intubation was performed in 48 patients, and no neurologic deteriorations were recognized. In-line immobilization was used during the airway maneuvers, and agitated or combative patients were sedated, paralyzed, or both. Talucci et al. reviewed their experience with 335 patients requiring urgent intubations. Seven patients with unstable CSI underwent orotracheal intubation after induction of anesthesia and paralysis; none experienced neurologic compromise as a result of airway management.

Suderman et al. reviewed the experience of 150 patients with traumatic CSI and well-preserved neurologic function presenting for operative stabilization. General anesthesia before intubation was induced in 83 patients, of whom 65 had their tracheas intubated with the direct laryngoscope; 22 patients were intubated while awake using the direct laryngoscope. The remainder had tracheal intubation performed with a variety of alternatives to the direct laryngoscope, most commonly the bronchoscope; the majority of those latter intubations were performed with the patient awake. Two patients experienced new neurologic deficits; one had a wire passed through the cervical cord accidentally during operative stabilization and was rendered quadriplegic, the second recovered from a new single level radiculopathy attributed to the operative decompression. Both of these patients had their tracheas intubated with a direct laryngoscope while anesthetized. McCrory performed a similar retrospective analysis of the records of 45 patients who presented for operative stabilization of cervical injuries resulting from trauma. Tracheal intubation was performed after induction of general anesthesia with neuromuscular block in 40% of cases; in the remainder, intubation was performed with a bronchoscope while the patient was awake. One awake tracheal intubation was abandoned as a result of patient noncompliance; this patient’s trachea was intubated after induction of general anesthesia. Weighted traction was used in all cases to immobilize the spine. No patient developed either a new neurologic finding or worsening of a pre-existent deficit.

Wright et al. reviewed the records of 987 blunt trauma patients; 60 of the patients had a cervical fracture, and 53 of these were deemed to be unstable. Twenty-six patients’ tracheas were intubated orally, 25 were intubated nasally, and two were intubated by cricothyrotomy. One patient who underwent nasotracheal intubation experienced a neurologic deterioration. Lord et al. reviewed the case records of 102 patients who had a CSI and were admitted to their center after trauma. Sixty-two patients required airway management. The most common method used was orotracheal intubation facilitated by direct laryngoscopy (43%), followed by bronchoscope-assisted intubation (27%), nasotracheal intubation (22%), and tracheostomy (2%); in 4%, the method could not be determined. No patient was recognized to have experienced a neurologic deterioration associated with airway management. Other authors have reported similar findings in smaller series of trauma patients with CSI.

These studies are limited by both their small sample size and their retrospective nature. However, they do reveal that neurologic deterioration in CSI patients is uncommon after airway management, even in high-risk patients undergoing urgent tracheal intubation. They are not sufficient to rule out the potential that airway management provided in isolation or as part of a more complex clinical intervention, even provided with the utmost care, may rarely result in neurologic injury. To do so would require a study of enormous proportions. As noted previously, progressive neurologic deterioration occurs in a minority of CSI patients. If this incidence was set at 2% and a study was designed to prove that an airway intervention did not double this baseline incidence, approximately 1,800 patients would need to be studied. No method of airway intervention has been evaluated with such a study, or anything close to it, and therefore, statements comparing the relative safety of different methods have tenuous evidentiary support.

The Use of the Direct Laryngoscope after Cervical Spine Injury: The Debate. As part of the early efforts aimed at reducing secondary injuries in spine-injured patients, a hypothesis was generated that the tracheas of patients with unstable cervical spines could not be safely managed by direct laryngoscopy and oral intubation. Oral intubation was deemed dangerous because it alleg-
edly caused excessive spinal movement, and this movement could lead to secondary injury. Such secondary injury could theoretically be avoided by the careful performance of nasotracheal intubation or cricothyrotomy. These techniques were advocated as the emergency airway maneuvers of choice in patients at risk for spinal injury. There were no data at that time to support this thesis, and the data collected since seem to suggest that secondary neurologic injury associated with any form of airway management is exceedingly rare. The early Advanced Trauma Life Support protocols for airway management were consistent in their support for the nasal intubation/cricothyrotomy strategy, implying a lack of support for the use of direct laryngoscopy in this clinical setting. Not all practitioners agreed that the use of direct laryngoscopy was contraindicated in patients at risk for cervical injury. There was evidence made available soon after publication of these protocols that some experienced trauma centers (including our own) were ignoring the Advanced Trauma Life Support recommendations and performing direct laryngoscopy in at-risk populations.

McLeod and Calder examined the association between the use of the direct laryngoscope in patients and subsequent spinal injury or pathology. They suggested that the following five case features would add credence to the diagnosis of a laryngoscopy-induced cord injury: (1) a short period of unconsciousness, (2) myelopathy present on recovery, (3) autonomic disturbances after laryngoscopy, (4) difficult laryngoscopy, and (5) cranio-cervical disease or gross instability below C3. These criteria were then used to evaluate the likelihood that laryngoscopy was the causative factor for neurologic deterioration in the reports. Although they do make intuitive sense, whether these criteria discriminate well in assigning cause to injury recognized after intubation is not established. Six reports dealing with 10 patients in which it was alleged that direct laryngoscopy contributed to a neurologic injury were reviewed.

With the possible exception of one case, they concluded after review and analysis of the case reports, that the reports did not provide sufficient data to allow them to make the determination that the use of the direct laryngoscope was the cause of the neurologic injuries reported.

The first report analyzed was that of Farmer et al., who reviewed their institutional experience with cord-injured patients. They reported that four patients had neurologic deteriorations associated with tracheal intubation. Two deteriorations were classified as minor and two were classified as major, but no further details were provided regarding the cases or the intubations. The second report was that of Muckart et al., who reported two cases of neurologic deterioration after clinical interventions. The first patient was a 45-yr-old man involved in a motor vehicle accident who sustained bilateral femoral fractures and a closed head injury. Despite the mechanism of injury, a period of unconsciousness, and the presence of neck pain, no imaging was performed, and his spine was not immobilized. He underwent anesthesia for operative repair of the femoral fractures and was quadriplegic on awakening; a C2 fracture-dislocation was subsequently diagnosed, and he recovered completely. The second patient was a 22-yr-old man with multiple gunshot wounds to the neck; he arrived in the hospital neurologically intact. Imaging of the neck revealed no apparent injury to the cervical spine to a level of C5; the radiograph showed only the upper five vertebrae. He underwent emergency surgery during general anesthesia without neck immobilization and was quadriplegic after. A CT scan demonstrated a burst fracture of C6 with a retropulsed fragment impinging on the canal. He was placed in traction, had operative fixation, and recovered completely. Although direct laryngoscopy and tracheal intubation were component parts of the care of both patients, they were not the sole interventions; the lack of immobilization and the potential for malpositioning cannot be excluded as significant risk factors in both cases. The complete recovery in both patients suggests that malpositioning may have been an etiologic factor inducing a transient, compressive neuropraxia-like injury.

The third report analyzed was that of Redl, who described the case of an 18-yr-old man with undiagnosed spondyloepiphyseal dysplasia congenita resulting in unrecognized craniocervical instability. He underwent general anesthesia and direct laryngoscopy with tracheal intubation for removal of retained knee hardware. The intraoperative and early postoperative course was uneventful, but he developed a spastic quadriparesis the day after surgery. A CT scan demonstrated a congenitally abnormal craniocervical junction with an os odontoideum (congenitally nonfused odontoid process) in the foramen magnum compressing the spinal cord. Although he made a full recovery, he awoke quadriplegic after a subsequent craniocervical stabilization procedure for which his trachea was intubated using a fiberoptic bronchoscope. The precise role of the laryngoscopy in the development of transient neurologic symptoms in a patient with a congenitally abnormal and unstable spine is uncertain; the development of symptoms on the day after laryngoscopy reduces the strength of a causative association. The fourth report reviewed is that of Yan and Diggan, who described the occurrence of a central cord syndrome in a 42-yr-old woman with acquired immune deficiency syndrome who underwent urgent laryngoscopy and intubation for respiratory failure. Before her admission, she was using a walker and wheelchair to ambulate. Following the recognition of upper extremity weakness after intubation and resuscitation, she underwent imaging and evaluation of her central and peripheral nervous system. There was no evidence of...
spinal anomaly or instability; there was imaging evidence of marked and generalized cerebral atrophy and a spinal cord contusion and electrodagnostic evidence of both central and peripheral neuropathy. The etiology of injury was attributed to hyperextension, but there was also evidence of advanced neurologic disease likely related to infection with human immunodeficiency virus. The fifth report was that by Yaszemski et al.,125 who reported the case of a 59-yr-old woman with advanced rheumatoid arthritis. She underwent a right wrist fusion during general anesthesia, and her trachea was intubated with a bronchoscope while she was awake. Her trachea was extubated at the end of the procedure, and the early postoperative course was uneventful. She had a cardiac arrest 10 h postoperatively and was intubated with direct laryngoscopy, but could not be resuscitated. At autopsy, she was confirmed to have atlantoaxial instability (recognized preoperatively), and there was microscopic evidence of focal areas of ischemia and infarction in the upper cord and lower medulla oblongata. The authors attributed the damage and the cause of death to the resuscitation intubation, although she was already dead at the time of that intubation. Further, the pathologic finding of infarction suggests that the injury likely took place remotely from the time of death, perhaps during the surgery, and may well have been a positioning injury that was progressive.

The case that MacLeod and Calder cited as being most likely (four of five features present) a laryngoscopy-induced cord injury was that reported by Hastings and Kelley.124 They reported of the case of a 65-yr-old man admitted to hospital after a motor vehicle accident. Despite reporting neck pain and exhibiting left arm weakness, CSI was not ruled out, nor was spinal immobilization enforced. His condition deteriorated some hours subsequently, and after repeated, failed attempts at direct laryngoscopy without spinal immobilization, he underwent cricothyrotomy; 3 h later, he was found to be paraplegic. A review of the original cervical spine radiograph demonstrated a widened disc space at C6–C7 suggesting disruption of the anterior longitudinal ligament. CT scans confirmed that finding as well as noting congenital spinal stenosis from C3 to C7, osteophyte fragments in the spinal canal at C6, a fracture of the C6–C7 facet joint, a C7 laminar fracture, and a C6 spinous fracture. The constellation of symptoms could not be attributed to a single cord lesion, and he was diagnosed as having both an anterior cord syndrome affecting the T11 and subjacent levels and a central cord syndrome at the cervical level. No MRI study was performed to detail the nature of the cord injuries, and it is possible that his neurologic deterioration was inevitable and perhaps the cause of his respiratory insufficiency. However, at no time from admission until the occurrence of his neurologic deterioration was his spine immobilized.

Two additional cases of intubation-associated neurologic injury not reviewed by MacLeod and Calder have been reported.125,126 Liang et al.125 reported a case similar to that of Hastings and Kelley of a man involved in a motor vehicle accident with a suspected CSI who was left quadriplegic after airway management. Despite the evidence of a CSI (nature of injury not reported) and a neurologic deficit (limited movement in both upper extremities), repeated and failed attempts were made at both nasal (five attempts) and then oral intubation with a direct laryngoscopy (five attempts). The last three attempts at oral intubation were made after removal of the cervical collar, but MILI was not used. The trachea was eventually intubated via a surgical airway. There is no discussion of the care afforded after intubation with respect to the spine injury or any description of subsequent imaging studies performed. The next day, it was recognized that he was quadriplegic. Powell and Heath126 reported the case of a 59-yr-old man found collapsed and unconscious. Paramedics found him to be apneic, cyanosed, and unresponsive and attempted but failed to intubate his trachea. Tracheal intubation was performed in the emergency room, and then the spine was immobilized. A lateral cervical radiograph revealed an odontoid peg fracture, and the patient’s condition was consistent with a complete cord injury at the C2 level. Although it was inferred that the cord injury may have been caused or aggravated by the airway management, it was acknowledged by the authors that the injury was probably sustained at the time of the accident.

A number of reports detailing a relation between airway management and the occurrence of secondary neurologic injury in CSI patients have been reviewed. These reports consist typically of observations made in a single patient or in a small series of patients admitted to a single institution. Although the deterioration has often been associated temporally with airway management, in most cases, it is impossible to determine with certainty the cause of the deterioration because confounding factors are typically present and acknowledged by the reporting authors. As well, it is possible in some instances that the association between airway management and a worsening neurologic state arises not because of cause and effect but because the airway intervention was made necessary by a progressively deteriorating clinical condition such as an ascending myelopathy. It may well be that the magnitude of the deterioration does not become apparent until after clinical interventions, at which time they, themselves, become suspect culprits. As unsatisfactory as it might be, determining the true nature of the association (causal or otherwise) between airway management and adverse neurologic outcomes in CSI patients is not possible at this time, given the current state of our knowledge.
The Use of the Flexible Fiberoptic Bronchoscope in Cervical Spine Injury. There is considerable enthusiasm, particularly among anesthesiologists, for the use of the fiberoptic bronchoscope in patients at risk for cervical spine disease. The advantages are its potential for use in awake patients, the minimal cervical movement required to achieve tracheal intubation, and the ability to perform postintubation neurologic assessments in cooperative and cognitively intact patients. However, there have been relatively few reports recognized in the literature regarding the use of the bronchoscope in the emergency management of the airway after trauma. The overall success rate for intubation using the bronchoscope in the trauma setting has been cited at 83.3% (95% CI, 72–94.6%). There is a report detailing the successful use of the bronchoscope to facilitate awake intubation in 327 consecutive patients presenting for elective cervical spine surgery; the bulk of the procedures were surgeries for cervical disc prolapse, and there were no patients with traumatic injuries included in the review. Although the procedure was well tolerated by the majority of the patients, 38 (12%) developed low oxygen saturations; in this group, the mean oxygen saturation measured by pulse oximetry was 84 ± 4% (range, 72–89%). The potential for desaturation during bronchoscope-facilitated intubation seems to be as great or greater in CSI patients compromised by traumatic injury as in these elective surgical patients; the incidence and magnitude of hypoxemia in a series of CSI-trauma patients undergoing such management has not been reported.

There are no published data in the English literature that would indicate that the cited advantages of the fiberoptic bronchoscope translate into improved outcomes among CSI patients compared with other intubation techniques. As well, Ezri et al. reported, after a survey of American anesthesiologists, that more than 40% of respondents acknowledged that they were not comfortable using a bronchoscope for airway management. McGuire and El-Beheiry reported two cases of complete airway obstruction during elective awake bronchoscope-assisted intubation in patients with unstable cervical spine fractures; both patients were salvaged with emergency surgical airways. In patients with brain injury, a common concurrent injury to CSI, the use of the bronchoscope is associated with significant increases in ICP that are not prevented by the administration of morphine, midazolam, and nebulized lidocaine.

Comparing Rigid and Flexible Fiberoptic Endoscopes in At-risk Populations. Cohn and Zornow compared the fiberoptic bronchoscope and the Bullard laryngoscope with respect to rapidity of glottic visualization and intubation in patients requiring cervical immobility during tracheal intubation. Seventeen adult patients scheduled to undergo neurosurgical correction of a cervical spine problem were studied. Each patient was considered at risk for neurologic injury during tracheal intubation based on a request for awake fiberoptic tracheal intubation by the neurosurgical team, or radicular symptoms initiated or exacerbated by neck extension. Most showed evidence of spinal canal impingement on a preoperative MRI. Patients were allocated randomly to one of two study groups for tracheal intubation with the Bullard (n = 8) or the fiberoptic bronchoscope (n = 9); before intubation, glottic visualization was performed using the alternative technique. All intubations were performed with the neck in a comfortable position for the patient and with any preexisting immobilization device (e.g., collar, traction) in place. Glottic visualization was uniformly successful on the first attempt in both groups. Tracheal intubation was also uniformly successful, although one intubation in the bronchoscope group took 183 s because of difficulty passing the endotracheal tube through the glottis after an easy laryngoscopy. No new neurologic deficits were observed after tracheal intubation in either group.

Practice Options for Airway Management after Cervical Spine Injury. There is discordant opinion expressed in the literature regarding the optimal means of securing the airway in patients with CSI. Enthusiasm is expressed by some neuroanesthesia experts for the exclusive use of the fiberoptic bronchoscope to facilitate tracheal intubation in spine-injured patients. There are a number of theoretical factors that would support such a choice. The head and neck may be left in a neutral position, and little spinal movement is required to achieve laryngeal visualization and tracheal intubation. The patient’s protective reflexes are largely left intact, and the potential for deleterious movements and positioning is perhaps reduced. A neurologic assessment can be made after intubation to ensure that there has been no change in the patient’s status, although the accuracy of this evaluation may be diminished by sedation. Finally, the patient could be positioned awake to increase the likelihood that potentially injurious position could be avoided. These considerations support the use of the tracheal intubation facilitated by a fiberoptic bronchoscope and performed by an experienced care provider as a practice option in the management of the airway in spine-injured patients. Survey evidence also supports the conclusion that many anesthesiologists are of the opinion that it is the preferred option, especially in elective scenarios. This preference persists even among physicians who acknowledge limited skills with the device. However, there are no data to suggest that better neurologic outcomes are achieved with its use. In fact, the application of a technique by practitioners not expert in its use may carry risk. Failed awake intubation has been identified as a cause of morbidity and mortality in the latest analysis of difficult airway claims by the American Society of Anesthesiologists’ Closed Claims Project. The use of a direct laryngoscope after induction of

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Direct laryngoscopy can also be performed considering themselves similarly skilled with other practice options. \(^{106}\) The principle advantages of the direct laryngoscope are that anesthesiologists are very experienced in its use and that it is a highly effective tool; many anesthesiologists do not consider themselves similarly skilled with other practice options. \(^{106}\) Direct laryngoscopy can also be performed more quickly than some, but not all, alternative techniques, and it does not require time to obtain and set up specialized equipment. However, it has the potential to cause greater spinal movement than indirect techniques. In addition, if laryngoscopy is performed after the induction of general anesthesia, the potential for difficult ventilation, a failed intubation, and a cannot-intubate, cannot-ventilate scenario cannot be excluded. Finally, if there is underlying severe, chronic cervical spinal pathology, difficult laryngoscopy should be anticipated because it is more likely to occur. \(^{3}\) This is particularly true if the upper cervical spine is severely impacted by the disease process.

The use of the direct laryngoscope is a practice option accepted by expert practitioners; its use is commonly encouraged in urgent or emergent situations. Other practice options, such as light wands, rigid fiberoptic laryngoscopes, and laryngeal mask airways, are also deemed appropriate. There is no published evidence that would indicate that one intubation option is superior to others with respect to outcomes in general and, in particular, with respect to neurologic outcomes. Any comparative study that could or would support a single practice option would have to be very large to be persuasive.

**Summary of the Literature**

There is an incidence of CSI approximating 2% among victims of blunt trauma, and this incidence is trebled if the patient presents unconscious or with a GCS score reduced to 8 or below. A finding of a focal neurologic deficit also significantly increases the likelihood of a cervical injury. The need to evaluate all at-risk patients with a complete and technically adequate imaging series seems to be accepted as the standard of care, although there is debate as to what constitutes the at-risk population and an acceptable imaging series. A three-view spine series (lateral, antero-posterior, and odontoid views) supplemented by computerized tomographic imaging through areas that are difficult to visualize or suspicious is effective in ruling out injury in both cooperative and noncooperative patients. MRI studies may be useful in patients with neurologic symptoms but negative radiography and CT imaging; they seem to add little to the evaluation of patients with persistent pain but a normal neurologic examination and negative imaging. As well, although MRI may identify CSI not captured by CT, these injuries are not usually unstable. Failure to diagnose the injury at time of presentation is associated with a worse neurologic outcome; it occurs most commonly as a result of either failure to appropriately image the spine or misinterpretation of appropriate imaging.

Immobilization of the spine in at-risk patients at the time of first system contact and maintenance of the immobilization until the spine is cleared is accepted by expert consensus as the standard of care. However, there is some debate about the need for immobilization in patients at low risk. Prolonged spinal immobilization is costly in terms of system resources and not without risk to the patient. Strategies that permit efficient and prudent spine clearance are available and their use is encouraged so as to reduce costs, conserve resources, and, most importantly, to prevent harm.

Secondary neurologic injury occurs after CSI and may be associated with clinical care interventions. There is now recognized a syndrome of progressive, ascending myelopathy that occurs in some patients and that is characterized by a widely distributed cord injury. It may occur after a period of relative clinical stability and in the absence of both mechanical instability and canal compromise at the spinal levels to which the injury has ascended. The use of MRI (especially T2-weighted studies) has been instrumental in documenting both the occurrence and the nature of this injury. It may also present at a time when clinical interventions are ongoing to treat the original traumatic injuries. Although there has been a past tendency to attribute many secondary injuries to clinical interventions, especially in a medical–legal context, critical examination of these cases, supplemented with MRI evaluations, may reveal that some, and perhaps most, are an inevitable consequence of the primary injury.

The routine use of some form of immobilization during airway maneuvers in at-risk patients is accepted as the standard of care. All airway maneuvers will result in some degree of neck movement, both in general and specifically at the sites of injury. The amounts of movement are small and may be restrained by in-line immobilization, but they are not eliminated. The available data and the accumulated clinical experience support a conclusion at the current time that these movements are unlikely to result in neurologic injury provided that reasonable care is taken during airway interventions. However, a study of sufficient size to validate this statement has not been performed.

The most appropriate technique for performing tracheal intubation in patients with cervical spine injury continues to be debated. There are no clinical outcome data that suggest better neurologic outcomes with any
References


41. Seuine M, Tjardes EJ, Hackett DS, Becher J, Schull M, Rowe BH:

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vertebrae by the standard and intubating laryngeal mask airways. A randomized, controlled, cross-over study in fresh cadavers. Anesth Analg 1999; 89:1296–300


120. Muckart DJ, Bhagwanjee S, van der Merwe R. Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. Anesthesiology 1997; 87:418–20


Anesthesia for neuroradiology
Jee Jian See and Pirjo H. Manninen

Purpose of review
The role of anesthesia outside the operating room is rapidly expanding and evolving alongside with the advances in interventional neuroradiology. Increasingly complex diagnostic and therapeutic neuroradiological procedures are being performed on sicker patients. This review provides an overview of the principles of anesthetic management and summarizes recent advances in interventional neuroradiology.

Recent findings
There are many new areas of development in interventional neuroradiology, but each also brings with it controversy. Use of newer agents for anesthesia and for anticoagulation may change the intraoperative management of patients. The role of neurophysiological monitoring during endovascular procedures is still to be validated. There has been increasing interest in and evidence of the efficacy of carotid artery stenting in the treatment of carotid artery disease. The utility of intraoperative magnetic resonance imaging in neurosurgery is expanding rapidly.

Summary
Providing anesthesia in the interventional neuroradiology suite continues to be a challenge to the anesthesiologist. Understanding the anesthetic constraints and complexities and keeping abreast of the current developments in neuroradiology are crucial in ensuring the maximal benefits to and safety of patients.

Keywords
cerebrovascular disorders, interventional neuroradiology, intraoperative magnetic resonance imaging

Introduction
Recent advances in the field of interventional neuroradiology have resulted in more patients with diseases of the central nervous system to be managed in neuroradiological suites. There is increasing evidence to suggest that the outcome of the patient may be improved with endovascular therapy for some cerebrovascular disorders. The aim of this review is to provide an overview of the recent developments in the anesthetic management of patients undergoing procedures in the neuroradiology suite.

General considerations
The optimal conduct of anesthesia in the neuroradiology suite requires forethought and thorough planning for each procedure [1,2]. Detailed patient evaluation and an understanding of the underlying neuropathology are essential components for a successful anesthetic. The establishment of an open channel of communication among the neuroradiologist, anesthesiologist, nurses and radiographer is essential for routine care but crucial for the management of disasters that may occur. Adherence to the basic principles of neuroanesthesia should continue in the management of patients in the neuroradiology suite. This includes the optimization of cerebral blood flow, perfusion pressure, control of intracranial pressure, and careful monitoring of the blood pressures, fluid status and temperature of the patient. The question of cerebral neuroprotection during periods of ischemia should also be considered. A smooth and rapid recovery from the procedure is desirable for early neurological assessment and safe transfer of the patient.

Conduct of anesthesia
The choice of the anesthetic agents and techniques remains largely in the hands of the anesthesiologist; however, the needs of the neuroradiologist and the procedure should be considered. Most institutions develop their own protocols for specific procedures, whether the patient is under general anesthesia or conscious sedation. There is little evidence favoring one technique over the other. The superior image quality obtained from a motionless patient during digital subtraction angiography favors the use of general anesthesia with apnea over conscious sedation techniques. The increasingly complex nature of procedures, the need for precise blood pressure control and preparation for potential catastrophic complications are considerations for general anesthesia. Conversely, when an assessment of neurological function is desired, conscious sedation techniques are required.
During procedures such as stenting of the carotid artery and balloon occlusion tests, patients should only be minimally sedated as they need to be awake periodically so that cerebral function integrity can be determined. Other factors including pediatric age group, uncooperative patients and the severity of underlying disease may play a role in the choice of anesthetic technique.

The ideal anesthetic agents should not impair cerebral autoregulation, carbon dioxide reactivity or cerebral metabolism. Sevoflurane, desflurane and propofol are all widely used. Castagnini et al. [3] compared the speed of recovery in 103 patients after sevoflurane with propofol for the maintenance of anesthesia during neuroradiology procedures. Sevoflurane was associated with a more rapid recovery. The limitations of the study were that the intraoperative depth of anesthesia was not controlled and may not have been the same for the two groups of patients. The time to discharge was also no different between the two groups. The superiority of sevoflurane compared with desflurane in neuroanesthesia is still debatable. Potential increases in cerebral blood flow and the loss of autoregulation associated with the use of higher doses of desflurane have raised questions regarding its use in neuroanesthesia [4]. Holmström and Åkeson [5], in an experimental porcine model of intracranial hypertension, recently found that desflurane at 0.5 and 1 MAC were associated with more cerebral vasodilation and higher intracranial pressures at normocapnia compared with isoﬂurane or sevoflurane. However, the difference in intracranial pressure was less evident during hyperventilation. These findings were not consistently evident in human subjects. Sponheim et al. [6] did not find any significant increase in intracranial pressure in 36 children between the use of sevoflurane or desflurane.

Dexmedetomidine is a selective alpha2-adrenoceptor agonist with centrally mediated sympatholytic effects [7]. It significantly reduces the intraoperative and postoperative anesthetic requirements. Patients sedated using dexmedetomidine remain rousable and able to cooperate when stimulated. A lack of respiratory depression offers another distinct advantage over other sedatives [7–9]. The successful use of dexmedetomidine has been reported in awake craniotomy procedures in which neuropsychological tests were required [8,9]. However, Bustillo et al. [10] reported their experience with the use of dexmedetomidine for endovascular embolization of cerebral arteriovenous malformations in five patients, and found that cognitive and neurological testing were impaired when dexmedetomidine was used. The patients were unable to perform complex neuropsychological tests 45 min after the discontinuation of dexmedetomidine infusion. The use of dexmedetomidine in the neuroradiology suite, including the ‘ideal’ dosages, requires further evaluation.

Anticoagulation
One of the critical roles of the anesthesiologist in the interventional neuroradiology suite is to provide anticoagulation and to assist in the treatment of complications. A complication of endovascular treatment of cerebrovascular disease is the development of intraoperative thrombosis; therefore the management of anticoagulation is important [11,12]. Heparin is still the most commonly used anticoagulant. The preferred method of monitoring for the effect of heparin is the activated clotting time rather than the activated partial thromboplastin time [13]. The activated partial thromboplastin time may be inaccurate, especially when high doses of heparin are used. The United States Food and Drug Administration has recently approved the use of argatroban, a direct thrombin inhibitor, as an anticoagulant in patients with or at risk of heparin-induced thrombocytopenia undergoing percutaneous coronary interventions [14]. The potential advantages of argatroban over heparin include a more predictable anticoagulant response and a minimal effect on platelets. Its use may expand into the neuroradiology suite in the future.

In some institutions, during the treatment of patients with acutely ruptured aneurysms heparin administration is delayed until the first coil has been deployed even though rupture of the aneurysm during the endovascular procedure is a rare event [12,15]. The pretreatment of patients with antiplatelet agents in the treatment of unruptured aneurysms is another strategy to reduce the risk of intra procedural thrombosis [12].

In spite of the use of heparin, the risk of thromboembolic events related to Guglielmi detachable coil embolization is still present. Thrombolytic agents are commonly used to treat intra procedural thrombosis but results have been mixed. Hähnel et al. [16] described the use of local intraarterial fibrinolysis using recombinant tissue plasminogen activator, and achieved a recanalization rate of 44%. Fiorella et al. [12] examined the use of intravenous and intra-arterial abciximab (ReoPro), a GPIIb/IIIa inhibitor, and found that the results were promising. The elevation of blood pressure to increase collateral cerebral blood flow during a thromboembolic event to maintain cerebral perfusion as well as the institution of neuroprotective strategies during this time may be helpful.

Neurophysiological monitoring
Neurophysiological monitoring in the neuroradiology suite is desirable but may be difficult to perform routinely. The lack of space in the neuroradiology suite, the need for trained personnel, additional costs and time are constraints to be considered. Monitoring the descending corticospinal pathways by using motor-evoked potentials has been shown to be useful in preventing permanent neurological deficits during cranial and spinal procedures [17,18]. Liu et al. [19]...
analysed the utility of intraprocedural neurophysiological monitoring during endovascular therapy of aneurysms in 35 patients, and found that changes were seen in nine patients, resulting in altered management in five patients including the abandonment of coiling in one patient. The authors concluded that neurophysiological monitoring may reduce ischemic complications and can be used to help guide therapeutic decisions [19]. The modification of anesthetic techniques, including the use of total intravenous anesthesia, may be needed when monitoring motor-evoked potentials [17].

**Intracranial aneurysms**

Since the publication of the International Subarachnoid Hemorrhage (ISAT) trial, comparing neurosurgical clipping with endovascular coiling in 2143 patients with ruptured intracranial aneurysms, debate regarding the optimal technique in the treatment of intracranial aneurysms continues [20]. The better results after endovascular treatment reported in that study implied that more patients will undergo coiling of their cerebral aneurysm, increasing the role of the anesthesiologist in the neuroradiology suite for the care of these patients.

Aneurysm rupture during endovascular procedures is not common but remains a potential risk. The incidence ranges from 2.3 to 3%, and may be higher in patients with ruptured aneurysms [15,21]. The rupture may be a slight leak or a massive subarachnoid hemorrhage. With increasing experience, the incidence of intraprocedural rupture should decrease. The occurrence of a rupture should be quickly communicated to the anesthesiologist by the radiologist. Treatment, which will depend on the severity of the bleed, includes maintaining cerebral perfusion pressure, lowering intracranial pressure and the reversal of anticoagulation. Transfer of the patient under general anesthesia may be needed for further scanning or for an immediate ventriculostomy in the operating room. The mortality rate after intraprocedural rupture has been reported to be as high as 20% [15].

Cerebral vasospasm continues to be the most common complication after subarachnoid hemorrhage. The effect of surgical clipping or endovascular coiling of aneurysms on the incidence of vasospasm remains unclear [22]. The theoretical advantages of surgical ligation and the ability to irrigate blood out of the subarachnoid space were balanced by ‘less invasiveness’ during endovascular coiling. Balloon angioplasty is widely considered to be the most effective procedure to treat vasospasm, despite the risk of vessel dissection and rupture [23]. It can also be utilized in combination with the delivery of intra-arterial vasodilators such as papaverine. Complications associated with the use of intra-arterial papaverine have been reported, including hypertension, tachycardia, transient elevation in intracranial pressure, paradoxical worsening of vasospasm, seizures and brainstem depression. Preliminary experiences with intra-arterial nimodipine and nicardipine to treat vasospasm in small groups of patients were recently reported to be favorable [23,24].

**Arteriovenous malformations**

Arteriovenous malformations (AVMs) of the brain are relatively uncommon and their pathophysiology remains poorly understood. Recent reviews by Fleetwood and Steinberg [25] and Soderman et al. [26] summarized the current management of patients with brain AVM. The development of newer tissue adhesives or blocking substances and in the delivery technology may herald a change in the role of interventional neuroradiology in the management of AVMs. There have been few new developments in anesthetic management for the embolization of AVMs. Deliberate hypotension to decrease the velocity of blood flow during embolization may be crucial for a successful procedure. At present, the preoperative embolization of AVMs remains largely an adjunctive therapy to surgery and radiosurgery [27,28].

**Carotid artery stenting**

The US Food and Drug Administration recently approved the use of stents for the treatment of atherosclerotic disease of the carotid bifurcation [29*]. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial results comparing carotid artery stenting using an emboli protection device with surgical endarterectomy in 334 high-risk patients were recently published. The findings showed that stenting was not inferior to surgery. In the secondary analysis, the cumulative incidence of stroke, death or myocardial infarction, as well as the cumulative incidence of cranial nerve palsy and revascularization, and hospital stay were lower in the patients who received a stent [30]. Currently, the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which is a large prospective randomized multicenter trial, is still ongoing [29**]. The results may impact on the future management of patients with carotid artery disease. These developments imply that an increasing number of elderly patients with multiple medical conditions will present for anesthesia in the neuroradiology suite. Mlekusch et al. [31] retrospectively analysed 471 patients who underwent elective carotid artery stenting for high-grade stenosis. The authors found that 7% of patients experienced bradycardia and hypotension during the procedure. The routine administration of anticholinergic agents did not eliminate the risk of bradycardia and hypotension [31]. Patients with elevated systolic blood pressure may also be at an increased risk of hemodynamic instability and neurological events during stent application [32].
Intraoperative magnetic resonance imaging

Magnetic resonance imaging (MRI) for intraoperative neuronavigation has attracted considerable attention. The ability to determine and assess the brain parenchyma immediately before, during and after therapy, the ability to assess brain perfusion and metabolism, as well as the extent of the surgical removal of tumors are reasons for rapid development in this area [33*]. The use of intraoperative MRI has increased significantly, and thus the anesthesiologist needs to be continually involved and to update anesthetic management of patients in this area.

Schmitz et al. [34] recently reported their experience with high-field (1.5 Tesla) intraoperative MRI in 80 patients. Modifications such as the use of an MRI-compatible ventilator and infusion pumps were necessary. Monitoring devices were equipped with visual alarms as acoustic alarms may not be heard during the loud noise of the scanner. Having properly trained personnel involved in the care of patients in the MRI suite was also important [33*,34]. General considerations for anesthesia in the MRI suite will continue to apply but may need further developments as more powerful MRI machines are developed and used [35]. Limitations of patient suitability for anesthesia in the MRI setting still exist. This includes the inability to monitor the ST segment on the electrocardiogram [34]. Therefore patients at risk of coronary heart disease may currently need to be excluded from intraoperative MRI. Birkholz et al. [36] reported that high-field MRI scanning could interfere with electrocardiogram monitoring, resulting in an electrocardiogram pattern that could imitate malignant arrhythmia or provoke ST segment changes. It was observed that an electrocardiogram alteration occurred when the patient’s thorax was entering the inner bore of the scanner. The observed electrocardiogram effects were possibly caused by current induction by the static magnetic field or the Hall effect.

Conclusion

The field of interventional neuroradiology is rapidly and continually evolving. This provides opportunities for the anesthesiologist to be part of this exciting branch of medicine. In order to provide safe and effective care to patients, an understanding of neuropathology as well as keeping up to date in our knowledge of interventional neuroradiology and neuroanesthesia is essential. In spite of the relatively non-invasive nature of the procedures, serious complications can occur. An ability to respond and treat these complications requires pre-planning, anticipation and close cooperation among the different disciplines involved.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest

33 Keles GE. Intracranial neuronavigation with intraoperative magnetic resonance imaging. Curr Opin Neurol 2004; 17:497–500. This is a comprehensive review of fast changing trends in intraoperative MRI.
Spinal cord injury is a devastating event, often resulting in long-term disability. The injury may occur in isolation or in conjunction with other injuries. A thorough understanding of the pathophysiological processes involved aids management. This article aims to provide advice on understanding and managing some of the problems encountered by the anaesthetist.

Aetiology and incidence
There are approximately 1000 new cases of spinal cord injury per year in the UK, predominantly young males. Over 50% of spinal cord injuries occur as a result of road traffic accidents, the other major causes are sports injuries, assaults and industrial accidents.

Classification
Level
Spinal cord injury may occur at any level (Table 1) but certain areas, particularly the lower cervical spine and the thoracolumbar junction, are structurally more vulnerable. The level of the injury determines the extent of the neurological deficit with higher cervical lesions having the most serious consequences.

Stability
Anatomically, the vertebral column is described as being composed of anterior, middle and posterior columns. These columns include bony and ligamentous structures which are both important for maintaining stability. An isolated anterior or posterior column injury will be stable but injuries involving more than one column are not.

In the cervical spine, C1–C2 and C5–C7 cervical vertebrae are the most vulnerable to injury. These injuries are often unstable requiring immobilisation to prevent further damage. Although injuries of the cervical vertebral column are more common, the spinal canal is relatively spacious at this level and cord injury is not inevitable. However, the mid-thoracic region is much less mobile and the small circular vertebral canal leaves little space around the spinal cord making cord compression more likely. The same principle of immobilisation should be adhered to for thoracic and lumbar spine injuries, although, in general, these injuries are more stable.

Instability allows actual or potential abnormal movement of one vertebral segment upon another, thereby compromising neural structures. Defining the stability of a vertebral column injury is important, as it may influence the anaesthetic and surgical management. All spinal injuries should be treated as potentially unstable until proven otherwise.

Neurological deficit
In general, a spinal cord injury can be described as being complete or incomplete. An incomplete spinal cord injury is defined by partial preservation of neurological function more than one level below the level of spinal cord injury. Sacral sparing and preserved sensory or motor function are examples of incomplete lesions. There are several recognised patterns of incomplete lesions (e.g. anterior cord syndrome, Brown-Sequard syndrome, cauda equina syndrome). If a lesion is complete there is absence of motor and sensory function below the level of the lesion. Complete transection occurs in approximately 50% of spinal cord injuries.

Key points
Spinal cord injury should be considered in every trauma patient
Assessment and initial management of the injured patient is according to ATLS principles
Prevention of further damage depends on protecting the unstable spine and maintaining spinal cord perfusion
Sympathetic denervation may lead to neurogenic shock and loss of compensatory mechanisms
Anaesthetic management is complex and challenging and depends on an understanding of the pathophysiology involved

Table 1. Distribution of spinal cord injury (10% of patients sustain injuries at more than one level)

<table>
<thead>
<tr>
<th>Level</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical spine</td>
<td>48</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>41</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>11</td>
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</tbody>
</table>

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The level of the injury determines the extent of respiratory involvement (Table 2). Abdominal muscle paralysis contributes to the respiratory embarrassment and poor cough. Neurogenic cardiovascular complications are seen in higher lesions (above T7) due to the effects of traumatic sympathectomy. Loss of sympathetic vasoconstrictor tone to blood vessels results in vasodilatation. Cardiac sympathetic supply (T1–T4) may also be affected; loss of chronotropic and inotropic effects and unopposed vagal reflexes may result in severe sinus bradycardia. Profound bradycardia and even sinus arrest may occur during intubation or suction of the airway.

### Pathophysiology

#### Spinal shock

Spinal shock describes the initial phase after an insult to the spinal cord and may be defined as a temporary interruption of the physiological function of the spinal cord following injury. It may, in part, be a vascular phenomenon. All reflex activity is lost and the cord below the level of the lesion also becomes isolated from the higher centres. This accounts for the characteristic picture of flaccid paralysis. An accurate prognosis is not possible until the stage of spinal shock has ended (up to 4 weeks). If there is evidence of neurological sparing, i.e., residual sensory, motor or reflex function below the level of the lesion, full recovery may follow.

Autonomic and reflex activity gradually returns to the injured cord. Loss of descending inhibitory control leads eventually to spasticity and autonomic hyperreflexia. Respiratory function improves as spasticity of chest and abdominal wall muscles reduces paradoxical movement.

It is important not to confuse spinal shock with spinal neurogenic shock. The latter term describes the hypotension seen as a result of traumatic sympathectomy.

#### Secondary injury

Trauma to the spinal cord results in an immediate physical injury (i.e., primary injury). A combination of small intramedullary vessel damage, haemorrhage into grey matter and local vasoconstriction causes a critical fall in cord perfusion. The cord becomes ischaemic leading to the onset within minutes of secondary injury which may become progressively worse over the ensuing hours. The release of mediators of postschaemic injury is implicated in secondary damage as are hypotension, hypoxaemia and hyperthermia. After a period of ischaemia, apoptosis or programmed cell death occurs. This peaks at 8 h and results in irrecoverable damage.

Many interventions have been tried to reduce the severity of secondary injury, mainly in experimental animal work. Steroids, free radical scavengers, barbiturates, hypothermia, hyperbaric oxygen therapy and NMDA and opioid antagonists are some examples. The results of these interventions are disappointing. Many spinal centres have a spinal injury protocol that includes the early administration of high dose methylprednisolone. The evidence for this intervention comes from the National Acute Spinal Cord Injury Study (NASCIS) trials which demonstrated an improvement in long-term neurological outcome following high dose methylprednisolone. Unfortunately, there is no good evidence that this equates to an improvement in functional outcome and the risk of infection is increased.

Measures aimed at ensuring adequate oxygenation and perfusion of the injured cord and avoidance of hyperglycaemia and hyperthermia are the mainstay of prevention of secondary injury.

### Initial assessment and management

#### Presentation

The patient with an acute spinal cord injury typically presents to the accident and emergency department having already been immobilised on a spinal board. Use of pre-hospital spinal immobilisation in trauma patients is now routine but the positioning and immobilisation of the patient should be scrutinised as part of the primary survey. The correct technique is placement of a hard cervical collar of the appropriate size, sandbags either side of the head and adhesive tape across the forehead onto each side of the trolley. Thoracic and lumbar spine injuries simply require the patient to be kept supine on a solid surface, avoiding any excessive movement. If the patient is to be moved, this should be by ‘log-rolling’, maintaining vertebral column alignment.
Spinal cord injury should be considered in all trauma victims. An appropriately qualified person can rule out cervical spine injury in the fully conscious patient. Full precautions must be strictly adhered to in any patient with midline tenderness, neurological symptoms or signs, a reduced level of consciousness, or a painful ‘distracting’ injury.

**Initial management**

The initial management of the trauma victim with a spinal cord injury is as for any seriously injured patient. The ATLS approach is proven, standardised and effective and initial management should be based upon its principles.

**Airway**

The airway must be examined for patency and, if required, manipulated with a jaw thrust as opposed to a chin lift. This airway-positioning manoeuvre is associated with less displacement of the cervical spine. A trauma mask with high flow oxygen should be applied to the patient if the airway is patent. If not, a decision to intubate the trachea should be made earlier rather than later, in order to maximise oxygen delivery and limit secondary hypoxic damage to the injured spinal cord. A difficult intubation should be anticipated because of: (i) suboptimal positioning due to immobilisation of the cervical spine; (ii) the requirement for a rapid sequence induction with cricoid pressure; (iii) the potential for pre-vertebral swelling due to haematoma; and (iv) the potential for poor visibility at laryngoscopy due to debris or distorted anatomy in maxillofacial trauma.

There is a great deal of debate in the literature regarding the safest approach to intubation in the patient with a cervical spine injury and the likelihood of causing further damage to the spinal cord. One concern is that unstable bony fragments may be maintained in position only by muscular spasm and that muscle relaxation may contribute to the instability. The options for intubation are: (i) direct laryngoscopy and intubation in the presence of manual in-line immobilisation; (ii) blind nasal intubation if there is no compromise to the cribriform plate; (iii) blind oral intubation using the intubating laryngeal mask airway (ILMA); (iv) awake fibre-optic intubation; and (iv) surgical airway if intubation is not possible.

Awake fibre-optic intubation with adequate local anaesthesia and intubation under direct vision has the advantage of avoiding movement of the unstable cervical spine. It may be performed with the patient immobilised and in halo traction and allows neurological assessment following intubation. However, this method requires skill and specialist equipment and is often impractical in the acute situation, particularly if intubation is required urgently. The choice depends on the situation and experience of the individual.

Direct laryngoscopy with in-line immobilisation is a safe and acceptable method. It requires at least three trained personnel and involves four stages: preparation, manual in-line immobilisation, rapid sequence induction and intubation. Succinylcholine is the muscle relaxant of choice. The release of potassium associated with the use of succinylcholine in spinal cord injury has not been shown to be a problem until 3 days post-injury at the earliest. Atropine must be available immediately as should equipment for obtaining a surgical airway. The hard collar is opened at the front to expose fully the mandible and allow maximum possible mouth opening. In order to avoid displacement of the injured cervical spine by cricoid pressure, the back of the rigid collar is left in place. Otherwise, a bimanual technique should be employed. A small amount of movement of the neck may be inevitable, even with manual in-line immobilisation. This is unlikely to be significant enough to cause injury to the cord and must be allowed for in order to secure the airway.

**Breathing**

Adequate oxygenation is imperative in order to prevent secondary hypoxic damage. Supplemental oxygen must be administered to all patients. Ventilation must be assessed both clinically and with oxygen saturation measurements and arterial blood gas analysis. Inadequate ventilation causing hypoxaemia or hypercapnia should be rectified by tracheal intubation and ventilation. Hypoxaemia is found in about 50% of patients with high spinal cord injury, usually due to the neuromuscular deficit resulting from the injury. Associated injuries may also be the cause of inadequate ventilation or oxygenation. Chest injuries are common in polytrauma patients, pulmonary aspiration and pulmonary oedema are common in head injury and some patients may have been victims of near-drowning.

**Circulation**

Maintenance of an adequate circulation is essential in spinal cord injury in order to minimize secondary ischaemic damage to the injured cord. Hypotension must be treated promptly with fluid boluses in the first instance. In the polytrauma patient who is hypotensive, hypovolaemia secondary to haemorrhage from concurrent injuries must be excluded according to ATLS principles. Remember that the patient with a high spinal cord injury will not complain of pain from a fractured pelvis or other injuries. Intra-abdominal bleeding is more difficult to diagnose when the abdominal muscles are flaccid. This must be ruled out by diagnostic peritoneal lavage, abdominal ultrasound or computed tomography (CT).

Damage to the spinal cord above T6 may result in spinal neurogenic shock. Loss of sympathetic function leading to neurogenic shock should be actively managed in order to preserve the perfusion.
of the injured cord. Bradycardia affecting cardiac output should be treated with intravenous atropine or glycopyrrolate.

Fluid resuscitation is complex in these patients. Judicious volume loading with crystalloid or colloid solutions guided by central venous pressure measurement is the first step. Loss of cardiac sympathetic innervation affects myocardial contractility. In the acute phase, these patients have a limited capacity to respond to volume stress and are prone to develop pulmonary oedema if volume overloaded. If hypotension persists despite fluid loading, low doses of vasopressors are indicated to counteract the loss of vasoconstriction. If vasoconstrictors are used, care must be taken to avoid a fall in cardiac output resulting from a high systemic vascular resistance. Pulmonary artery flotation catheter or trans-oesophageal Doppler may be used to guide cardiovascular support in more complex cases.

Assessment of disability

Full neurological examination is important and, whenever possible, must be carried out before anaesthesia for intubation. It must be recorded and repeated at regular intervals. Any changes should be clearly documented and include: (i) sensory level; (ii) motor level; and (iii) anal tone and reflex activity.

The neurological level of injury is designated as the most distal uninvolved segment of the spinal cord. This differs from the bone level of injury, which is the level of the spine at which bony damage is actually visualised. There is usually a correlation between the two levels but there can be some discrepancy, especially in cervical spine injuries. Ascending spinal cord oedema may result in deteriorating signs. Improvement in the deficit may be predictive of some neurological recovery.

Radiology

A detailed discussion of imaging in spinal injury is beyond the scope of this article. According to ATLS guidelines, all patients with multiple injuries or significant head injury require a lateral cervical spine X-ray. If there is a suspicion of an injury in the thoracic or lumbar spine, the relevant area should also be X-rayed. Of patients with cervical spinal injury, 10% will have spinal injury at another level and this must be excluded.

The lateral cervical spine X-ray must be adequate, i.e. extending as far as the cervicothoracic junction. All anaesthetists should have a system for examining cervical spine films but an expert opinion is often required. Plain radiography of the cervical spine may also include an anteroposterior and an open mouth (odontoid peg) view. Upper thoracic spine injuries are difficult to visualize on plain radiography.

Magnetic resonance imaging (MRI) is particularly useful for imaging the spinal cord and soft tissues and for identifying cord compression and oedema. Specialist spinal units will usually perform an early CT and often also MRI of the entire spine in any patient with a spinal injury. However, it is important to avoid sending unstable patients to distant radiology departments and into inaccessible scanners.

Anaesthetic management

Indications for surgery

Surgical intervention may be indicated in the early or intermediate phase of spinal cord injury. If the clinical picture at 48 h is of a complete injury, no type of surgery has been shown to improve neurological function. Despite this, operative spinal fusion may be appropriate in order to confer stability thereby aiding rehabilitation and preventing further complications. Stabilisation procedures may be best delayed until the patient has recovered from other injuries or is more cardiovascularly stable.

Early surgery may be indicated if the neurological deficit is incomplete or due to spinal shock and there is felt to be some potential for recovery. The surgery is carried out in order to permit: (i) urgent decompression of the spinal cord, followed by stabilisation; (ii) restoration of vertebral column alignment if this has not been achieved by conservative means (halo traction); (iii) exploration for decompression and stabilisation if the neurological deficit is worsening; and (iv) exploration of open penetrating spinal wounds.

The anaesthetic management of patients with high spinal cord injury may be challenging and the potential hazards should not be underestimated. Spinal surgery should be carried out in specialist centres but an anaesthetist in any hospital receiving trauma patients may be called upon to manage a spinal injuries patient who requires urgent surgery for other injuries.

Pre-operative assessment and planning

Early assessment at presentation to hospital has been outlined above. Before surgery, it is important to re-assess the patient carefully and plan accordingly.

Airway

If the patient has not been intubated, the airway must be assessed and a plan made for airway management. The patient may be in halo traction and surgeons should be involved if this is to be removed.

Breathing

In cervical and higher thoracic lesions, respiratory function may have become compromised. Absent or impaired cough leads to the retention of secretions. Increased work of breathing means patients relying on diaphragmatic breathing may start to tire. Lung volumes reach their lowest point at 3–4 days post-injury and spirometry is
useful to monitor pulmonary function. If the vital capacity has fallen to less than 1 litre, the patient is hypoxaemic or has a high respiratory rate, arrangements must be made for assisted ventilation postoperatively.

**Circulation**

In the patient with a cervical or high thoracic lesion and sympathetic denervation, the systolic blood pressure will often have stabilised at 90–100 mmHg. This should be adequate in the supine position but loss of compensatory mechanisms may jeopardize cord perfusion during positioning for surgery or periods of intra-operative blood loss. Consequently, it is necessary to make plans for central venous catheterisation and the availability of infusion pumps and vasoactive drugs which may be needed to support the circulation. ECG abnormalities, including signs of subendocardial ischaemia and arrhythmias, are sometimes seen in high cord injuries.

Major blood loss should be anticipated and blood cross-matched in advance.

**General considerations**

A more general anaesthetic assessment must not be overlooked and all management plans discussed with the patient. A spinal cord injury is a devastating event and these patients may be in a state of considerable psychological distress. Good communication and a humane and sensitive approach are essential.

**Intra-operative management**

**Monitoring**

In addition to standard monitoring, intra-arterial blood pressure measurement and central venous pressure monitoring are required. As discussed above, a pulmonary artery flotation catheter or transoesophageal Doppler may be helpful for optimal cardiovascular management. Urine output should be measured hourly. Thermoregulation is impaired in spinal cord injury. Core temperature must be monitored and patient and fluid warming devices used.

Spinal cord monitoring may be used in specialist centres, particularly for the patient with an unstable vertebral column injury and no or partial neurological deficit. It is vital to preserve cord function in these patients and cord monitoring during, or immediately after, positioning during surgery facilitates this. The commonest method is the use of sensory evoked potentials.

**Induction and maintenance**

The main goal is to maintain adequate cord perfusion and oxygenation during surgery and anaesthesia to prevent any further damage. Autoregulation of blood flow is lost in the injured cord and mean arterial blood pressure should be at least 60 mmHg. A controlled ventilation technique is appropriate due to the prolonged nature of the surgery and the position required for surgical access. Mild hypocapnia is of theoretical benefit in decompressing the spinal cord.

At induction, the anaesthetic agents may be of individual preference but should be titrated slowly. The usual precautions are taken if the patient has a potential full stomach but succinylcholine should be avoided if the patient is > 3 days post-injury. Airway management has been discussed earlier and is not a particular issue if the lesion is below C7 or there is no chance of neurological recovery. Atropine or glycopyrrrolate should be available to treat any bradycardia.

Large bore intravenous access is essential. A nasogastric tube should be placed as high acute cord injury leads to gastric stasis and gastrointestinal ileus. Spinal injury patients are at particular risk of venous thrombo-embolism. Compression stockings should be worn and calf compression devices used intra-operatively.

Most spinal decompression and stabilisation procedures involve posterior surgery with the patient in the prone position. Halo traction may be maintained during surgery. For unstable fractures, great care must be taken to maintain vertebral column alignment during positioning. For some injuries, access to the anterior spinal column may be indicated. If this is the case in a thoracic spine injury, a thoracotomy will be needed and, if possible, provision should be made for one lung ventilation. These procedures may take many hours and the usual precautions must be taken to avoid peripheral nerve injuries and pressure sores. Major blood loss is not uncommon and intra-operative blood cell salvage should be used if it is available.

A balanced anaesthetic technique is appropriate but analgesic requirements postoperatively depend on the nature of surgery and the extent of the neurological injury. The use of epidural analgesia may lead to difficulty with neurological assessment postoperatively and great care should be taken with the use of systemic opioids in patients with respiratory compromise.

**Key references**


See multiple choice questions 94–96.
Anaesthesia for spinal surgery in adults

D. A. Raw1*, J. K. Beattie2 and J. M. Hunter1

1University Department Anaesthesia, University Clinical Department, The Duncan Building, Daulby Street, Liverpool, L69 3GA, UK. 2Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot Road, Liverpool L7 8XP, UK

*Corresponding author. E-mail:daveraw@doctors.org.uk

The spectrum of spinal surgery in adult life is considerable. Anaesthesia for major spinal surgery, such as spinal stabilization following trauma or neoplastic disease, or for correction of scoliosis, presents a number of challenges. The type of patients who would have been declined surgery 20 yr ago for medical reasons, are now being offered extensive procedures. They commonly have preoperative co-morbid conditions such as serious cardiovascular and respiratory impairment. Airway management may be difficult. Surgery imposes further stresses of significant blood loss, prolonged anaesthesia, and problematical postoperative pain management. The perioperative management of these patients is discussed. The advent of techniques to monitor spinal cord function has reduced postoperative neurological morbidity in these patients. The anaesthetist has an important role in facilitating these methods of monitoring.

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Keywords: anaesthesia, general; monitoring; surgery, spinal

The scope of spinal surgery is considerable. Both adult and paediatric patients present for surgery, which may be elective or urgent. They mainly present with one of five pathologies: trauma, for example an unstable vertebral fracture; infection, for example vertebral abscess; malignancy (metastatic or primary disease with spinal instability, pain, and neurological compromise); congenital/idiopathic, for example scoliosis; or degenerative disease. In excess of 25 000 spinal operations were performed in the UK in 2001–2.1,12 Surgery may be required at any site in the spine from cervical to lumbosacral. Procedures range from minimally invasive microdiscectomy, to prolonged operations involving multiple spinal levels and significant blood loss. An osteotomy is a decompressive procedure, which releases compressive forces at a localized site. Stabilization of the spine involves instrumentation above and below the unstable spinal level. Distractive forces may also be applied to the spine, for example in surgery for scoliosis, with instrumentation placed over multiple spinal levels. Insertion of such devices may be through a posterior, anterior, or a combined approach involving repositioning of the patient part way through the procedure and major blood loss.

The challenge to the anaesthetist is to provide optimal surgical conditions whilst ensuring adequate oxygenation to the brain and spinal cord, and facilitating the use of intraoperative spinal cord monitoring techniques if appropriate.

Pathological conditions requiring spinal surgery in adult practice

Scoliosis

Scoliosis involves a lateral and rotational deformity of the spine, which occurs in up to 4% of the population.98 Most cases are idiopathic (70%) and occur with a male:female ratio of 1:4 (Table 1). Surgery is usually considered when the Cobb angle exceeds 50° in the thoracic, or 40° in the lumbar spine (Fig. 1A and B). Surgery aims to halt progression of the condition and to at least partially correct the deformity, preventing further respiratory and cardiovascular deterioration. Left untreated, idiopathic scoliosis rapidly progresses and is often fatal by the fourth or fifth decade of life, as a result of pulmonary hypertension, right ventricular failure, or respiratory failure.95

Muscle disorders

Muscular dystrophy and cerebral palsy are important causes of scoliosis. Of the muscular dystrophies, Duchenne
muscular dystrophy (DMD) is the most common, with an incidence of one in 3300 male births. It is inherited as a sex-linked recessive condition affecting skeletal, cardiac, and smooth muscle. Patients lack a membrane cytoskeletal protein, ‘dystrophin’, and typically present between the ages of 2 and 6 yr with progressive weakness of proximal muscle groups. Up to one-third of patients have intellectual impairment. DMD patients have a high incidence of cardiac abnormalities (50–70%). In the later stages of the disease, a dilated cardiomyopathy may occur associated with mitral valve incompetence. Dysrhythmias occur and up to 50% of patients have cardiac conduction defects. Cardiac arrest in DMD patients has been reported during spinal surgery, from which some patients have been resuscitated, and others have died. Surgery improves the patient’s quality of life, slows the decline in respiratory function, and increases life expectancy.

Muscular dystrophic patients are sensitive to non-depolarizing neuromuscular blocking agents, and hyperkalaemia may occur with the use of succinylcholine.

Carcinomatosis
Patients with primary or secondary malignant disease of the vertebral column and spinal cord are increasingly being considered for surgery, the aims of which are primarily to relieve pain but also to excise the lesion, prevent further neurological deterioration, and stabilize the vertebral column. These patients have commonly lost a large amount of weight and have reduced physiological reserve.

Respiratory complications of malignancy are common in such patients, and include infection, pleural effusion, and pulmonary toxicity from alkylating agents (cyclophosphamide, chlorambucil, busulfan) or antimetabolites (methotrexate, azathioprine). Myocardial injury may also occur secondary to the use of chemotherapy (busulfan, cyclophosphamide, mitomycin). Metabolic derangements such as hypercalcaemia, and inappropriate secretion of antidiuretic hormone may develop. The latter is associated with small cell lung tumours, carcinoma of the prostate, pancreas and bladder, and central nervous system neoplasms.

It is usual for these patients to have acute-on-chronic pain problems. They are often receiving regular opioids, non-steroidal anti-inflammatory drugs, and simple analgesics. Patients may therefore have an increased requirement for intraoperative and postoperative analgesia as a result of pharmacodynamic-related opioid tolerance, and pharmaco-kinetic factors such as liver enzyme induction.

Spinal trauma
Patients with traumatic injury frequently present for surgical spinal stabilization during the period of spinal shock, which begins almost immediately after the insult and may last for up to 3 weeks. Some degree of spinal cord dysfunction may also be present in patients with malignant disease presenting for spinal stabilization. The clinical effects depend on the level of injury to the spinal cord. A physiological sympathectomy occurs below the level of the spinal cord lesion, possibly causing hypotension secondary to arteriolar and venular vasodilatation. Injuries at or above T6 are particularly associated with hypotension, as the sympathetic outflow to splanchnic vascular beds is lost. Bradycardia also occurs if the lesion is higher than the cardiac sympathetic outflow (T2–T6), the parasympathetic cranial outflow being preserved. A complete cervical cord injury produces a total sympathectomy and therefore hypotension will be more marked.

above the level of the lesion, sympathetic outflow is preserved. Vasoconstriction in upper body vascular beds and tachycardia may be observed in response to the hypotension resulting from reduced systemic vascular resistance (SVR) in the lower part of the body. Hypotension associated with spinal cord injury responds poorly to i.v. fluid loading, which may cause pulmonary oedema. Vasopressors are the treatment of choice. Other causes of hypotension should be excluded such as blood loss associated with other injuries. Hypoxia or manipulation of the larynx or trachea may cause profound bradycardia in these patients. Positive pressure ventilation (IPPV) causes marked arterial hypotension as the SVR cannot be raised to offset the changes in intrathoracic pressure caused by IPPV.

Mid to low cervical spine injuries (C4–C8) spare the diaphragm but the intercostal and abdominal muscles may be paralysed (Fig. 1C–E). This leads to an inadequate cough, paradoxical rib movement on spontaneous ventilation, a decrease in vital capacity by up to 50% of predicted values (as a result of a reduction in inspiratory capacity to 70% and expiratory reserve volume to 20% of predicted), a decrease in functional residual capacity to 85% of predicted, and a loss of active expiration. There is also an increased risk of venous thromboembolism in patients with spinal trauma, together with delayed gastric emptying, and impairment of thermoregulation. Administration of succinylcholine may cause hyperkalaemia from 48 h after the injury.

Autonomic dysreflexia may be present from 3 to 6 weeks after the spinal cord injury. This condition is
characterized by extreme autonomic responses such as hypertension and tachycardia after stimulation of nerves below the level of the spinal cord lesion (for example, rectal, urological, peritoneal stimulation). Injuries higher than T7 have an 85% chance of producing serious cardiovascular derangement.5

Preoperative assessment
When assessing patients before spinal surgery, particular care should be given to the respiratory, cardiovascular, and neurological systems; all may be affected by the pathology for which the spinal surgery is proposed.

Airway assessment
The potential for difficulty in airway management should always be considered, particularly in those patients presenting for surgery of the upper thoracic or cervical spine. A careful assessment should be made for previous difficulty in intubation, restriction of neck movement, and the stability or otherwise of the cervical spine. Stability is defined as the ability of the spine, under physiological loads, to resist displacement, which causes neurological injury. It is essential to discuss preoperatively the stability of the spine with the surgeon. The cervical spine may be assessed clinically (presence of pain or neurological deficits), and
radiographically (lateral or flexion/extension plain films, computer aided tomography, and magnetic resonance imaging). The stability of the cervical spine is dependent on ligamental and vertebral elements. Damage to these elements may not be detectable by plain x-rays alone. The adult cervical spine below C2 is unstable or on the brink of instability when one of the following conditions are met: (i) all the anterior or all the posterior elements are destroyed; (ii) there is >3.5 mm horizontal displacement of one vertebra in relation to an adjacent one on a lateral x-ray; or (iii) there is more than 11° of rotation of one vertebra to an adjacent one.119 Above the level of C2, examples of unstable injuries include: disruption of the transverse ligament of the atlas (a distance of greater than 3 mm in adults between the posterior corpus of the anterior arch of C1 and the anterior border of the odontoid process, when measured on a lateral plain x-ray film, is diagnostic); and a Jefferson burst fracture of the atlas following axial loading, which causes atlantoaxial instability. Disruption of the tectorial and alar ligaments and some occipital condylar fractures also cause atlanto-occipital instability.

Some inherited disorders such as DMD may lead to glossal hypertrophy, and previous radiotherapy to tumours of the head and neck can cause difficulty in direct laryngoscopy. A decision must be made, whether to intubate the patient awake or asleep.

Respiratory system

Patients presenting for spinal surgery frequently have impaired respiratory function. Those who have sustained cervical or high thoracic trauma or who have multiple injuries may be artificially ventilated preoperatively. Others have recurrent chest infections.

Preoperatively, respiratory function should be assessed by a thorough history, focusing on functional impairment, physical examination, and appropriate investigations (Table 2). Scoliosis causes a restrictive pulmonary deficit, with reduced vital capacity and reduced total lung capacity (TLC). The residual volume is unchanged. The severity of functional impairment is related to the angle of the scoliosis, the number of vertebrae involved, a cephalad location of the curve, and a loss of the normal thoracic kyphosis.53 The extent of functional impairment cannot, therefore, be directly inferred from the angle of scoliosis alone. The most common blood-gas abnormality is a reduced arterial oxygen tension with a normal arterial carbon dioxide tension, as a result of the mismatch between ventilation and perfusion in hypoventilated lung units.48 Respiratory function should be optimized by treating any reversible cause of pulmonary dysfunction, including infection, with physiotherapy and nebulized bronchodilators as indicated.

There is controversy over whether surgery for idiopathic scoliosis improves,55 59 or worsens14 63 pulmonary function. However, the type of surgery proposed may have a significant influence upon postoperative pulmonary function, and may explain the contradictory findings in studies of non-homogenous groups of patients. Surgery involving the thorax (anterior approach, combined approach, or rib resection) was associated with an initial decline in forced vital capacity (FVC, 19% of baseline values), forced expiratory volume in 1 s (FEV1, 13%), and TLC (11%) at 3 months.117 This was followed by subsequent improvement to preoperative baseline values at 2 yr postoperatively. Surgery involving an exclusively posterior approach, however, was associated with an improvement in pulmonary function tests by 3 months (although not reaching statistical significance); and an improvement that was statistically significant at 2-yr follow-up: FVC (14% increase from baseline), FEV1 (14%), TLC (5%).

Older studies have reported that if preoperative vital capacity is less than 30–35% of predicted, postoperative ventilation is likely to be required.45 A history of dependence on continuous nasal positive airways pressure at night is also a sign of severe functional impairment and of reduced physiological reserve. These findings should prompt serious consideration as to whether surgery repre-

<table>
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<tr>
<th>Table 2</th>
<th>Suggested preoperative investigations before major spinal surgery</th>
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<tr>
<td><strong>Minimum investigations</strong></td>
<td><strong>Optional investigations</strong></td>
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<tr>
<td><strong>Airway</strong></td>
<td>Cervical spine lateral x-rays with flexion/extension views (for patients with rheumatoid arthritis)</td>
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<tr>
<td><strong>Respiratory system</strong></td>
<td>Plain chest radiograph</td>
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<td>Arterial blood gas analysis</td>
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<td>Spirometry (FEV1, FVC)</td>
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<td>Electrocardiograph</td>
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<td><strong>Cardiovascular system</strong></td>
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<td>Clotting profile</td>
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<td></td>
<td>Urea, electrolytes</td>
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<tr>
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<td>Albumin, calcium (neoplastic disease)</td>
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sents an appropriate balance between its potential benefits and the high risk of long-term postoperative ventilation in such patients.

**Cardiovascular system**
Cardiac compromise may be a direct result of the underlying pathology, for example in patients with muscular dystrophies. Cardiac dysfunction may also occur secondary to scoliosis, which causes distortion of the mediastinum, and cor pulmonale secondary to chronic hypoxaemia and pulmonary hypertension. Assessment of functional cardiovascular impairment is difficult in patients who are wheelchair-bound. Minimum investigations should include an electrocardiograph, and echocardiography to assess left ventricular function and pulmonary arterial pressures (Table 2). Dobutamine stress echocardiography may be used to assess cardiac function in patients with a limited exercise tolerance.

**Thromboembolic prophylaxis**
Patients undergoing spinal surgery may be at increased risk of thromboembolic disease as a result of prolonged surgery, prone positioning, malignancy, and extended periods of postoperative recumbency. The use of compression stockings and/or pneumatic boots is recommended. Many surgeons prefer not to administer anticoagulants because their use may be associated with haemorrhagic complications, including increased blood loss and epidural haematoma.

**Neurological system**
A full neurological assessment of the patient should be made preoperatively. This should be documented for three reasons. First, in patients undergoing cervical spine surgery, the anaesthetist has a responsibility to avoid further neurological deterioration during manoeuvres such as tracheal intubation and patient positioning. Secondly, muscular dystrophies may involve the bulbar muscles, increasing the risk of postoperative aspiration. Thirdly, the level of injury and the time elapsed since the insult are predictors of the physiological derangements of the cardiovascular and respiratory systems which occur perioperatively. If surgery is contemplated within 3 weeks of the injury, spinal shock may still be present. After this time, autonomic dysreflexia may occur.

**Anaesthesia technique**
The type of monitoring chosen to assess spinal cord integrity has a bearing on the anaesthetic technique used.

**Premedication**
The use of bronchodilating agents may be of value in optimizing respiratory function preoperatively. In patients with a high spinal cord lesion, or those in whom fibre-optic intubation is to be undertaken, administration of anticholinergic agents such as atropine or glycopyrrolate (200–400 µg by i.v. or i.m. injection) should be considered. Many patients will have factors which increase the risk of regurgitation and aspiration of gastric contents, such as recent opioid administration, high spinal cord injury, or recent traumatic injury. In these circumstances, it may be prudent to premedicate patients with a histamine-2 receptor antagonist such as ranitidine, or a proton pump inhibitor such as omeprazole, and with sodium citrate. Some patients may have nasogastric tubes *in situ*, which decrease the competence of the upper oesophageal sphincter.

**Induction**
Choice of induction technique, i.v. or inhalation, is guided primarily by the patient’s condition and by consideration of the ease with which the trachea may be intubated.

Preoxygenation is advisable in all patients. Unless there are concerns over the stability of the cervical spine or airway maintenance (see below), i.v. induction is suitable for all but the sickest patients.

The use of succinylcholine in patients with muscular dystrophies has long been known to cause cardiac arrest secondary to hyperkalaemia, and should be avoided. In patients with denervation as a result of spinal cord lesions, the increased number of perijunctional nicotinic acetylcholine receptors on skeletal muscle can cause hyperkalaemia after administration of succinylcholine. The time between denervation and the risk of a potentially fatal hyperkalaemic response is not known in humans. In animal studies, the peak increase in serum K⁺ was 14 days after injury, with a half-peak increase at 8.4 days. Changes in potassium levels began 4 days after injury. It is probably safe to use succinylcholine in the first 48 h after injury to the spinal cord. Thereafter, hyperkalaemia may occur for an indeterminate period, but most authors agree it is safe to use it again 9 months after the injury. The use of bolus doses of i.v. induction agents reduces the amplitude of evoked potential responses, and in particular, cortical responses, but these effects do not prevent useful intraoperative recording of cortical somatosensory potentials and transcranial electrical motor evoked potentials (MEP). Inhalation agents reduce the amplitude of evoked potential responses to a greater degree than do i.v. induction agents, but no studies have compared an inhalation induction technique with an i.v. technique in this respect.

**Intubation**
A decision must be made at preoperative assessment whether to intubate the patient awake or asleep, and whether fibre-optic laryngoscopy will be required. The patient must be counselled fully about the decision at this time (Fig. 2).
Awake or asleep?
Indications for awake intubation include the risk of delayed gastric emptying, the need to assess neurology after intubation is complete (in cases such as an unstable cervical spine), or the presence of a neck stabilization device (such as halo traction), which prevents adequate airway maintenance in an unconscious patient. Otherwise, i.v. induction of anaesthesia followed by a non-depolarizing neuromuscular blocking drug is the technique of choice.

Direct or fibre-optic laryngoscopy?
There is controversy as to whether direct laryngoscopy is a major factor contributing to cord injury in patients with cervical spine instability. Other factors such as hypotension and patient positioning may be equally important. Direct laryngoscopy with manual in-line stabilization or a hard collar, is an accepted means of intubation for many patients provided this can be achieved without any neck movement. Fixed flexion deformities, which involve the upper thoracic and cervical spine may make direct laryngoscopy impossible. These patients require the use of fibre-optic laryngoscopy to facilitate tracheal intubation. The intubating laryngeal mask airway may be a useful alternative, with or without fibre-optic guidance, for anaesthetists familiar with its use.

Awake fibre-optic intubation will be required in patients wearing stabilization devices such as halo vests, which make conventional airway access impossible, and in those where difficulty is anticipated because of anatomical reasons, for example micrognathia, limited mouth opening. In patients with an unstable cervical spine, instillation of local anaesthesia into the airway to facilitate awake intubation may cause vigorous coughing. In such cases, it is preferable to use nebulized lidocaine rather than a cricothyroid injection or administration of local anaesthetic through the fibre-optic scope.

Anterior approaches to the thoracic spine may necessitate the use of a double-lumen endobronchial tube. Alternatively, the surgeon and anaesthetist may agree that a single lumen tracheal tube will suffice, allowing more limited intraoperative lung retraction.

Maintenance
A stable anaesthetic depth is required in order that changes to somatosensory or MEPs can be interpreted reliably. A technique involving nitrous oxide 60% and isoflurane less than 0.5 MAC is compatible with somatosensory evoked potential (SSEP) monitoring, but in nitrous oxide 60%, end-tidal isoflurane concentrations greater than 0.87% make MEP monitoring uninterpretable. An i.v. technique using propofol is therefore recommended. Neurophysiologists monitoring evoked potentials should be made aware of any sudden decrease in arterial pressure, or the need to

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*Fig 2 Algorithm for decision making when intubating a patient for proposed surgery involving the upper thoracic or cervical spine. ILMA, intubating laryngeal mask airway; FO, fibre-optic; RSI, rapid sequence induction; NDNMB, non-depolarizing neuromuscular blocking agent.*

*e.g. presence of: halo vest
severe kyphoscoliosis
anatomical variance: micrognathia, restricted mouth opening*
administer a bolus of opioid or change the anaesthetic depth. Sudden cardiovascular instability during anaesthesia may result from spinal cord and brain stem reflexes, from mediastinal distortion as a result of surgical manipulation, or more commonly from blood loss.

**Induced hypotension**

Hypotensive anaesthesia may be used to improve the surgical field and to reduce blood loss during major spinal surgery. A number of hypotensive agents have been studied during surgery to correct scoliosis. They include ganglion blocking agents, volatile agents, calcium channel antagonists, sodium nitroprusside, nitroglycerin, and, in children, the dopamine-1 receptor agonist, fenoldopam. Mean arterial pressure (MAP) is typically maintained at 60 mm Hg. There is little evidence that any particular agent is superior, but the avoidance of tachycardia is an essential part of a good anaesthetic technique.

Caudal epidural anaesthesia has also been shown to reduce surgical bleeding by 50% in patients undergoing lumbar spinal surgery. This was thought to be as a result of a reduction in sympathetic tone causing a measurable decrease in lumbar vertebral intraosseus pressure. This technique, however, is not as controllable as continuous i.v. titration of a short-acting hypotensive agent, nor suitable for operations involving the thoracic and cervical spine. It may also hinder early postoperative neurological assessment.

**Muscle relaxation**

When myogenic motor evoked responses are to be recorded, neuromuscular block must be carefully monitored and a constant depth of block maintained. It is advisable to administer a non-depolarizing neuromuscular blocking agent such as atracurium using a continuous i.v. infusion device during major spinal surgery.

**Intraoperative monitoring and positioning of the patient**

**Cardiovascular monitoring**

Prolonged anaesthesia in unusual positions, combined with significant blood loss, the haemodynamic effects of thoracic surgery, and where appropriate controlled hypotension, necessitates detailed monitoring of the cardiovascular system. Invasive arterial pressure monitoring is mandatory.

In the prone position, central venous pressure (CVP) may be a misleading indicator of right and left ventricular end-diastolic volume. A study of 12 paediatric patients undergoing surgery for scoliosis in the prone position, compared CVP and transoesophageal echocardiography (TOE) in assessment of ventricular filling. Measurements were made before and after positioning. CVP rose from 8.7 (1.3) mm Hg (mean (SEM)) supine to 17.7 (2.5) mm Hg prone, but left ventricular end diastolic diameter measured by TOE, fell from 37.1 (2.9) to 33.2 (3.0) mm. In three patients in whom pulmonary artery occlusion pressure (PAOP) was also measured, there was an increase in PAOP on being turned from the supine (mean 12.7 mm Hg) to the prone position (mean 28.0 mm Hg), although there were insufficient data for statistical analysis. These results demonstrate that there is no correlation between the measurement of cardiac volume indicators by TOE and CVP or PAOP in such conditions. High CVP values may be misleading indicators of adequate cardiac filling in the prone position. The changes are probably a result of raised intrathoracic pressure causing reduced ventricular compliance and compression of the inferior vena cava. Dependent lower limbs cause a reduced venous return to the heart.

**Respiratory monitoring**

Respiratory system monitoring should always include end-tidal carbon dioxide concentration and peak airway pressure. In major surgery, serial measurements of arterial oxygen tension are recommended. Patients with severe respiratory dysfunction as a result of scoliosis may have an increased alveolar-arterial oxygen gradient, which may be further increased during prolonged anaesthesia because of regional hypoventilation.

**Temperature monitoring**

Thermoregulation may already be impaired in patients who have spinal cord lesions before surgery. Prolonged anaesthesia causes significant heat loss. The use of temperature monitoring, warming of all i.v. fluids, and a warm air mattress device is recommended.

**Positioning**

Patient position for spinal surgery varies depending on the level of the spine to be operated upon and the nature of the proposed surgery. Patients may be repositioned intraoperatively. It is important that venous pressures at the surgical site are kept low to reduce bleeding (reverse Trendelenburg tilt and a free abdomen), and peripheral nerves, bony prominences, and the eyes are protected. It is also important to avoid displacement of unstable fractures during patient positioning. Intraoperative x-ray imaging is frequently required. The relevant spinal level must, therefore, be placed away from the central support of a radiolucent operating table.

**Lumbar surgery**

Anterior approaches require a laparotomy, and general surgical input may be required in difficult cases. Posterior surgery requires a prone patient with a free abdomen to keep epidural venous pressure low (the patient supported on a Wilson frame, for example, or a raised mattress with a hole for the abdomen). For disc surgery, patients are placed in
the knee-chest position with a well padded, secure support behind the upper thigh to support the patient’s weight. This gives a horizontal lumbar spine with vertical intervertebral discs.

**Thoracic surgery**

Anterior approaches to the thoracic spine are via a thoracotomy with the patient supported in a lateral position. If a double lumen endobronchial tube is used to allow deflation of one lung for surgical access, a fibre-optic laryngoscope should always be used to check tube placement after the patient is finally positioned. Posterior approaches to the thoracic spine require a prone patient with an uncompressed abdomen.

**Cervical surgery**

Patients are usually positioned with their feet close to the anaesthetic machine. This allows surgical access to the head and neck. Extensions are needed to breathing circuits and i.v. lines, and it may be useful to place an i.v. cannula in the patient’s foot. Tracheal tubes must be carefully secured without impinging on the surgical field.

For anterior surgery, a reinforced tracheal tube will reduce the risk of airway obstruction as tracheal retraction occurs during surgery. The head is supported on a padded head ring, or the ‘horseshoe’ of a Mayfield neurosurgical operating table attachment. Traction may be required by tongs and weights placed into the outer bone plate of the skull for some or all of the procedure. Reverse Trendelenburg positioning minimizes venous bleeding and provides counter traction for the weight attached to the head. Venous pooling in the lower limbs and intraoperative retraction of the carotid artery make an arterial line advisable for most patients.

For posterior approaches to the cervical spine, the head of the prone patient can be supported on the gel-padded horseshoe of the Mayfield table attachment, or placed in a skull clamp. The orbits, the superior orbital nerve and the skin over the maxilla are at particular risk of ischaemic injury if positioning is incorrect. These problems are avoided by using a skull clamp. The head height and degree of neck flexion may be adjusted intraoperatively, and pressure areas must be rechecked after such manoeuvres. Support for the tracheal tube and breathing circuitry is difficult; care must be taken if equipment has been taped to the operating table, that tubes are not dislodged as the head position is altered.

Venous air embolism is a risk for these patients because veins at the operative site are above the level of the heart. Unfortunately, methods to reduce blood loss such as reduced venous pressure increase the risk of this complication.

**Blood conservation**

Blood loss during single level procedures, especially for intervertebral disc-related disease, should not be excessive, but during more extensive spinal surgery, it can be considerable; typically losses are 10–30 ml kg⁻¹, a result of loss from decorticated bone and disruption of rich vascular networks. The degree of blood loss is associated with: the number of spinal levels fused; body weight; surgery for tumours; raised intra-abdominal pressure in the prone position, and the presence of DMD.

Blood loss is associated with increased operative time, delayed wound healing, wound infections, and increased requirement for blood transfusion. The risks of allogeneic blood transfusion include: hypothermia, impairment of coagulation, hyperkalaemia, hypocalcaemia, transfusion reactions, acute lung injury, immunomodulation, and viral and bacterial infection. Allogeneic blood transfusion should therefore be reduced to a minimum. This can be accomplished by techniques to reduce blood loss and by autologous blood transfusion.

**Reducing blood loss**

Blood loss can be minimized by careful patient positioning, good surgical technique, controlled hypotensive anaesthesia, and by the use of agents such as antifibrinolytics. When patients are placed in the prone or knee-chest positions, care must be taken to minimize intra-abdominal pressure. It has been shown that positioning devices, such as the Relton-Hall frame, which allow the abdominal viscera to hang freely, reduce inferior vena caval (IVC) pressure by one-third compared with conventional pads. Raised IVC pressure is associated with lumbar venous engorgement and increased blood loss. One study has shown minor changes to patient positioning on the Wilson frame can reduce blood loss per vertebral level by approximately 50%.

**Hypotensive anaesthesia**

Hypotensive anaesthesia has long been established as a safe and effective method for reducing blood loss by up to 58% during spinal surgery. Antifibrinolytic agents

Drugs such as the synthetic lysine analogues, tranexamic acid, and aminocaproic acid, and the protease inhibitor, aprotinin, have been used to reduce blood loss during spinal surgery. Only aprotinin, however, has been shown to cause a statistically significant reduction in intraoperative blood loss. Aprotinin is a polypeptide derived from bovine lung, which is an inhibitor of plasmin and kallikrein, forming a reversible complex with the serine binding site on the enzyme. It also preserves platelet function.

Urban and colleagues compared the use of aprotinin, aminocaproic acid, or neither in 60 adult patients undergoing anterior-posterior thoracolumbar fusion under hypotensive anaesthesia using sodium nitroprusside and esmolol. Aprotinin (1 million KIU load over 30 min followed by 0.25 million KIU h⁻¹) and aminocaproic acid (5 g load over...
30 min followed by 15 mg kg⁻¹ h⁻¹) were both shown to reduce blood loss when compared with control subjects, but this reduction only reached statistical significance in the aprotinin group (mean intraoperative loss in control group 3556 ml, in aminocaproic acid group 2929 ml, and in aprotinin group 2685 ml). Desmopressin has been shown to reduce bleeding times in patients with platelet disorders. In spinal surgery, it may have a tendency to reduce blood loss but this was not found to reach statistical significance.¹⁶

In major spinal surgery, it is the authors’ practice to ensure good patient positioning, use a controlled hypotensive anaesthesia technique, and to use an infusion of aprotinin.

**Provision of autologous blood**

Autologous blood can be made available to the patient by three methods; pre-deposit autologous transfusion, intraoperative acute normovolaemic haemodilution, and intraoperative red blood cell salvage.¹¹⁵

**Pre-deposit autologous transfusion**

The patient donates blood 3–5 weeks before surgery for use intraoperatively. This technique has been used widely in orthopaedic, general, and cardiothoracic surgery. It has been shown to reduce the requirement for allogeneic blood by up to 75% in lumbar fusion surgery.¹³ Disadvantages of this method include repeated visits for preoperative phlebotomy, wastage of unused blood, high cost, and possible risks of incompatibility because of clerical errors. Furthermore, difficulties arise in using the technique in children less than 30 kg and in adults with pre-existing anaemia or cardiovascular disease. Recombinant erythropoietin has been used before major surgery to raise preoperative haemoglobin levels in patients, such as Jehovah’s Witnesses, who object for ethical reasons to the use of blood products.¹⁰² It reduces allogeneic blood requirements in children undergoing scoliosis surgery,¹¹⁸ and it may also be used to facilitate autologous collection of blood, and intraoperative normovolaemic haemodilution.

**Intraoperative normovolaemic haemodilution**

This is performed immediately before surgery. Up to 1 litre of whole blood is removed, and stored in bags with anticoagulant according to the formula:

\[
\text{Volume to be removed} = \text{EBV} \times (\text{initial Hct} - \text{target Hct}) / \text{mean Hct}
\]

where \(\text{EBV}\) = estimated blood volume; \(\text{Hct}\) = haematocrit; mean \(\text{Hct}\) = arithmetic mean of initial \(\text{Hct}\) and the target \(\text{Hct}\).

The removed blood is replaced by i.v. infusion of colloid or crystalloid to achieve normovolaemia with a reduced haematocrit. During surgery, less red cell mass is lost for a given volume of blood. The donated whole blood may be re-transfused once haemostasis is achieved, or a critical value of haemoglobin reached. The technique has been shown to reduce homologous blood requirements in spinal surgery.³⁵ ⁴²

**Intraoperative cell salvage**

Blood lost during surgery is collected using commercially available equipment and is then anticoagulated, filtered for clots and debris, centrifuged, and resuspended in saline before re-infusion to the patient. Many litres of blood can be salvaged. It is the authors’ practice to use cell-salvaged blood where blood loss is anticipated to be greater than 15 ml kg⁻¹. Disadvantages are that re-infused red cells may contain residual anticoagulant, and also that coagulation factors and platelets are consumed at the wound site. Clotting factors may therefore need to be replaced using donor fresh frozen plasma. Only approximately half of the blood lost during surgery can be salvaged, and the technique is unsuitable if the operative field contains malignant cells or infection, as these may be disseminated through the body. The use of intraoperative cell salvage has been recommended by a consensus conference,³ concluding that despite the initial capital investment in equipment and disposables, ‘... it appears to be relatively inexpensive and may be cost saving...’. Nevertheless, a recent survey of UK surgeons found that logistical considerations were the main obstacles to using autologous blood transfusion, and that more surgeons were keen to use it than were actually doing so.¹⁰⁹

**Spinal cord monitoring**

During surgery, when corrective forces are applied to the spine, while the spinal canal is surgically invaded, or when an osteotomy is to be undertaken, the spinal cord is at risk of injury. The incidence of motor deficit or paraplegia after surgery to correct scoliosis in the absence of spinal cord monitoring techniques has been quoted as between 3.7 and 6.9%.²¹ ⁷⁰ This figure may be reduced by intraoperative monitoring (IOM) to 0.5%.⁷⁸ The American Academy of Neurology has published guidelines on IOM concluding ‘considerable evidence favours the use of monitoring as a safe and efficacious tool in clinical situations where there is a significant nervous system risk, provided its limitations are appreciated’.⁶ It is now considered mandatory to monitor spinal cord function for these types of procedures.

IOM ideally detects perturbations in spinal cord function early in order that the surgeon can take appropriate steps to correct them before irreversible damage occurs. The time, however, between a change in the electrophysiological recordings from the cord after over-distraction, and the onset of irreversible ischaemic damage is in the order of only 5–6 min in animal studies.⁸⁰

A motor deficit is functionally more devastating to the patient than a sensory deficit. This is important to consider when evaluating the relative merits of each method of monitoring, some of which assess motor tracts, and some the sensory tracts of the cord (Fig. 3).
A knowledge of the methods of intraoperative spinal cord monitoring is important to the anaesthetist, as the anaesthetic technique can have profound effects on the ability to monitor spinal cord function accurately. There are four main methods of IOM: the ankle clonus test, the Stagnara wake-up test, SSEP, and MEP. These will be considered briefly, as there have been recent reviews on this subject.32 82

Ankle clonus test

Historically, this was the first test to be used. Clonus is repeated rhythmic movement elicited by the stretch reflex. The clonus test is usually performed during emergence, either at the end of surgery or during a wake-up test. All muscle paralysis must be antagonized. There is only a brief period between anaesthesia and wakefulness when it is possible to elicit clonus. The foot is sharply dorsiflexed at the ankle joint. Spinal cord injury is indicated by complete absence of repeated movements at the ankle joint.

In the neurologically intact, awake individual, higher cortical centres have a descending inhibitory influence on the reflex, and clonus is not observed after ankle stretch. In healthy individuals during anaesthesia, cortical centres are inhibited and there is a loss of descending inhibition via the spinal cord pathways on the ankle joint reflex. Clonus may, therefore, be elicited on ankle stretch, especially during emergence from anaesthesia. If the spinal cord is injured, however, the cord undergoes a period of spinal shock, and there is a loss of reflex activity accompanied by flaccid paralysis. During emergence from anaesthesia in these individuals, the ankle clonus reflex will not be present.

The test is easy to administer. Proponents of its use point to a high level of sensitivity (100%) and specificity (99.7%).40 However, the test can only be performed intermittently, and the absence of clonus could be a result of not only spinal cord damage, but also to an inadequate or too great a depth of anaesthesia. Furthermore, the presence of clonus does not exclude spinal cord damage; other parts of the spinal cord may be damaged leaving the ankle stretch reflex intact.

Stagnara wake-up test

This was first described in 1973.116 Preoperatively, the need for the test is explained; it will involve the patient making a specified motor response, usually in the lower limbs, to verbal command part way through the surgery. The test evaluates the gross functional integrity of the motor pathways (lower and upper motor neurons and muscles) involved in performance of this motor task (Fig. 3). The test does not assess the integrity of any part of the peripheral sensory system.

The surgeon must give the anaesthetist adequate warning of the need to perform a wake-up test as neuromuscular block must be antagonized and the plane of anaesthesia lightened. As the patient becomes more conscious, they are instructed first to perform an action involving muscle groups above the level of any potential cord damage, usually involving the upper limbs (for example, to grip the anaesthetist’s fingers). When a positive response is obtained, the patient is then instructed to move their legs,

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Fig 3 Diagrammatic representation of motor and sensory pathways of the spinal cord. The lateral and anterior corticospinal tracts subserve voluntary movement. The upper motor neurone axon, with its cell body in the primary motor cortex, descends via the internal capsule to the medulla oblongata. Most motor fibres (85%) cross the midline at the pyramidal decussation to descend the contralateral spinal cord as the lateral corticospinal tract. The remainder (15%) do not cross the midline and descend the ipsilateral spinal cord as the anterior spinal tract. The corticospinal tracts must be functionally intact in order for MEP to be recorded, and the Stagnara wake-up test to be performed. The dorsomedial sensory tracts subserve discriminatory touch, proprioception, and vibration senses. The primary sensory neurone, with its cell body in the dorsal root ganglion of the spinal cord, sends fibres in the dorsal aspect of the ipsilateral spinal cord to the medulla oblongata where they synapse. The second order sensory neurone projects fibres to the thalamus after crossing the midline. After synapsing with the tertiary sensory neurone in the thalamus, fibres are projected to the primary somatosensory cortex. This pathway must be functionally intact in order for SSEPs to be recorded.
and the response to this command noted. If the patient can move their legs, anaesthesia is deepened and surgery recommenced. If the patient is unable to move their legs, corrective measures are instituted immediately.

A wake-up test should be as easy and as rapid to institute as possible. This necessitates an anaesthetic technique that is reliable, but which may be quickly antagonized as many times as the surgeon requires. Wakening should also be smooth to minimize the risk of tracheal extubation. Furthermore, the patient should not experience any pain during the test and have no subsequent recall of intraoperative events.

A number of different anaesthetic techniques for the Stagnara wake-up test have been advocated, including volatile-based anaesthesia. A Danish group,\textsuperscript{58} in a randomized trial involving 40 patients, described the successful use of a midazolam-based anaesthetic, antagonized by \textsuperscript{11}umazenil at the time of the wake-up test, compared with a propofol infusion technique. The midazolam/\textsuperscript{11}umazenil group was found to have a shorter intraoperative arousal. Five patients in the midazolam group, however, became resedated in the recovery room and required further doses of \textsuperscript{11}umazenil. Remifentanil is a potent \textsubscript{11}μ-receptor agonist. Its ester linkage renders it susceptible to hydrolysis by tissue esterases, producing a half-life at its site of action of less than 10 min. It therefore has a pharmacokinetic profile suitable for use when a wake-up test must be performed. Preliminary reports using remifentanil suggest a delay between the surgeon’s request for a wake-up test and adequate conditions for neurological assessment of only 5 min.\textsuperscript{94}

Despite the use of such techniques, the test has a number of disadvantages. First, it requires the patient’s cooperation. Second, it poses risks to the patient of moving on or falling from the operating table and of tracheal extubation, often in the prone position. Thirdly, it requires inconsiderable operator skill on the part of the anaesthetist. Fourthly, it is a valid measure of motor function at only one moment in time the test is instituted; it does not allow continuous IOM of motor pathways. The onset of a change in electrophysiological recordings and permanent neurological injury can occur more than 20 min after the last corrective force is applied to the spine.\textsuperscript{80} It is, therefore, conceivable that a wake-up test could be normal after the last corrective manoeuvre has been applied but before the onset of the resultant neurological deficit.

The place of the Stagnara wake-up test in spinal cord monitoring during spinal surgery should therefore be confined to situations in which electrophysiological monitoring techniques are not available, fail, or produce equivocal results.

**Somatosensory evoked potentials**

SSEPs are elicited by stimulating electrically a mixed peripheral nerve (usually the posterior tibial, peroneal, or sural nerves), and recording the response from electrodes at distant sites cephalad to the level at which surgery is performed (Fig. 4). Guidelines on stimulation and recording methods have been published.\textsuperscript{48 1} Typically, the stimulus is applied to the peripheral nerve on the left and the right limb alternately as a square wave for 0.1–0.3 ms, at a rate of 3–7 Hz. The intensity of the stimulus varies depending upon the electrodes and quality of skin contact, but is in the 25–40 mA range. Recording electrodes are placed in the cervical region over the spinous processes or over the somatosensory cortex on the scalp, or are sited during surgery in the epidural space. Baseline data are obtained after skin incision. This allows a stable plane of anaesthesia to be established during baseline recordings as anaesthetic agents affect SSEPs. During surgery, responses are recorded repeatedly. The functional integrity of the somatosensory pathways is determined by comparing the amplitude change and the latency change of the responses obtained during surgery to baseline values. A reduction in the amplitude of the response by 50% and an increase in the latency by 10% are considered by most workers as significant.\textsuperscript{17 78} The amplitude response is considered the primary criterion.\textsuperscript{80}

The pathways involved in the recorded responses include a peripheral nerve, the dorsomedial tracts of the spinal cord and, depending on the electrode placement, the cerebral cortex (Fig. 3). The physiological role of these tracts is to

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*Raw et al.*
subserve sensations of proprioception and light touch. It must be emphasized that responses are not obtained from motor tracts, or from the anteriolateral sensory tracts of the spinal cord (subserving pain and temperature sensation). This has two important ramifications for the validity of SSEPs. First, because of the close proximity of the dorsomedial sensory tracts with the motor tracts in the cord, it is assumed that when using SSEPs, any damage to the motor tracts will be signalled by a change in SSEPs. This, however, cannot be guaranteed. Secondly, the blood supply of the corticospinal motor tracts differs from that of the dorsomedial tracts (Fig. 5). Hypoperfusion in the territory of the anterior spinal artery may cause ischaemia in the anteriolateral tracts, but not affect the dorsomedial tracts. It is, therefore, possible to have normal recordings from SSEPs throughout surgery, but to have a paraplegic patient postoperatively. Furthermore, in patients with pre-existing neurological disorders, reliable data can be recorded in only 75–85% of patients.

### Effects of anaesthetic agents on SSEPs

Anaesthetic agents can have a significant impact upon SSEPs. Inhalation anaesthetic agents and nitrous oxide cause a dose-dependent reduction in SSEP amplitude and an increase in latency. Nitrous oxide 60% with isoflurane 0.5 MAC or enflurane 0.5 MAC is compatible with effective SSEP monitoring. A recent retrospective study of 442 cases found that 13/60 ‘false-positives’ (abnormal SSEPs with no neurological deficit postoperatively) were attributable to an increased concentration of inhalation agent. I.V. anaesthetic agents also cause changes to SSEPs but to a lesser degree than inhalation agents. The cortical response appears to be most susceptible to anaesthetic agents; subcortical, spinal, and peripheral responses are less affected. A recent study of the use of propofol or midazolam as a continuous i.v. infusion combined with sufentanil was associated with maintenance of the amplitude of the cortical SSEP from baseline values to the end of surgery (propofol from 1.8 (0.6) to 2.2 (0.3) μV; midazolam from 1.7 (0.5) to 1.6 (0.5) μV). However, propofol and nitrous oxide used in combination caused a significant reduction in the amplitude of cortical SSEPs (from 2.0 (0.3) to 0.6 (0.1) μV). The latencies of the responses were not increased in any of the three groups of patients, but recovery was significantly delayed in the midazolam group. The authors recommended a propofol technique for surgery during which cortical SSEPs are to be recorded.

Opioids such as remifentanil and fentanyl administered via the i.v. route cause a small reduction in the amplitude and increase in the latencies of SSEPs. Intrathecal opioids have little effect on SSEPs. Neuromuscular blocking agents, as may be expected, cause no change in SSEPs.
Effect of controlled hypotension on SSEP

MAP during spinal surgery is usually maintained at lower than pre-induction values in order to minimize blood loss. Typically, controlled normovolaemic hypotension to a MAP of 60 mm Hg is used. MAP should not be allowed to decrease to less than 60 mm Hg as, at this point, SSEPs are lost and neurological ischaemic injury can occur. Maintaining MAP greater than 60 mm Hg is, however, no guarantee of safety. SSEPs demonstrate that the feline spinal cord is more vulnerable to distractive injury during pharmacologically induced hypotensive anaesthesia than during normotensive anaesthesia. Earlier animal work has shown that peripheral nerves, which do not have an autoregulated blood flow, are more sensitive to the effects of hypotension than the spinal cord. SSEPs may, therefore, be reduced by even moderate hypotension. Papastefanou, in a retrospective series of 442 cases, found 17/60 ‘false-positive’ SSEP changes attributable to hypotension. Changes in SSEPs, whether a result of hypotension, or mechanical distractive forces, or a combination of both, must not be ignored.

Other factors

A decrease in core body temperature in animals causes a reduction in the amplitude of SSEPs by approximately 7% and an increase in latency of 3% for each 1°C reduction. There does, however, appear to be a protective effect of hypothermia on spinal cord function.

It is clear from a large multicentre study that the experience of monitoring teams in spinal surgery has a significant effect on outcome. Teams with experience of less than 100 cases had more than twice the postoperative neurological complication rate of teams with greater experience.

Effectiveness of SSEP monitoring

In a large retrospective multicentre study of over 51 000 procedures, SSEP monitoring was found to have a sensitivity of 92% and specificity of 98.9%. The false negative rate was 0.127% (normal SSEPs throughout the case but a neurological deficit postoperatively), or 1 in 787 procedures. The false positive rate was 1.51% (SSEP had changed, but no new neurological deficit postoperatively), or one in 67 procedures. Other studies have found a higher false positive rate (14.7%), and that SSEP monitoring has a lower specificity, 85.33%, but a sensitivity of 100%, probably explained by the smaller number of cases.

SSEP monitoring is currently the mainstay of spinal cord monitoring techniques. It is, overall, a reliable technique with a high sensitivity and specificity for early detection of intraoperative neurological compromise, and has a proven record over the last decade.

Motor-evoked potentials

As a result of the inherent problems using SSEPs as a monitoring tool during spinal surgery, and reports of postoperative paralysis despite apparently normal intraoperative SSEPs, efforts have been made to monitor motor tracts of the spinal cord (Fig. 3) as a more sensitive indicator of motor function.

MEP monitoring was first used clinically over 10 yr ago. Monitoring techniques are subdivided according to: the site of stimulation (motor cortex, spinal cord); the method of stimulation (electrical potential, magnetic field); and the site of recording (spinal cord, peripheral mixed nerve, muscle). Each variation of the technique has advantages and disadvantages. The principle is the same; stimulation by whatever means cranial to the site of surgery causes prodromic stimulation of motor tracts in the spinal cord, and of peripheral nerve and muscle caudal to the site of surgery. Perturbation of motor pathway function by surgery leads to a reduction in amplitude and an increase in latency of the recorded responses.

The motor cortex can be stimulated by electrical, or magnetic means. Magnetic equipment is bulky and cumbersome but is not affected by the quality of electrode contact. Recorded responses are classified as myogenic or neurogenic. Myogenic responses result from the summed EMG activity in a muscle, such as tibialis anterior, in response to stimulation (Fig. 4). Neurogenic recordings arise from the summed electrical activity in a peripheral nerve or the spinal cord. The advantage of recording EMG responses is their large amplitude. The main disadvantage is their variable morphology. When recording EMG responses, the depth of muscle relaxation is of critical importance: if it is too deep, responses are unobtainable; if only residual block is present, there is a risk of injury to the patient, if violent movements occur in response to stimulation. Neuromuscular blocking agents should be administered by continuous infusion, and the depth of neuromuscular block monitored. The first twitch of the train-of-four response should be maintained at 10–20% of control. Neurogenic responses, however, can be recorded under complete neuromuscular block to avoid patient injury, and are more reliable in terms of amplitude, latency, and morphology.

Effects of anaesthetic agents on MEPs

Cortical evoked responses are more prone to the effects of anaesthetic agents than spinal-evoked responses. Propofol is a powerful suppressant of cortical evoked responses, causing a dose-dependent reduction in the amplitude of the response. A bolus dose of propofol 2 mg kg⁻¹ abolishes cortical MEPs. Volatile agents are also powerful suppressants of cortical evoked MEPs; MEPs are abolished or are too inconsistent to interpret at end-tidal isoflurane concentrations of 0.87 (0.08)%. Midazolam and etomidate cause a significant but smaller reduction in the amplitude of the response. Opioids such as fentanyl have been variously reported as reducing the amplitude of the response, or causing no effect. Multiple pulse transcranial electrical stimulation...
stimulation techniques can improve the reliability of MEP recording further.

These findings have led to the need for significant modifications to the anaesthetic technique when cortical-evoked MEPs are measured. In the past, ketamine-based techniques have been used, but not without complications such as unpleasant hallucinations. An i.v. propofol infusion with fentanyl or remifentanil has been advocated and provides for adequate MEP recording in 97% of neurologically intact patients, when used with a multiple pulse stimulation technique.

Effectiveness of MEP monitoring

MEP monitoring is less reliable in patients with a pre-existing neurological deficit. Furthermore, early hopes of greater sensitivity of MEPs over other monitoring techniques may have been premature. There are recent reports of preserved neurogenic MEPs associated with postoperative motor deficit, which suggest the sensitivity of MEPs is less than 100%.

SSEP monitoring has become an accepted standard of care during spinal surgery. It is less affected by the technical difficulties associated with MEP monitoring. MEP monitoring is, however, becoming more widely used and the two methods should be regarded as complementary, with the use of a wake-up test reserved for situations where neurological monitoring is not possible or responses are significantly perturbed during surgery.

Postoperative care

Patients undergoing spinal surgery frequently have significant co-morbidity. Surgery imposes the further stresses of significant blood loss, prolonged anaesthesia, and difficulties in acute postoperative pain management. Surgeons prefer patients to be conscious and able to respond to command immediately after anaesthesia, for early neurological assessment. It is also important that patients are able to expectorate, and to comply with physiotherapy as early as possible in the postoperative period.

Indications for postoperative ventilation

The decision to provide a period of postoperative artificial ventilation should have been made before surgery commences, and explained to the patient. The need for postoperative ventilation is suggested by patient and surgical factors. Patient factors include the presence of a pre-existing neuromuscular disorder, severe restrictive pulmonary dysfunction with a preoperative vital capacity of less than 35% of predicted, a congenital cardiac abnormality, right ventricular failure, and obesity. Surgical factors include a prolonged procedure, surgical invasion of the thoracic cavity, and blood loss greater than 30 ml kg⁻¹. Frequently, it is necessary only to provide artificial ventilation for a few hours in the postoperative care unit, until hypothermia and metabolic derangements have been corrected. Chest drains, if present, should be checked regularly to ensure patency; obstruction may lead to a pneumo- or haemothorax.

Postoperative analgesia

Pain management can be a considerable challenge. Patients undergoing spinal surgery, particularly through a thoracic approach, may have a large incision extending over several dermatomes. Many patients have pre-existing chronic pain conditions, may be cognitively impaired (some neuromuscular disorders), or be very young (children). A multimodal approach to analgesia is recommended, using a combination of simple primary analgesics, opioids, and regional anaesthesia techniques where appropriate. For initial postoperative analgesia, it is useful to restart, if possible, all the analgesics the patient was receiving preoperatively. Undoubtedly, the patient’s requirements will be increased postoperatively and additional therapy will be required.

Parenteral opioids

The use of parenteral opioids has been the mainstay of analgesia for all patients undergoing spinal surgery. Opioids can be administered via i.m., i.v. (continuous infusion and patient-controlled analgesia devices with or without background infusions), intrapleural, epidural, and intrathecal routes. Their use, via the i.v. route in particular, is associated with side-effects such as respiratory depression, nausea and vomiting, sedation, and gastrointestinal ileus. The latter may be especially disadvantageous after major spinal surgery, when some degree of paralytic ileus is common.

Patients with cancer may not be naïve to opioid drugs and such individuals must be assumed to have acquired a degree of opioid tolerance. For patients who have received long-term opioids preoperatively by other routes (e.g. enteral, transdermal), these should also be restarted as early as possible postoperatively, and gradually reduced over subsequent days or weeks.

Non-steroidal anti-inflammatory drugs

Simple analgesics alone afford inadequate analgesia even for relatively minor spinal surgery. Non-steroidal anti-inflammatory drugs (NSAIDs), both non-selective cyclooxygenase inhibitors, and selective cyclo-oxygenase 2 (COX 2) inhibitors, have however been used successfully after spinal surgery. But the use of a non-selective cyclo-oxygenase inhibitor NSAID cannot be recommended for intraoperative or early postoperative analgesia in such cases. Guidelines on the use of NSAIDs published by The Royal College of Anaesthetists do not specify their role for this purpose. The use of NSAIDs may increase bleeding time by 30–35%, cause gastritis, and be associated with acute renal failure, particularly in the presence of hypovolaemia and hypotension. The safety profile of selective COX 2 inhibitors in major spinal surgery is yet to be fully evaluated. If, however, patients have been taking NSAIDs to
help relieve their pain without complication preoperatively, it is useful to restart this medication in the immediate postoperative period for its opioid-sparing effects.

**Epidural analgesia**
The use of local anaesthetic agents, alone or in combination with opioids, by the epidural route after spinal surgery has been described, the epidural catheter being placed intraoperatively by the surgeon. Two recent studies compared epidural analgesia with parenteral morphine administered via patient controlled analgesia (PCA) devices after major spinal surgery. The retrospective study found time to full diet and hospital stay to be reduced in the epidural group, but the randomized study was unable to find any significant differences in pain scores, side-effects, or resumption of oral intake between the epidural and PCA groups.

Epidural anaesthesia with local anaesthetic agents can make neurological assessment difficult. Concerns over the rare but serious risks of epidural haematoma and infection associated with indwelling catheters have hindered its widespread use. The incidence of local superficial infection after routine epidural catheter placement has been quoted to be as high as 12%. However, the incidence of epidural abscess related to epidural catheter placement, although difficult to determine precisely, is rare. A recent review of the literature produced 42 case reports of epidural abscesses from 1974 to 1996, only 13 of which were sited for perioperative analgesia. The authors of this study identified in their own institution two catheter-related epidural abscesses in 13 000 epidural blocks (both of which were in obstetric patients). A higher incidence of epidural catheter-related abscesses may be anticipated for catheters inserted via a surgical wound.

The incidence of spinal haematoma in patients receiving spinal or epidural analgesia and low-molecular weight heparin is estimated to be between 1:1 000 and 1:10 000. The clinical signs of epidural haematoma or abscess may be masked by postoperative pain, and pre-existing abnormal neurology. The infrequency of these complications further increases the risk of failing to detect them.

**Intrathecal analgesia**
The thecal sac is readily accessible during spinal surgical procedures, and intrathecal medication can be injected with technical ease before wound closure. Early reports of the use of intrathecal opioids for analgesia in children after spinal surgery, and other major surgeries, suggested that the use of morphine (20–30 μg kg⁻¹) was associated with excellent analgesia for up to 24 h, but was complicated by respiratory depression in 16% of patients. More recent studies suggest the optimum dose of morphine to be 2–5 μg kg⁻¹, which provides comparable analgesia for 24 h but with fewer side-effects such as respiratory depression, nausea, and pruritus. Doses of this order, in a large retrospective study of 5969 patients, produced respiratory depression in 3% of patients. There were no cases of neurological injury or spinal haematoma.

Significant pain can be expected for up to 4 days postoperatively after major spinal surgery. Intrathecal opioids alone, therefore, will probably be insufficient over this period. Parenteral opioids made available in the immediate postoperative period (as patient-controlled analgesia regimen, for example), in patients who have received intrathecal opioids, provide for a smooth transition from predominate intrathecal opioid-based analgesia to parenteral opioid-based analgesia. The use of such a regimen is advisable in the setting of a postoperative critical care facility; animal data suggest systemic and intrathecal opioids may act synergistically.

**Other techniques**
Intrapleural infusions of local anaesthetic and/or opioids may be considered after a thoracotomy. Intrapleural infusions of local anaesthetic agents have been reported to reduce systemic opioid requirements in such circumstances. A number of studies, however, have found intrathecal analgesia with local anaesthetic agents to offer inferior analgesia to epidural opioids, and there remains concern over the blood levels of local anaesthetic agents achieved, and the risk of local anaesthetic toxicity.

**Late complications**
A retrospective study of 1223 anterior thoracic and lumbar spinal procedures found a respiratory complication rate of 7% (adult respiratory distress syndrome, pneumonitis, atelectasis, infection), pulmonary embolism 0.8%, cerebral vascular accident 0.25%, and death 0.33% (four patients: one died of ARDS on day 31, one myocardial infarction on day 1, and two died of fatal pulmonary emboli on days 3 and 8).

Screening studies for thromboembolic complications after spinal surgery have quoted varied incidences between 0.395 and 15.5%. One partially randomized study found an incidence of 0.3% when Doppler ultrasonography was used postoperatively to detect venous thrombosis in patients treated with either mechanical (compression stockings and pneumatic boots), or pharmacological (warfarin) methods of prophylaxis. If, however, no methods of thromboprophylaxis are used and venography is the screening method, incidences of venous thrombosis of 15.5% have been quoted. In one prospective study, symptomatic pulmonary emboli occurred in 2.2% of all spinal fusions, and these were more common after combined anterior/posterior approach procedures (6%), than posterior approach procedures alone (0.5%).

There has been a paucity of well-conducted randomized controlled trials comparing methods of thromboprophylaxis. Few would argue against the use of compression stockings and pneumatic boots, the use of which is relatively free of complications. However, the use of pharmacological...
methods of thromboprophylaxis (using heparin, for example) is contentious. Their use may be associated with haemorrhagic complications such as increased intraoperative and postoperative blood loss, and epidural haematoma. Further studies are required to adequately ascertain the most appropriate methods of prophylaxis against thromboembolism.

Treatment of thromboembolism produces the risk of major heparin-related complications (44%) such as epidural haematoma, gastrointestinal bleeding, and wound infection. Insertion of an IVC filter may be appropriate in these circumstances.

Conclusions
Spinal surgery presents a number of challenges to the anaesthetist. Patients are now undergoing major spinal surgery for conditions such as malignancy, scoliosis, and trauma, which would not have been contemplated 20 yr ago. Despite this, postoperative neurological morbidity has been reduced by advances in spinal cord monitoring techniques. The anaesthetist has an important role to play in facilitating the use of these new techniques. They must also manage the relief of postoperative pain in these patients, who have frequently been receiving several analgesics preoperatively.

References
30 Goodarzi M, Shier N-H, Grogan DP. Effect of intrathecal opioids
32 Guerit JM. Neuromonitoring in the operating room: why, when, and how to monitor? Electroenceph Clin Neurophysiol 1998; 106: 1–21
42 Hur SR, Huizenga BA, Major M. Acute normovolemic hemodilution combined with hypotensive anesthesia and other techniques to avoid homologous transfusion in spinal fusion surgery. Spine 1992; 17: 867–73
48 Kafer ER. Respiratory and cardiovascular functions in scoliosis and the principles of anesthetic management. Anesthesiology 1980; 52: 339–51
69 McPherson RW, Sell B, Traystman RJ. Effects of thiopental, fentanyl, and etomidate on upper extremity somatosensory evoked potentials in humans. Anesthesiology 1986; 65: 584–9


Owen JH, Naito M, Bridwell KH, Oakley DM. Relationship between duration of spinal cord ischaemia and postoperative neurologic deficits in animals. Spine 1990; 15: 846–51


Owen JH. The application of intraoperative monitoring during surgery for spinal deformity. Spine 1999; 24: 2649–62


Peterson DO, Drummond DC, Todd MM. Effects of halothane, enflurane, isoﬂurane and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 1986; 65: 35–40


Reid JM, Appleton PJ. A case of ventricular fibrillation in the prone position during back stabilisation surgery in a boy with Duchenne’s muscular dystrophy. Anaesthesia 1999; 54: 364–7


United Kingdom Department Of Health: http://www.doh.gov.uk/hes/free_data/index.html


Ischaemic/hypoxic insults to the brain during surgery and anaesthesia can result in long-term disability or death. Advances in resuscitation science encourage progress in clinical management of these problems. However, current practice remains largely founded on extrapolation from animal studies and limited clinical investigation. A major step was made with demonstration that rapid induction of mild sustained hypothermia in comatose survivors of out-of-hospital ventricular fibrillation cardiac arrest reduces death and neurological morbidity with negligible adverse events. This provides the first irrefutable evidence that outcome can be favourably altered in humans with widely applicable neuroprotection protocols. How far hypothermic protection can be extended to global ischaemia of other aetiologies remains to be determined. All available evidence suggests an adverse response to hyperthermia in ischaemic or post-ischaemic brain. Management of other physiological values can have dramatic effects in experimental injury models and this is largely supported by available clinical data. Hyperoxaemia may be beneficial in transient focal ischaemia but deleterious in global ischaemia. Hyperglycaemia causes exacerbation of most forms of cerebral ischaemia and this can be abated by restoration of normoglycaemia. Studies indicate little, if any, role for hyperventilation. There is little evidence in humans that pharmacological intervention is advantageous. Anaesthetics consistently and meaningfully improve outcome from experimental cerebral ischaemia, but only if present during the ischaemic insult. Emerging experimental data portend clinical breakthroughs in neuroprotection. In the interim, organized large-scale clinical trials could serve to better define limitations and efficacy of already available methods of intervention, aimed primarily at regulation of physiological homeostasis.
Clinical available therapies (e.g. mild hypothermia) or instead as promising candidates for future clinical use targeting events, such as oxidative stress, apoptosis, and neurogenesis.

The above logic is presented as a taste of where we are going with investigations aimed at ameliorating long-term improvement from an ischaemic/hypoxic insult that may occur in the perioperative period. However, the rest of this article will focus on the opportunities and limitations of currently available interventions (Table 1).

### Anaesthetics

#### Barbiturates

It has been postulated for more than 50 yr that anaesthetics increase the tolerance of brain to an ischaemic insult. The logic is simple. Most drugs selected to be anaesthetics suppress neurotransmission. This suppression reduces energy requirement, and reduction in energy requirement should allow tissue better to preserve energy balance during a transient interruption of substrate delivery. Since adenosine triphosphate (ATP) synthesis recovers rapidly after restoration of substrate delivery, anaesthetics would be expected to be protective if present during ischaemia but not if given after restoration of substrate delivery. It would also follow that efficacy of an anaesthetic is dependent upon the severity of the ischaemic insult. If the insult were sufficiently severe to cause loss of all electrical activity, there would be no activity for anaesthetics to suppress and thus no mechanism for such drugs to increase tolerance to ischaemia. In contrast, in less severe insults, suppression of activity by the anaesthetic before onset of ischaemia should delay decay of ATP concentrations and thus also delay loss of ionic gradients and calcium influx.

Many studies have supported this logic. Indeed, during abrupt onset of hypoxaemia, barbiturates and isoflurane slow deterioration of ATP concentrations. Furthermore, post-ischaemic treatment with either barbiturates or volatile anaesthetics has no effect on outcome. Surprisingly, irrefutable data supporting efficacy of pre-treatment with anaesthetics have proved difficult to acquire.

Early work testing intra-ischaemic anaesthetic efficacy was confounded by poor physiological control of experimental subjects. It was recognized later in the evolution of anaesthetic efficacy studies that factors such as blood glucose, brain temperature, and perfusion pressure were important determinants of ischaemic outcome and that anaesthetics independently modulated these factors. In addition, early studies typically compared one anaesthetic against another. The assumption was that the ‘control’ anaesthetic was not protective and thus failure to improve outcome by the ‘test’ anaesthetic indicated lack of a protective state. However, little work was done to confirm that the ‘control’ anaesthetic was not protective. Subsequent studies, which became feasible as experimental models evolved, often found considerable protection from the ‘control’ anaesthetic when compared with an awake state.

Thus, the field remained confused for more than a decade and insufficient data were generated to warrant human trials of anaesthetic efficacy when employed intraoperatively. Even then, the early results were mixed. One

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study found efficacy from thiopental when given in cardiac surgical patients, whereas another did not.\textsuperscript{50,67} However, only short-term outcomes were assessed, which prevented assessment of the full evolution of the ischaemic injury. Furthermore, surgical procedures and cardio-pulmonary bypass conditions were markedly different between the two trials. Numerous other explanations have been offered, but perhaps the overall potency of barbiturates as neuroprotective agents is weak in the face of severe ischaemic insults.\textsuperscript{65}

One problem with barbiturates is their prolonged duration of action. It was believed that optimal protection would be present only when massive doses were administered to abolish electroencephalographic (EEG) activity, thereby eliciting maximal suppression of cerebral metabolic rate (CMR) before onset of the insult. Some practitioners still adhere to this principle when using barbiturates to protect the brain but such large doses can markedly delay anaesthesia emergence, which has limited their clinical application. Although it is unlikely that these massive doses are necessary to obtain maximal efficacy,\textsuperscript{65} recognition that volatile anaesthetics can also produce EEG isoelectricity at doses which still allow rapid anaesthesia emergence was greeted with optimism because such compounds could be more widely applied in clinical settings.

\textbf{Volatile anaesthetics}

The efficacy of volatile anaesthetics as neuroprotective agents has undergone more than 30 yr of scrutiny and still no human outcome trials have been conducted to guide clinical practice. We know the following facts from the laboratory. Volatile anaesthetics provide major improvement in ischaemic outcome. The dose required to obtain this protection is within a clinically relevant range, with higher doses potentially worsening outcome.\textsuperscript{36} Volatile anaesthetics protect against both focal (e.g. obstruction of flow distal to the circle of Willis) and global (e.g. complete cessation of blood flow to the brain or forebrain) ischaemia. However, the improvement in outcome is transient in global ischaemia,\textsuperscript{23} whereas it is persistent in focal ischaemia.\textsuperscript{58} Sevoflurane has also been shown to provide long-term protection in one experimental model.\textsuperscript{51} The mechanism by which volatile anaesthetics protect is, in part, attributable to suppression of energy requirements.\textsuperscript{47} Both inhibition of excitatory neurotransmission and potentiation of inhibitory receptors are likely to be involved.\textsuperscript{15,22,30} It is also likely that volatile anaesthetics have other important effects that include regulation of intracellular calcium responses during ischaemia,\textsuperscript{29} and activation of TREK-1 two-pore-domain K\textsuperscript{+} channels.\textsuperscript{25}

Although a great deal has been learned from the laboratory, in the absence of human outcome data, it cannot be stated that volatile anaesthetics improve outcome from perioperative ischaemic insults. However, if an anaesthetic is required for a surgical procedure, inclusion of volatile anaesthetics can be considered. Isoflurane and sevoflurane carry the largest data set to this decision. Desflurane also offers promise,\textsuperscript{33,38} but has been insufficiently studied to determine whether it should be equally considered in this class of potential neuroprotective compounds.

\textbf{Other anaesthetics}

Other anaesthetics possess properties that suggest potential for intra-ischaemic neuroprotection. These include propofol, etomidate, and lidocaine. Study of these drugs has not been as extensive as for either barbiturates or volatile anaesthetics. The principle feature of propofol and etomidate is suppression of CMR by inhibition of synaptic activity.\textsuperscript{19,35} Propofol may also have free radical scavenging and anti-inflammatory properties.\textsuperscript{57} Propofol appears unique among anaesthetics in the laboratory setting because it offers efficacy with post-ischaemic therapy onset, although such treatment provides only transient protection.\textsuperscript{9} Propofol appears to offer efficacy similar to barbiturates but a dose-dependent study of its efficacy has not been completed, leaving little guidance for potential clinical use. Furthermore, propofol infused to induce EEG burst suppression failed to improve outcome in cardiac valve surgery patients.\textsuperscript{56} Etomidate, although initially heralded as a substitute for barbiturates,\textsuperscript{8} has never met rigorous evaluation for neuroprotective properties. In fact, some work has indicated that etomidate may paradoxically exacerbate ischaemic injury by inhibiting nitric oxide synthase, thereby intensifying the ischaemic insult.\textsuperscript{21} As a result of this and other studies, the use of etomidate for neuroprotection has fallen out of favour in clinical settings.

Lidocaine also suppresses CMR, but this effect is only meaningful at doses beyond those typically employed in clinical environments. Numerous laboratory studies have found efficacy for lidocaine, with perhaps its principle mechanism of action relating to inhibition of apoptosis.\textsuperscript{39} The efficacy of lidocaine appears dependent on dose, with doses in the range used to manage cardiac dysrhythmias having greatest efficacy.\textsuperscript{61} There have been no long-term outcome studies of lidocaine efficacy in experimental stroke. One small human trial found benefit from low-dose lidocaine infusion during cardiac surgery on long-term neuropsychological impairment.\textsuperscript{44} Lidocaine should be further evaluated for neuroprotective properties since its use is supported by a litany of laboratory successes such as short-duration of action and ease of use. However, because it has not been evaluated in a large-scale clinical trial, efficacy in clinical environments remains speculative.

Ketamine offers potent inhibition of glutamatergic neurotransmission at the N-methyl-D-aspartate (NMDA) receptor. There is a long history of NMDA receptor antagonists as potential neuroprotective agents but, overall, such compounds offer little or no protection against global
insults. Protection against focal insults is substantial, but only if the drug is given before ischaemia onset. Because ketamine is clinically available, it is tempting to argue that it should be considered when a focal ischaemic insult is anticipated. To date, however, there are no human data supporting this practice. Little is also known about dose–response properties, even in animals. Thus, it is difficult to recommend ketamine for the purposes of neuroprotection in the clinical environment at this time.

**Physiological management**

**Temperature**

Hypothermia has been proposed to offer therapeutic benefit for more than 60 yr. Early investigators examined its effects in both neurosurgery and cardiac surgery patients. In the same era, it was also considered to offer benefit in survivors of cardiac arrest and hypoxic insults.

It remains unclear why hypothermia fell out of favour in subsequent decades. One factor may have been its apparent lack of efficacy, which reduced enthusiasm for the logistical issues necessary routinely to cool and re-warm a large patient population. Another factor may have been the influence of mechanistic studies conducted in the laboratory. That work examined effects of hypothermia on brain energy metabolism and found hypothermia to reduce CMR in a temperature-dependent fashion, which became the presumed mechanism of action. The most impressive effects on CMR were at very low temperatures, and those temperatures required use of cardiopulmonary bypass. The effects of mild (32–35°C) hypothermia on CMR were negligible. In contrast, barbiturate rates can reduce CMR by 50–60% without the use of cardiopulmonary bypass and were therefore viewed as having a greater potential benefit. Perhaps for those reasons, the use of perioperative hypothermia persisted only in the context of caring for some cardiac surgical patients.

There is no doubt that deep hypothermia (e.g. 18–22°C) is highly neuroprotective. We know that only a few minutes of complete global ischaemia will cause neuronal death in normothermic brain. This has been best examined in the laboratory, but human evidence is consistent with those findings. In contrast, it is widely observed that induction of deep hypothermia before circulatory arrest routinely allows the brain to tolerate intervals of no-flow exceeding 40 min, and substantially greater intervals of arrest with complete or near-complete neurological recovery are frequently reported. As a result of this *prima facie* evidence, the efficacy of deep hypothermia has not been subjected to randomized controlled trials. However, there is still much to be learned with respect to optimizing cooling and re-warming methods, optimal magnitude of hypothermia, determination of brain temperature using surrogate sites, and defining within individual patients when the duration of circulatory arrest approaches the limits of deep hypothermic neuroprotection.

The story might have ended there had it not been for several laboratory studies that ignored the CMR hypothesis. Those studies re-visited the possibility that mild hypothermia could protect the brain against ischaemia insults. To most people’s surprise, reduction in brain temperature by only a few degree Celsius provided major protection. These findings stimulated numerous clinical trials in both adults and newborns, which have since provided a scientific basis defining the opportunities and limitations of using off-bypass hypothermia to provide meaningful neuroprotection.

The first reported work related to traumatic brain injury (TBI). Three pilot studies provided suggestive evidence that mild hypothermia improved either brain physiology or outcome. However, those studies employed small sample sizes and more definitive evidence was needed. Thus, a large-scale prospective human trial was conducted, but disappointing results were obtained. Cooling TBI patients within the first several hours after injury failed to improve outcome. The design and conduct of this trial have been vigorously debated but what is clear is that induced hypothermia is not a panacea for TBI. If it is proven effective in later trials, it will probably be shown to have efficacy only in certain patient populations and only when conducted with specific protocols. Such work is ongoing.

If the TBI study had been performed in isolation, perhaps off-bypass hypothermia would have been abandoned in the clinic again. However, other studies were already underway, two of which markedly altered the mood of the investigative community. Both studies were reported simultaneously and used similar experimental designs wherein comatose survivors of out-of-hospital cardiac arrest were randomized to normothermia or mild hypothermia, which involved rapid surface cooling as soon as spontaneous circulation was restored. Both studies found significantly more patients with good outcome in the hypothermia group and negligible adverse events. Finally, convincing evidence is available that off-bypass hypothermia can appreciably improve outcome from at least cardiac arrest in humans.

These findings have prompted publication of guidelines recommending that comatose survivors of out-of-hospital cardiac arrest undergo cooling after restoration of spontaneous circulation. The extent to which the efficacy of induced hypothermia can be extrapolated to other conditions of cardiac arrest (loss of airway, asphyxia, and drowning) may never be known given the sporadic and relatively rare nature of those events. However, such intervention may be considered.

In addition, there is an increasing evidence that peripartum neonatal asphyxial brain injury favourably responds to treatment with hypothermia. Two trials have been reported. The first employed selective head cooling and
could only find a beneficial effect of hypothermia in a subset of the study population. The second employed total body cooling. In this study, the benefit of induced mild hypothermia was clear. Despite this, some feel additional trials are required before such intervention can be widely advocated.

In the course of defining hypothermia efficacy, it has also become apparent that hyperthermia has adverse effects on post-ischaemic brain. Spontaneous post-ischaemic hyperthermia is common and, in animals, intra-ischaemic or even delayed post-ischaemic hyperthermia dramatically worsens outcome. Spontaneous hyperthermia has also been associated with poor outcome in humans. These facts provide sufficient evidence to advocate frequent temperature monitoring in patients with cerebral injury (and those at risk for cerebral injury). Aggressive treatment of hyperthermia should be considered.

**Glucose**

Glucose is a fundamental substrate for brain energy metabolism. Deprivation of glucose in the presence of oxygen can result in neuronal necrosis, but the presence of glucose in the absence of oxygen carries a worse fate. The mechanistic basis for this dichotomy remains unclear. The most persistent hypothesis is that glucose, in the absence of oxygen, undergoes anaerobic glycolysis resulting in intracellular acidosis, which amplifies the severity of other deleterious cascades initiated by the ischaemic insult. Many animal studies have demonstrated adverse effects of hyperglycaemia from a wide variety of brain insults. Human studies remain principally correlative in nature, that is, patients having worse outcomes from stroke, TBI, etc. also tend to have higher blood glucose concentrations on hospital admission. For some time, it was unclear whether admission hyperglycaemia simply represented a stress response to the brain insult, or instead was contributing to a worsened injury. The animal data clearly favour the latter interpretation. More importantly, human research has demonstrated more rapid expansion of ischaemic lesions in hyperglycaemic, compared with normoglycaemic patients. In addition, there is accumulating evidence that regulation of blood glucose yields a higher incidence of good outcome in stroke patients. For all of these reasons, it is rational to maintain normoglycaemia in all patients at risk for, or recovering from acute brain injury.

**Arterial carbon dioxide partial pressure (PaCO₂)**

Because cerebral blood flow and PaCO₂ are linearly related within physiologically relevant ranges, hyperventilation had become an entrenched practice in cerebral resuscitation. Reduction in PaCO₂ was presumed to augment cerebral perfusion pressure favourably by reducing the cross-sectional diameter of the arterial circulation and thus cerebral blood volume. This would offset increases in intracranial pressure. Although the logic behind this practice can be appreciated, in fact, it is contradicted by direct examination of cerebral well being. The most salient evidence is derived from TBI investigations. These studies support a different concept, that being worsening of perfusion by hyperventilation-induced vasoconstriction in ischaemic tissue. Indeed, the volume of ischaemic tissue, elegantly assessed with positron emission tomography in TBI patients, was markedly increased when moderate hypocapnia was induced. This is consistent with the only prospective trial of hyperventilation on TBI outcome, which observed a decreased number of patients with good or moderate disability outcomes when chronic hyperventilation was employed. It remains unevaluated whether acute hyperventilation improves outcome from pending transtentorial herniation or when rapid surgical decompression of a haematoma (e.g. epidural) is anticipated. Within the context of focal ischaemic stroke, clinical trials have found no benefit from induced hypocapnia, although hyperventilation is sometimes employed in cases of refractory brain oedema. Use of hyperventilation during cardiopulmonary resuscitation may serve to increase mean intrathoracic pressure thereby decreasing perfusion pressure and is not advocated. Consequently, there are few data to support use of hyperventilation in the context of cerebral resuscitation.

**Arterial oxygen partial pressure**

It makes sense that optimization of oxygen delivery to ischaemic tissue should improve outcome. Indeed, oxygen deprivation is the fundamental fault leading to tissue demise. However, reperfusion presents deranged oxygen metabolism with the opportunity to increase formation of reactive oxygen species that plausibly induce secondary insults, thereby worsening outcome. There are few human data regarding the effects of normobaric hyperoxaemia in human resuscitation. One retrospective perinatal resuscitation analysis found worse long-term outcome in children when either hyperoxaemia or hypocapnia was present during resuscitation or early recovery. Others found more rapid normalization of Apgar scores when 40% oxygen compared with 100% oxygen was used for resuscitation.

In animal models, it is becoming evident that the effect of hyperoxaemia is dependent on the nature of the ischaemic insult. Rats subjected to middle cerebral artery occlusion had smaller infarcts when normobaric hyperoxaemia was present during both ischaemia and reperfusion. This is consistent with the demonstrated efficacy of hyperbaric oxygen (HBO) in rats undergoing a similar focal ischaemic insult. Evidence for HBO efficacy in humans is weak. In contrast, in dogs subjected to cardiac arrest, it has been repeatedly observed that outcome is worsened by normobaric hyperoxaemia present during early recirculation. This has been attributed to oxidation and decreased pyruvate dehydrogenase activity, the enzymatic link between anaerobic and aerobic glycolysis. Management of oxygen
delivery after restoration of spontaneous circulation, so as to maintain pulse oximeter values within the range of 94–96, optimized short-term neurological outcome. These compelling data should serve as a stimulus for a randomized clinical trial and stimulates re-consideration of the necessity for hyperoxaemia in the early post-resuscitation interval.

**Steroids**

Steroids such as dexamethasone reduce oedema surrounding brain tumours. Beyond that, evidence for benefit from the use of steroids is weak. Evidence that methylprednisolone improves outcome from acute spinal cord trauma is controversial, but some surgeons have extended this observation to intraoperative use in spinal cord surgery. There is insufficient evidence to define the role of glucocorticoids in focal ischaemic stroke. A large retrospective analysis found no benefit from glucocorticoid treatment in patients with cardiac arrest. In fact, there is animal evidence that such glucocorticoids exacerbate injury from global ischaemia by increasing plasma glucose concentration. Given the potential adverse effects of steroids and lack of demonstrable efficacy in ischaemic brain, their use cannot be advocated.

**Conclusion**

Ischaemic brain injury remains a potentially devastating disorder, although progress is being made in resuscitation science. Two key advances occurred in the past decade. The first was repeated demonstration that induced mild hypothermia reduces neurological morbidity and mortality associated with out-of-hospital ventricular fibrillation cardiac arrest. Beyond the immediate potential to apply this intervention is the larger message that post-ischaemic intervention can favourably influence outcome in humans. The second advance was recognition that efficacy of mild hypothermia depends at least in part upon the type of ischaemic lesion being treated. Trauma and focal ischaemia could not be shown to be amenable to hypothermic intervention, at least within the bounds of the clinical trial protocols employed.

Other than the use of mild hypothermia for ventricular fibrillation cardiac arrest, practice of clinical neuroprotection rests on extrapolation from animal studies and weak clinical trials. Review of these data allows some recommendations to be made (Table 2). Such recommendations are likely to be advanced with increased understanding of cellular responses to ischaemia and appropriately conducted clinical trials.

**Table 2** Considerations when anticipating or managing a perioperative ischaemic insult

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Assure absence of hyperthermia</td>
<td>Manage blood glucose with insulin to induce normoglycaemia</td>
</tr>
<tr>
<td>Optimize haemoglobin-oxygen saturation (increasing concern that hyperoxaemia may be adverse in global ischaemia)</td>
<td>Establish normocapnia</td>
</tr>
<tr>
<td>Establish normocapnia</td>
<td>Consider the use of volatile anaesthetics if surgery ongoing (consistent sustained benefit in experimental animal studies, reversible allowing neurological examination, human trials not performed)</td>
</tr>
<tr>
<td>Resist the use of glucocorticoids (no evidence of efficacy, preclinical evidence of adverse effect in global ischaemia)</td>
<td>Consider the use of postoperative sustained induced moderate hypothermia if global ischaemia (not tested by clinical trials in perioperative environment, but supported by consistent evidence of efficacy when used in out-of-hospital ventricular fibrillation cardiac arrest)</td>
</tr>
</tbody>
</table>

**References**

24 Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. Assoc Res Nerv Ment Dis Proc 1943; 24: 611–19
28 Goldstein A, Jr, Wells BA, Keats AS. Increased tolerance to cerebral anoxia by pentobarbital. Arch Int Pharmacodyn Ther 1966; 161: 138–43
41 McDonagh DL, Allen IN, Keifer JC, Warner DS. Induction of hypothermia after intraoperative hypoxic brain insult. Anesth Analg 2006; 103: 180–1
43 Michenfelder JD, Theye RA. Cerebral protection by thiopental during hypoxia. Anesthesiology 1973; 39: 510–7
48 Newberg LA, Michenfelder JD. Cerebral protection by isoflurane during hypoxemia or ischemia. Anesthesiology 1983; 59: 29–35
50 Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by barbiturate. Anesthesiology 1986; 64: 165–70
This talk will outline the roles of the Anesthesiologist in the Interventional Neuroradiology (INR) suite with an emphasis on management strategies to prevent complications and minimize their effects if they occur. We will discuss fundamental management principles of affording "protection," of which direct pharmacological protection is perhaps the least important. Planning the anesthetic and perioperative management is predicated on understanding the goals of the therapeutic intervention and anticipating potential problems. Endovascular neurosurgery / INR is firmly established in the management of cerebrovascular disease, most notably in the management of intracranial aneurysms. For the overall management approach to the patient with cerebrovascular disease, there is accelerating interest and discussion in appropriate management of asymptomatic or unruptured lesions.

There are several anesthetic concerns that are particularly important for INR procedures, including: (1) maintaining immobility during the procedure to facilitate imaging; (2) rapid recovery from anesthesia at the end of the case to facilitate neurological examination and monitoring, or provide for intermittent evaluation of neurological function during the procedure; (3) managing anticoagulation; (4) treating and managing sudden unexpected procedure-specific complications during the procedure, i.e., hemorrhage or vascular occlusion, which may involve manipulating systemic or regional blood pressures; (5) guiding the medical management of critical care patients during transport to and from the radiology suites; (6) self-protection issues related to radiation safety.

PRE-OPERATIVE PLANNING AND PATIENT PREPARATION
Baseline blood pressure and cardiovascular reserve should be assessed carefully. This almost axiomatic statement is particularly important for several reasons. Blood pressure manipulation is commonly required and treatment-related perturbations should be anticipated. Therefore, a clear sense of “where the patient lives” needs to be established. One must keep in mind that “autoregulation” as presented in the textbooks is a description of a population; individual patients are likely to vary considerably, a concept based on the historical observations that underlie our modern notions of autoregulatory behavior. In those cases where intra-arterial catheters are used, the concordance between blood pressure cuff and intra-arterial readings needs to be considered; pre-operative blood pressure range is likely to be known through blood pressure cuff values.

Pre-operative calcium channel blockers for prophylaxis for cerebral ischemia may be used and can affect hemodynamic management. In addition, these agents or trans-dermal nitroglycerin are sometimes used to lessen the incidence of catheter-induced vasospasm.

For cases managed with an unsecured airway, routine evaluation of the potential ease of laryngoscopy in an emergent situation should take into account that direct access to the airway may be limited by table or room logistics. Recent pterional craniotomy can sometimes result in impaired tempomandicular joint mobility.

For i.v. sedation cases, careful padding of pressure points and working with the patient to obtain final comfortable positioning may assist in the patient’s ability to tolerate a long period of lying supine and motionless, decreasing the requirement for sedation, anxiolysis, and analgesia. The possibility of pregnancy in female patients and a history of adverse reactions to radiographic contrast agents should be explored.

Secure intravenous (iv) access should be available with adequate extension tubing to allow drug and fluid administration at maximal distance from the image intensifier during fluoroscopy. Access to intravenous or arterial catheters can be difficult when the patient is draped and the arms are restrained at the sides; connections should be secure. Infusions of anticoagulant, primary anesthetics or vasoactive agents should be through proximal ports with minimal dead space.

In addition to standard monitors, capnography sampling via the sampling port of nasal cannula is useful for i.v. sedation cases. A pulse oximeter probe can be placed on the great toe of the leg that will receive the femoral introducer sheath to provide an early warning of femoral artery obstruction or distal thromboembolism. For intracranial procedures and post-operative care, beat-to-beat arterial pressure monitoring and blood sampling can be facilitated by an arterial line. A side port of the femoral artery introducer sheath can be used, but the sheath is usually removed immediately after the procedure. In a patient who requires continuous blood pressure monitoring post-operatively or frequent blood sampling, it is convenient to have a separate radial arterial blood pressure catheter. Using a co-axial or tri-axial catheter system, arterial pressure at the carotid artery, vertebral artery, and the
distal cerebral circulation can be measured. Pressures in these distal catheters usually underestimate systolic and overestimate diastolic pressure; however, mean pressures are reliable. Bladder catheters assist in fluid management as well as patient comfort. A significant volume of heparinized flush solution and radiographic contrast is may be used.

Radiation Safety is a critical part of pre-operative planning. It is probably reasonable to assume that the x-ray machine is always on. There are three sources of radiation in the INR suite: direct radiation from the X-ray tube, leakage (through the collimators' protective shielding), and scattered (reflected from the patients and the area surrounding the body part to be imaged). A fundamental knowledge of radiation safety is essential for all staff members working in an INR suite. The amount of exposure decreases proportionally to the inverse of the square of the distance from the source of radiation (inverse square law). Digital subtraction angiography (DSA) delivers considerably more radiation than fluoroscopy.

Optimal protection would dictate that all personnel should wear lead aprons, thyroid shields, and radiation exposure badges. The lead aprons should be periodically evaluated for any cracks in the lead lining that may allow accidental radiation exposure. Movable lead glass screens may provide additional protection for the anesthesia team. Clear communication between the INR and anesthesia teams is also crucial for limiting radiation exposure. With proper precautions the anesthesia team should be exposed to far less than the annual recommended limit for health care workers (see URL http://pdg.lbl.gov/).

**ANESTHETIC TECHNIQUE**

**Choice of Anesthetic Technique**

Most centers routinely involved use general endotracheal anesthesia for aneurysm coiling and endovascular treatment of vasospasm. Choice of anesthetic technique varies between centers with no clear superior method.

**General Anesthesia**

A primary reason for employing general anesthesia is to minimize motion artifacts and to improve the quality of image. Relative normocapnia or modest hypocapnia consistent with the safe conduct of positive pressure ventilation should be maintained unless intracranial pressure is a concern. The specific choice of anesthesia may be guided primarily by other cardio- and cerebrovascular considerations. Total intravenous anesthetic techniques, or combinations of inhalational and intravenous methods, may optimize rapid emergence. To date, pharmacological protection against ischemic injury during neurosurgical procedures has not been proven. A theoretical argument could be made for eschewing the use of N₂O because of the possibility of introducing air emboli into the cerebral circulation and reports that it worsens outcome after experimental brain injury.

**Intravenous Sedation**

Intravenous sedation in aneurysm management is used most often for patients coming for interim follow-up angiography to assess the necessity for retreatment after primary coiling. If further treatment is indicated, the technique can be converted to a general anesthetic. Goals of anesthetic choice for intravenous sedation are to alleviate pain, anxiety, and discomfort, provide patient immobility and allow rapid recovery. There may be a discomfort associated with injection of contrast into the cerebral arteries (burning) and with distention or traction on them (headache). A long period of lying can cause significant discomfort.

A variety of sedation regimens are available, and specific choices are based on the experience of the practitioner and the goals of anesthetic management. Common to all intravenous sedation techniques is the potential for upper airway obstruction. Placement of nasopharyngeal airways may cause troublesome bleeding in anticoagulated patients and is generally avoided.

Dexmetetomidine is a new agent that may have applicability in the setting of INR. It is a potent, selective α₂-agonist with sedative, anxiolytic, and analgesic properties, with recent regulatory approval for sedation. Dexmedetomidine is especially noteworthy for its ability to produce a state of patient tranquility without depressing respiration. However, there are two caveats to consider. First, there are still unclear effects on cerebral perfusion. More importantly, there is a tendency for patients managed with dexmedetomidine to have relatively low blood pressure in the post-anesthesia recovery period. Because patients with aneurismal subarachnoid hemorrhage may be critically dependent on adequate collateral perfusion pressure, use of regimens that may result in blood pressure decreases should be used with great caution.
ANTICOAGULATION

Heparin:
Careful management of coagulation is required to prevent thromboembolic complications during and after the procedure. Generally, after a baseline activated clotting time (ACT) is obtained, intravenous heparin (70 units/kg) is given to a target prolongation of 2 ~ 3 times of baseline. Then heparin can be given continuously or as an intermittent bolus with hourly monitoring of ACT. Occasionally, a patient may be refractory to attempts to obtain adequate anticoagulation. Switching from bovine to porcine heparin or vice versa should be considered. If antithrombin III deficiency is suspected, administration of fresh frozen plasma may be necessary.

Direct Thrombin Inhibitors:
Heparin-induced thrombocytopenia (HIT) is a potentially devastating prothrombotic syndrome caused by heparin dependent antibodies after exposure. Direct thrombin inhibitors may be used in patients with or at risk of HIT, although they entail their own risks, including a small risk of anaphylaxis. They inhibit thrombin both in the free form or bound to the clot. Monitoring of action is done by measuring the aPTT, or ACT. Lepirudin is FDA-approved for anticoagulation in patients with HIT. The half-life of lepirudin is 40 to 120 minutes, and it undergoes renal elimination. For HIT patients with renal impairment, Argatroban, predominantly metabolized in the liver, may be preferrable. Bivalirudin, a synthetic derivative of lepirudin, has a short half-life of about 25 minutes. Since bivalirudin is partially renally eliminated, dose adjustments may be needed in patients with renal dysfunction. A recent report described bivalirudin as a potential alternative during INR procedures to heparin for intravenous anticoagulation and intra-arterial thrombolysis.10

Antiplatelet agents:
Antiplatelet agents (aspirin, the glycoprotein IIb/IIIa receptor antagonists and the thienopyridine derivatives) are increasingly being used for cerebrovascular disease management, as well as rescue from thromboembolic complications.11,12 Activation of the platelet membrane glycoprotein (GP) IIb/IIIa leads to fibrinogen binding and is a final common pathway for platelet aggregation. Abciximab, epifibatide and tirofiban are glycoprotein IIb/IIIa receptor antagonists. The long duration and potent effect of Abciximab also increase the likelihood of major bleeding. The smaller molecule agents, epifibatide and tirofiban, are competitive blockers and have a shorter half-life (about 2 hours). Thienopyridine derivatives (ticlopidine and clopidogrel) bind to the platelet’s ADP receptors and permanently alter the receptor; therefore, the duration of action is the life span of the platelet. The addition of clopidogrel to the antiplatelet regimen is used when stent-assisted coiling is anticipated, and also for management of unruptured aneurysms.

Reversal of Anticoagulation:
At the end of the procedure or at occurrence of hemorrhagic complication, heparin may be reversed with protamine. Since there is no specific antidote for the direct thrombin inhibitors or the antiplatelet agents, the biological half-life is one of the major considerations in drug choice and platelet transfusion is a non-specific therapy, should reversal be indicated. There is no currently available accurate test to measure platelet function in patients taking the newer antiplatelet drugs. Desmopressin (DDAVP) has been reported to shorten the prolonged bleeding time of individuals taking antiplatelet agents such as aspirin and ticlopidine. There are also increasing recent reports on using specific clotting factors, including recombinant factor VIIa and factor IX complex, to rescue severe life-threatening bleeding, including intracranial hemorrhage uncontrolled by standard transfusion therapy. The safety and efficacy of these coagulation factors remain to be investigated.

DELIBERATE HYPERTENSION
During acute arterial occlusion or vasospasm, the only practical way to increase collateral blood flow may be an augmentation of the collateral perfusion pressure by raising the systemic blood pressure. The Circle of Willis is a primary collateral pathway in cerebral circulation. However, in as many as 21% of otherwise normal subjects, the circle may not be complete. There are also secondary collateral channels that bridge adjacent major vascular territories, most importantly for the long circumferential arteries that supply the hemispheric convexities. These pathways are known as the pial-to-pial collateral or leptomeningeal pathways.

The extent to which the blood pressure has to be raised depends on the condition of the patient and the nature of the disease. Typically, during deliberate hypertension the systemic blood pressure is raised by 30-40% above the baseline, in the absence of some direct outcome measure such as resolution of ischemic symptoms or imaging evidence of improved perfusion. Phenylephrine is usually the first line agent for deliberate hypertension and is
titrated to achieve the desired level of blood pressure. The risk of causing hemorrhage into the ischemic area must be weighed against the benefits of improving perfusion, but augmentation of blood pressure in the face of acute cerebral ischemia is probably protective in most settings.

DELIBERATE HYPOTENSION
The two primary indications for induced hypotension are: (1) to test cerebrovascular reserve in patients undergoing carotid occlusion, and (2) to slow flow in a feeding artery of BAVMs before glue injection. The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the patient physiologically stable. The choice of agent should be determined by the experience of the practitioner, the patient's medical condition, and the goals of the blood pressure reduction in a particular clinical setting. Intravenous adenosine has been used to induce transient cardiac pause and may be a viable method of partial flow arrest.13

MANAGEMENT OF NEUROLOGICAL AND PROCEDURAL CRISES
A well thought-out plan, coupled with rapid and effective communication between the anesthesia and radiology teams, is critical for good outcomes. The primary responsibility of the anesthesia team is to preserve gas exchange and, if indicated, secure the airway. Simultaneous with airway management, the first branch in the decision-making algorithm is for the anesthesiologist to communicate with the INR team and determine whether the problem is hemorrhagic or occlusive.

In the setting of vascular occlusion, the goal is to increase distal perfusion by blood pressure augmentation with or without direct thrombolysis. If the problem is hemorrhagic, immediate cessation of heparin and reversal with protamine is indicated. As an emergency reversal dose, 1 mg protamine can be given for each 100 units of initial heparin dosage that resulted in therapeutic anticoagulation. The ACT can then be used to fine-tune the final protamine dose. Complications of protamine administration include hypotension, true anaphylaxis and pulmonary hypertension. With the advent of new long-acting direct thrombin inhibitors such as bivalirudin, new strategies for emergent reversal of anticoagulation will need to be developed.

Bleeding catastrophes are usually heralded by headache, nausea, vomiting and vascular pain related to the area of perforation. Sudden loss of consciousness is not always due to intracranial hemorrhage. Seizures, as a result of contrast reaction or transient ischemia, and the resulting post-ictal state can also result in an obtunded patient. In the anesthetized or comatose patient, the sudden onset of bradycardia and hypertension (Cushing response) or the endovascular therapist’s diagnosis of extravasation of contrast may be the only clues to a developing hemorrhage. Most cases of vascular rupture can be managed in the angiography suite. The INR team can attempt to seal the rupture site endovascularly and abort the procedure; a ventriculostomy catheter may be placed emergently in the angiography suite. Patients with suspected rupture will require emergent CT scan, but emergent craniotomy is usually not indicated.

SPECIFIC PROCEDURES

Intracranial Aneurysm Ablation
The two basic approaches for INR therapy of cerebral aneurysms are occlusion of proximal parent arteries and obliteration of the aneurysmal sac. With the publication of the ISAT trial,14 coil embolization of intracranial aneurysms has become a routine first choice therapy for many lesions. The anesthesiologist should be prepared for aneurysmal rupture and acute SAH at all times, either from spontaneous rupture of a leaky sac or direct injury of the aneurysm wall by the vascular manipulation. There is great interest in the development of stent-assisted coiling methods. The stent can provide protection of the parent vessel. Stent placement requires a greater degree of instrumentation and manipulation, probably increasing the ever-present intra-procedural risk of parent vessel occlusion, thromboembolism or vascular rupture.

Angioplasty of Cerebral Vasospasm from Aneurysmal SAH
Roughly 1 out of 4 patients with SAH will develop symptomatic vasospasm. Angioplasty, either mechanical (balloon) or pharmacological (intraarterial vasodilators), may be used as a treatment.15 Angioplasty is ideally done in patients that have already had the symptomatic lesion surgically clipped and for patients in the early course of symptomatic ischemia in order to prevent hemorrhagic transformation of an ischemia region. A balloon catheter is guided under fluoroscopy into the spastic segment and inflated to mechanically distend the constricted area. It is also possible to perform a “pharmacologic” angioplasty by direct intra-arterial infusion. There
is the greatest experience with papaverine, but there are potential CNS toxic effects.\textsuperscript{16} Other agents such as calcium channel blockers (nicardipine and verapamil) are being used.\textsuperscript{17} Intraarterial vasodilators may have systemic effects (bradycardia and hypotension).

Patients who come for angioplasty are often critically ill with a variety of challenging co-morbidities, including neurocardiac injury, volume overload from “triple-H” therapy, hydrocephalus, brain injury from recent craniotomy, and residual effects of the presenting hemorrhage. Procedural complications include arterial rupture, reperfusion hemorrhage, thromboembolism, and arterial dissection.

**Carotid Test Occlusion and Therapeutic Carotid Occlusion**
Large or otherwise unclippable aneurysms may be partly or completely treated by proximal vessel occlusion. In order to assess the consequences of carotid occlusion in anticipation of surgery, the patient may be scheduled for a test occlusion in which cerebrovascular reserve is evaluated in several ways. A multimodal combination of angiographic, clinical, and physiologic tests can be used to arrive at the safest course of action for a given patient’s clinical circumstances. The judicious use of deliberate hypotension can increase the sensitivity of the test.\textsuperscript{18} The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the patient physiologically stable. The choice of agent should be determined by the experience of the practitioner, the patient's medical condition and the goals of the blood pressure reduction in a particular clinical setting.

**Brain Arteriovenous Malformations (BAVMs)**
Also called cerebral or pial AVMs, these are typically large, complex lesions made up of a tangle of abnormal vessels (called the nidus) frequently containing several discrete fistulae served by multiple feeding arteries and draining veins. The goal of the therapeutic embolization is to obliterate as many of the fistulae and their respective feeding arteries as possible. BAVM embolization is usually an adjunct for surgery or radiotherapy.

The cyanoacrylate glues offer relatively “permanent” closure of abnormal vessels. Passage of glue into a draining vein can result in acute hemorrhage; in smaller patients, pulmonary embolism of glue can be symptomatic. For these reasons, deliberate hypotension may increase safety of glue delivery. Although less durable, polyvinyl alcohol microsphere embolization is also commonly used. If surgery is planned within days after PVA embolization, the rate of recanalization is low.

**Dural AVMs**
Dural AVM is considered an acquired lesion resulting from venous dural sinus stenosis or occlusion, opening of potential AV shunts, and subsequent recanalization. Symptoms are variable according to which sinus is involved. Venous hypertension of pial veins is a risk factor for intracranial hemorrhage. Dural AVMs may be fed by multiple meningeal vessels, and therefore, multi-staged embolization is often necessary. Dural AV fistulas can induce markedly increased venous pressure and decrease net cerebral perfusion pressure. Therefore, presence of venous hypertension should be factored into management of systemic arterial and cerebral perfusion pressure.

**Angioplasty and Stenting for Atherosclerotic Lesion**
Angioplasty and stenting for atherosclerosis for treatment of atherosclerotic disease involving the cervical and intracranial arteries continue to supplant open surgical management.\textsuperscript{19,20} Risk of distal thromboembolism is a major issue in this procedure. Catheter systems employing some kind of trapping system distal to the angioplasty balloon are being developed. There are multiple ongoing trials to compare the utility of stenting to carotid endarterectomy for extracranial carotid disease. It is likely that use of stenting will continue to increase as favorable data supporting its safety and efficacy emerge.

Preparation for anesthetic management may include placement of transcutaneous pacing leads, in case of severe bradycardia or asystole from carotid body stimulation during angioplasty. Intravenous atropine or glycopyrrolate may be also used in an attempt to mitigate against bradycardia, which almost invariably occurs to some degree with inflation of the balloon. This powerful chronotropic response may be difficult or impossible to prevent or control by conventional means. Adverse effects of increasing myocardial oxygen demand need to be considered in anti-bradycardia interventions.
Potential complications include vessel occlusion, perforation, dissection, spasm, thromboemboli, occlusion of adjacent vessels, transient ischemic episodes, and stroke. Similar to carotid endarterectomy, there is about a 5% risk of symptomatic cerebral hemorrhage and/or brain swelling after carotid angioplasty. Although the etiology of this syndrome is unknown, it has been associated with cerebral hyperperfusion, and it may be related to poor post-operative blood pressure control.

Thrombolysis of Acute Thromboembolic Stroke
In acute occlusive stroke, it is possible to recanalize the occluded vessel by superselective intra-arterial thrombolytic therapy. Thrombolytic agents can be delivered in high concentration by a microcatheter navigated close to the clot. Neurological deficits may be reversed without additional risk of secondary hemorrhage if treatment is completed within 4-6 hours from the onset of carotid territory ischemia and 24 hours in vertebrobasilar territory. One of the impediments in development in this area has been the fear of increasing the risk of hemorrhagic transformation of the acute infarction patient. Despite an increased frequency of early symptomatic hemorrhagic complications, treatment with intra-arterial pro-urokinase within 6 hours of the onset of acute ischemic stroke with MCA occlusion significantly improved clinical outcome at 90 days. Details of anesthetic management are reviewed elsewhere.

POST-OPERATIVE MANAGEMENT
Endovascular surgery patients pass the immediate post-operative period in a monitored setting, to watch for signs of hemodynamic instability or neurologic deterioration. Control of blood pressure may be necessary during transport and post-operative recovery, e.g., induced hypertension, if indicated. Abrupt restoration of normal systemic pressure to a chronically hypotensive (ischemic) vascular bed may overwhelm autoregulatory capacity and result in hemorrhage or swelling (normal perfusion pressure breakthrough, NPPB). In the absence of collateral perfusion pressure inadequacy, fastidious attention to preventing hypertension is warranted. Complicated cases may go first to CT or some other kind of tomographic imaging; critical care management may need to be extended during transport and imaging.

References:
Interventional neuroradiology—anesthetic considerations

Tomoki Hashimoto, MD^a,d, Dhanesh K. Gupta, MD^a,d, William L. Young, MD^a,b,c,d,*

^aDepartment of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94110, USA
^bDepartment of Neurological Surgery, University of California, San Francisco, CA 94110, USA
^cDepartment of Neurology, University of California, San Francisco, CA 94110, USA
^dCenter for Cerebrovascular Research, University of California, San Francisco, San Francisco General Hospital, 1001 Potrero Avenue, Room 3C-38, San Francisco, CA 94110, USA

Interventional neuroradiology (INR) is a hybrid of traditional neurosurgery and neuroradiology, with certain overlaps with aspects of head-and-neck surgery. It can be broadly defined as treatment of central nervous system (CNS) disease by endovascular access for the purpose of delivering therapeutic agents, including both drugs and devices [1]. Because of a recent advancement in the field of INR [2], more anesthesiologists are involved in care of patients undergoing INR procedures. Anesthesiologists have several important concerns when providing care to patients who undergo INR procedures, including (1) maintenance of patient immobility and physiologic stability; (2) manipulating systemic or regional blood flow; (3) managing anticoagulation; (4) treating and managing sudden unexpected complications during the procedure; (5) guiding the medical management of critical care patients during transport to and from the radiology suites; and (6) rapid recovery from anesthesia and sedation during or immediately after the procedure to facilitate neurologic examination and monitoring [3,4]. To achieve these goals, anesthesiologists should be familiar with specific radiological procedures and their potential complications.
Preanesthetic considerations

The preanesthetic evaluation of a patient undergoing a potentially long diagnostic and therapeutic procedure in the neuroradiology suite expands on the routine preanesthetic examination of the neurosurgical patient. Airway evaluation should include routine evaluation of the potential ease of laryngoscopy in an emergent situation, and also take into the account the fact that, with the head and neck kept in a neutral position, sedation may compromise airway patency. Further, this patient population often includes head-and-neck tumor patients with their associated airway considerations.

Baseline blood pressure and cardiovascular reserve should be assessed carefully, especially when blood pressure manipulation and perturbations are anticipated. A careful neurologic examination should be performed to characterize any deficits that may be present prior to the procedure, and special note should be made of the patient’s sensorium. Furthermore, careful padding of pressure points may assist in the patient’s ability to tolerate a long period of lying supine and motionless and decrease the requirement for sedation, anxiolysis, and analgesia.

In addition to the issues normally considered during the preanesthetic evaluation of the neurosurgical patient, the anesthesiologist should review the patient’s previous experiences with angiography, noting if there were adverse reactions to radiographic contrast agents, such as allergy or excessive dehydration. Because of the possibility of significant radiation exposure, the possibility of pregnancy in female patients should be explored.

Prophylaxis for cerebral ischemia is in a state of development. Some centers use a variety of agents such as oral nimodipine for this purpose. The use of calcium channel blockers has been suggested to decrease catheter-induced vasospasm as well; transdermal nitroglycerin has also been used for this purpose.

Monitoring and vascular access

Secure intravenous (i.v.) access should be available with adequate extension tubing to allow drug and fluid administration at maximal distance from the image intensifier during fluoroscopy. Access to i.v. or arterial catheters can be difficult when the patient is draped and the arms are restrained at the sides. Stopcocks and nonlocking tubing connections under the drapes should be minimized. Prior to covering the patient, the tightness of connections between segments of tubing should be verified. Infusions of anticoagulant or potent medications, such as nitroprusside and remifentanil, should be through minimal dead space, into ports that are as proximal to the patient as possible (e.g., into a T-connector at an i.v. catheter). This allows the infusion of medications to be relatively independent of the rate of the i.v. carrier fluid.

Standard monitors should be applied, regardless of anesthetic technique. For i.v. sedation, capnography sampling via the sampling port of special nasal cannula is especially useful. A pulse oximeter probe can be placed on the great
toe of the leg that will receive the femoral introducer sheath. This may give an early warning of femoral artery obstruction or distal thromboembolism.

For intracranial procedures and postoperative care, beat-to-beat arterial pressure monitoring and blood sampling can be facilitated by an arterial line. A side port of the femoral artery introducer sheath can be used, but most radiologists will remove the sheath immediately after the procedure. Using a coaxial or triaxial catheter system, arterial pressure at the carotid artery, vertebral artery, and the distal cerebral circulation can be measured [5]. The presence of a coaxial catheter frequently underestimates the systolic and overestimates the diastolic pressure; however, mean pressures are reliable, and may be used to safely monitor the induction of either hyper- or hypotension. In a patient who requires continuous blood pressure monitoring postoperatively, it is convenient to have a separate radial arterial blood pressure catheter. Bladder catheters are required for most of the procedures; they assist in fluid management as well as patient comfort. A significant volume of heparinized flush solution and radiographic contrast is often used.

**Radiation safety**

There are three sources of radiation in the INR suite: direct radiation from the x-ray tube, leakage (through the collimators’ protective shielding), and scattered (reflected from the patients and the area surrounding the body part to be imaged). A fundamental knowledge of radiation safety is essential for all staff members working in an INR suite. It must be realized that the amount of exposure decreases proportionally to the square of the distance from the source of radiation (inverse square law). It should also be realized that digital subtraction angiography delivers considerably more radiation than fluoroscopy.

Optimal protection would dictate that all personnel should wear lead aprons, thyroid shields, and radiation exposure badges. The lead aprons should be periodically evaluated for any cracks in the lead lining that may allow accidental radiation exposure. Movable lead glass screens may provide additional protection for the anesthesia team. Clear communication between the INR and anesthesia teams is crucial for limiting radiation exposure. With proper precautions, the anesthesia team should be exposed to less than the annual recommended limit for health care workers (see http://pdg.lbl.gov/).

**Anesthetic technique**

Choice of anesthetic technique is a controversial area, and varies between centers. There are no data that support improved outcome with one technique or another. There appears to be a trend to move more towards general endotracheal anesthesia, but it is highly dependent on local practice and training.
Intravenous sedation

Primary goals of anesthetic choice for i.v. sedation are to alleviate pain, anxiety and discomfort, and to provide patient immobility. A rapid recovery from sedation is often required for neurologic testing.

Many neuroangiographic procedures, while not painful per se, can be psychologically stressful. This is especially true when there is a risk of serious stroke or death, particularly patients who have already suffered a preoperative hemorrhage or stroke. There may be an element of pain associated with injection of contrast into the cerebral arteries (burning) and with distention or traction on them (headache). A long period of lying can cause significant pain and discomfort.

A variety of sedation regimens are available, and specific choices are based on the experience of the practitioner and the aforementioned goals of anesthetic management. Common to all i.v. sedation techniques is the potential for upper airway obstruction. Placement of nasopharyngeal airways may cause troublesome bleeding in anticoagulated patients, and is generally avoided. Laryngeal Mask Airways may be useful in rare emergencies in patients with difficult airway. Endotracheal intubation, however, remains a mainstay for securing the airway during neurological crises.

General anesthesia

The primary reason for employing general anesthesia is to reduce motion artifacts and to improve the quality of images, especially in small children and uncooperative adult patients. This is especially pertinent to INR treatment of spinal pathology, in which extensive multilevel angiography may be performed. The specific choice of anesthesia may be guided primarily by other cardio- and cerebrovascular considerations. Total i.v. anesthetic techniques, or combinations of inhalational and i.v. methods, may optimize rapid emergence [6]. To date, pharmacologic protection against ischemic injury during neurosurgical procedures has not been proven. A theoretical argument could be made for eschewing the use of N₂O because of the possibility of introducing air emboli into the cerebral circulation, but there are no data to support this.

Anticoagulation

Careful management of coagulation is required to prevent thromboembolic complications during and after the procedures. Whether heparinization should be used for every case of intracranial catheterization is not clear to date. Generally, after a baseline activated clotting time (ACT) is obtained, i.v. heparin (70 units/kg) is given to a target prolongation of two to three times baseline. Heparin can then be given continuously or as an intermittent bolus with hourly monitoring of ACT. Occasionally, a patient may be refractory to attempts to obtain adequate anticoagulation. Switching from bovine to porcine heparin or vice versa should be
considered. If antithrombin III deficiency is suspected, administration of fresh-frozen plasma may be necessary. At the end of the procedure, heparin may need to be reversed with protamine.

Antiplatelet agents (aspirin, ticlopidine, and the glycoprotein IIb/IIIa receptor antagonists) are used quite extensively in patients with coronary stents, and may have great relevance for patients undergoing INR procedures. Activation of the glycoprotein IIb/IIIa receptor is a final common pathway for platelet aggregation. Abciximab (ReoPro), a chimeric murine–human monoclonal antibody that directly binds to the receptor, has been shown to decrease mortality and morbidity after coronary stenting [7]. Other agents in this class include the peptide receptor antagonists, Eptifibatide (Integriilin) and Tirofiban (Aggrastat).

These agents have various pharmacokinetic and pharmacodynamic properties. Based on experiences in coronary stenting, several basic observations on their use become clear. First, the effects of these agents on platelet aggregation are difficult to monitor clinically because there is no accurate bedside test of platelet aggregation. Second, the duration of the effects is approximately 12–24 hours. Rapid reversal of antiplatelet activity can only be achieved by platelet transfusion. Finally, use of these agents along with heparin may result in unexpected hemorrhage. Therefore, reducing procedural heparin dosage and early removal of vascular access sheaths should be carefully considered to decrease bleeding complications. The sustained long-term reduction in morbidity and mortality of coronary thrombosis patients (undergoing angioplasty/stenting or thrombolysis) by an antiplatelet agent has led to great interest for use in endovascular procedures of the CNS, but their use is not clearly defined in the setting of cerebrovascular disease.

Superselective anesthesia functional examination (SAFE)

SAFE is carried out to determine, prior to therapeutic embolization, if the tip of the catheter has been inadvertently placed proximal to the origin of nutritive vessels to eloquent regions, either in the brain or spinal cord [8]. Such testing is an extension of the Wada and Rasmussen test in which amobarbital is injected into the internal carotid artery to determine hemispheric dominance and language function. Its primary application is in the setting of brain arteriovenous malformation (BAVM) treatment, but it may also be used for tumor or other vascular malformation work. Prior to the testing, the patient should be fully awake from sedation or general anesthesia. Careful selection of motivated patients and preoperative teaching may decrease the anxiolytic requirements of these patients and ensure ideal testing conditions. This topic is reviewed elsewhere [4].

Deliberate hypotension

The two primary indications for induced hypotension are (1) to test cerebrovascular reserve in patients undergoing carotid occlusion, and (2) to slow flow in a feeding artery of BAVMs before glue injection.
The most important factor in choosing a hypotensive agent is the ability to safely and expeditiously achieve the desired reduction in blood pressure while maintaining the physiological stability of the patients. The choice of agent should be determined by the experience of the practitioner, the patient’s medical condition, and the goals of the blood pressure reduction in a particular clinical setting.

Intravenous adenosine has been used to induce transient cardiac pause, and may be a viable method of partial flow arrest [9,10]. Further study for its safety and efficacy is needed.

**Deliberate hypertension**

During acute arterial occlusion or vasospasm, the only practical way to increase collateral blood flow may be an augmentation of the collateral perfusion pressure by raising the systemic blood pressure. The Circle of Willis is a primary collateral pathway in cerebral circulation. However, in as many as 21% of otherwise normal subjects, the circle may not be complete. There are also secondary collateral channels that bridge adjacent major vascular territories, most importantly for the long circumferential arteries that supply the hemispheric convexities. These pathways are known as the pial-to-pial collateral or leptomeningeal pathways.

The extent to which the blood pressure has to be raised depends on the condition of the patient and the nature of the disease. Typically, during deliberate hypertension the systemic blood pressure is raised by 30–40% above the baseline or until ischemic symptoms resolve. Phenylephrine is usually the first line agent for deliberate hypertension, and is titrated to achieve the desired level of blood pressure.

**Management of neurologic and procedural crises**

Complications during endovascular instrumentation of the cerebral vasculature can be rapid and life threatening, and require a multidisciplinary collaboration. Having a well thought-out plan for dealing with intracranial catastrophe may make the difference between an uneventful outcome and death. Rapid and effective communication between the anesthesia and radiology teams is critical.

The primary responsibility of the anesthesia team is to preserve gas exchange and, if indicated, secure the airway. Simultaneous with airway management, the first branch in the decision-making algorithm is for the anesthesiologist to communicate with the INR team and determine whether the problem is hemorrhagic or occlusive. In the setting of vascular occlusion, the goal is to increase distal perfusion by blood pressure augmentation with or without direct thrombolysis. If the problem is hemorrhagic, immediate cessation of heparin and reversal with protamine is indicated. As an emergency reversal dose, 1 mg protamine can be given for each 100 units heparin total dosage during the case. The ACT can then be used to fine tune the final protamine dose.

Bleeding catastrophes are usually heralded by headache, nausea, vomiting, and vascular pain related to the area of perforation. Sudden loss of consciousness
is not always due to intracranial hemorrhage. Seizures, as a result of contrast reaction or transient ischemia, and the resulting post-ictal state can also result in an obtunded patient. In the anesthetized patient, the sudden onset of bradycardia or the radiologist’s diagnosis of extravasation of contrast may be the only clues to a developing hemorrhage.

**Postoperative management**

After INR procedures, patients spend the immediate postoperative period in a monitored setting to watch for signs of hemodynamic instability or neurologic deterioration. Blood pressure control, either induced hypotension or induced hypertension, may be continued during the postoperative period. Complicated cases may go first to CT or some kind of physiologic imaging such as single photon emission computed tomography (SPECT) scanning; only rarely is an emergent craniotomy indicated.

**Specific procedures**

*Brain arteriovenous malformations (BAVMs).*

BAVMs are typically large, complex lesions made up of a table of abnormal vessels (called the nidus) frequently containing several discrete fistulae [5]. They are often called cerebral or pial arterio-venous malformations. There are usually multiple feeding arteries and draining veins. The goal of the therapeutic embolization is to obliterate as many of the fistulae and their respective feeding arteries as possible. BAVM embolization is usually an adjunct for surgery or radiotherapy [11]. In rare cases, embolization treatment is aimed for total obliteration. SAFE is frequently used during BAVM embolization.

There are generally two schools of thought on how to manage anesthesia in the patient undergoing endovascular therapy, especially with permanent agents such as cyanoacrylate glues. One must rely on the knowledge of neuroanatomy and vascular architecture to ascertain the likelihood of neurologic damage after deposition of the embolic agents. The “anatomy” school, therefore, will prefer to embolize under general anesthesia. Arguments for this approach include improved visualization of structures with the absence of patient movement, especially if temporary apnea is used. Further, it is argued that if the glue is placed “intranidal,” then, by definition, no normal brain is threatened. There are two major concerns for this approach. A considerable variation in the normal localization of function exists, and cerebral pathology may cause neurologic function to shift from its native location to another one. The other school, which we might call the “physiologic” school, trades off the potential for patient movement for the increased knowledge of the true functional anatomy of a given patient. Localization of cerebral function may not always follow textbook descriptions, as described in
the section on SAFE. Furthermore, the BAVM nidus or a previous hemorrhage may result in a shift or relocalization of function. The “physiologic” approach demands, at the present, careful titration of sedation to wake the patient for SAFE before injection of embolic material.

The cyanoacrylate glues offer relatively “permanent” closure of abnormal vessels. Although less durable, polyvinyl alcohol microsphere embolization is also commonly used. If surgery is planned within days after PVA embolization, the rate of recanalization is low and PVA is felt to be easier and safer to work with. Advances in polymer development may obviate some of the risks of glue therapy.

**Dural arterio-venous malformations**

Dural AVM is currently considered an acquired lesion resulting from venous dural sinus stenosis or occlusion, opening of potential arterio-venous shunts, and subsequent recanalization. Symptoms are variable according to which sinus is involved. Dural AVMs may be fed by multiple meningeal vessels, and therefore, multistaged embolization is usually performed. SAFE is performed in certain vessels such as the middle meningeal artery and the ascending pharyngeal artery to evaluate the blood supply to peripheral cranial nerves and the possible existence of dangerous extra- to intracranial anastomosis. Complete obliteration is not always necessary considering the purpose of treatment, which is to reduce risk of bleeding or to alleviate symptoms. Subsequent spontaneous thrombosis can be expected in view of pathogenesis of this disease.

It is important to bear in mind that dural AV fistulas can induce increased venous pressure. Venous hypertension of pial veins is a risk factor for intracranial hemorrhage. Additionally, the venous hypertension should be factored into estimating safe levels of reductions in systemic arterial, and therefore, cerebral perfusion pressure.

**Carotid cavernous and vertebral fistulae**

Carotid cavernous fistulae (CCF) are direct fistulae usually caused by trauma to the cavernous carotid artery leading to communication with the cavernous sinus, usually associated with basal skull fracture. Treatment of CCF, a challenging surgical procedure, has become relatively easier with the development of detachable balloons [12]. Vertebral artery fistulae are connections to surrounding paravertebral veins, usually as a result of penetrating trauma, but may be congenital, associated with neurofibromatosis, or result from blunt trauma. In addition to cerebral involvement, spinal cord function may also be impaired.

**Vein of Galen malformations**

These are relatively uncommon but complicated lesions that present in infants and require a multidisciplinary approach including an anesthesiologist skilled in
the care of critically ill neonates. The patients may have intractable congestive heart failure, myocardial lesions, intractable seizures, hydrocephalus, and mental retardation [13].

**Spinal cord lesions**

Embolization may be used for intramedullary spinal AVMs, dural fistulae, or tumors invading the spinal canal. Often, general endotracheal anesthesia with controlled ventilation is used to provide temporary apnea that may increase the ability to see small spinal cord arteries at the limits of angiography imaging resolution and exquisitely sensitive to motion artifact. For selected lesions, intraoperative somatosensory and motor-evoked potentials may be helpful in both anesthetized and sedated patients. Intraoperative wake-up tests may be requested to test neurologic function during embolization.

In cases where wake-up tests might be needed, preoperative discussion of the logistics of the wake-up procedure and the testing process may facilitate the intraoperative management of this part of the procedure.

**Carotid test occlusion and therapeutic carotid occlusion**

Carotid occlusion, both permanent and temporary, may be used in several circumstances. Skull base tumors frequently involve the intracranial or petrous portion of the carotid artery or its proximal Willisian branches. Large or otherwise unclippable aneurysms may be partly or completely treated by proximal vessel occlusion. To assess the consequences of carotid occlusion in anticipation of surgery, the patient may be scheduled for a test occlusion in which cerebrovascular reserve is evaluated in several ways. A multimodal combination of angiographic, clinical, and physiologic tests can be used to arrive at the safest course of action for a given patient’s clinical circumstances. The judicious use of deliberate hypotension can increase the sensitivity of the test [14,15].

**Intracranial aneurysm ablation**

The two basic approaches for INR therapy of cerebral aneurysms are occlusion of proximal parent arteries and obliteration of the aneurysmal sac. The aneurysmal sac may be obliterated by use of coils and balloons. However, obliterating the aneurysmal sac while sparing the parent vessel is still challenging [16]. Manipulation of the sac may cause distal thromboembolism and rupture. Incomplete obliteration may result in recurrence and hemorrhage. The anesthesiologist should be prepared for aneurysmal rupture and acute SAH at all times, either from spontaneous rupture of a leaky sac or direct injury of the aneurysm wall by the vascular manipulation. It should be noted after coil ablation of aneurysms, that at the present time, there is not the same degree of certainty that
the lesion has been completely removed from the circulation as with application
of a surgical clip. There may be areas of the aneurysmal wall that are still in
contact with the arterial blood flow and pressure. Therefore, attention to post-
operative blood pressure control is warranted.

Balloon angioplasty of cerebral vasospasm from aneurysmal SAH

Angioplasty may be used to treat symptomatic vasospasm with correlating
angiographic stenosis refractory to maximal medical therapy [17]. Angioplasty is
usually reserved for patients that have already had the symptomatic lesion sur-
gically clipped (for fear of rerupture), or for patients in the early course of symp-
tomatic ischemia to prevent transformation of a bland infarct into a hemorrhagic
one. A balloon catheter is guided under fluoroscopy into the spastic segment and
inflated to mechanically distend the constricted area.

It is also possible to perform a “pharmacologic” angioplasty. There is the
greatest experience with papaverine, but there are potential CNS toxic effects (see
ref. [18] for a review), but other agents such as calcium channel blockers may
find a place for this purpose.

Sclerotherapy of venous angiomas

Craniofacial venous malformations are congenital disorders causing significant
cosmetic deformities, that may impinge on the upper airway and interfere with
swallowing. Absolute alcohol (95% ethanol) opacified with contrast is injected
percutaneously into the lesion, resulting in a chemical burn to the lesion and
eventually shrinking it. The procedures are short (30–60 minutes) but painful, and
general endotracheal anesthesia is used. Complex airway involvement may require
endotracheal intubation with fiberoptic techniques [19]. Because marked swelling
often occurs immediately after alcohol injection, the ability of the patient to
maintain a patent airway must be carefully assessed in discussion with the
radiologist before extubation. Alcohol has several noteworthy side effects. First,
upon injection it can cause changes in the pulmonary vasculature and create a short-
lived shunt or a ventilation-perfusion mismatch. Desaturation on the pulse
oximeter is frequently noted after injection. Absolute alcohol may also cause
hypoglycemia, especially in younger children. Finally, the predictable intoxication
and other side effects of ethanol may be evident after emergence from anesthesia.

Angioplasty and stenting for atherosclerotic lesion

Angioplasty with or without stenting for atherosclerosis has been tried in
cervical and intracranial arteries with favorable results [20, 21]. Risk of distal
thromboembolism is the major issue to be resolved in this procedure and methods.
A catheter system that employs an occluding balloon distal to the angioplasty
balloon has been proposed [22]. Carotid angioplasty and stenting may provide a therapeutic option for patients particularly at risk of surgery. However, efficacy and indications in relation to carotid endarterectomy remain to be determined.

Preparation for anesthetic management include, in additional to the usual monitors and considerations already discussed, placement of transcutaneous pacing leads in case of severe bradycardia or asystole from carotid body stimulation during angioplasty. Intravenous atropine or glycopyrrolate may be used in an attempt to mitigate against bradycardia, which almost invariably occurs to some degree with inflation of the balloon. This powerful chronotropic response may be difficult or impossible to prevent or control by conventional means. If indicated by hemodynamic instability, the anesthesiologist must have the ability to immediately administer advanced cardiac life support, including catecholamine and temporary cardiac pacing therapy.

Potential complications include vessel occlusion, perforation, dissection, spasm, thromboemboli, occlusion of adjacent vessels, transient ischemic episodes, and stroke. Furthermore, compared to carotid endarterectomy, there appears to be an increased incidence of cerebral hemorrhage and/or brain swelling after carotid angioplasty [23]. Although the etiology of this syndrome is unknown, it has been associated with cerebral hyperperfusion, and it may be related to poor postoperative blood pressure control.

Thrombolysis of acute thromboembolic stroke

In acute occlusive stroke, it is possible to recanalize the occluded vessel by superselective intra-arterial thrombolytic therapy. Thrombolytic agents can be delivered in high concentration by a microcatheter navigated close to the clot. Neurologic deficits may be reversed without additional risk of secondary hemorrhage if treatment is completed within 6 hours from the onset of carotid territory ischemia and 24 hours in vertebrobasilar territory. One of the impediments in development in this area has been the fear of increasing the risk of hemorrhagic transformation of the acute infarction patient. Despite an increased frequency of early symptomatic hemorrhagic complications, treatment with intra-arterial pro-urokinase within 6 hours of the onset of acute ischemic stroke with middle cerebral artery (MCA) occlusion significantly improved clinical outcome at 90 days [24].

Important points and objectives

There is a rapidly expanding list of application of INR procedures in the field of the treatment of CNS disease. Anesthesiologists should be familiar with specific procedures and their potential complications. Constant and effective communication between the anesthesia and radiology teams is critical to safely carry out INR procedures and to deal with intracranial catastrophe.
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References


Methylprednisolone for acute spinal cord injury: not a standard of care

Herman Hugenholtz

It is time to clear the confusion about the utility of steroids in cases of acute spinal cord injury. A committee of Canadian neurosurgical and orthopedic spine specialists, emergency physicians and physiatrists (listed at the end of the article) has reviewed the evidence and concluded that high-dose methylprednisolone infusion is not an evidence-based standard of care for patients with such an injury.1

The consequences of a spinal cord injury are often devastating, and any possibility of mitigating neurologic loss is attractive. To this end, management of acute spinal cord injuries has included the use of steroids for the past 30 years, based in large part on physiological hypotheses with limited clinical support.2-3 Mechanical injury to the spinal cord initiates a cascade of secondary events that include ischemia, inflammation and calcium-mediated cell injury. Animal experiments have shown that methylprednisolone exhibits potential neuroprotective effects through its inhibition of lipid peroxidation and calcium influx and through its anti-inflammatory effects.4,5 Three well-designed, large, randomized clinical trials (the National Acute Spinal Cord Injury Studies [NASCIS I, II and III]) examined the effect of steroid administration in patients with acute spinal cord injury.6-11

NASCIS I examined the change in motor function in specific muscles and changes in light touch and pinprick sensation from baseline.6-7 The study detected no benefit from methylprednisolone, but the dose was considered to be below the therapeutic threshold determined from animal experiments. Therefore, NASCIS II used a much higher dose, and patients were randomly assigned to receive a 24-hour infusion of methylprednisolone, naloxone or placebo within 12 hours after acute spinal cord injury.8-9 Again, there was no benefit overall in the methylprednisolone group; however, post hoc analyses detected a small gain in the total motor and sensory score in a subgroup of patients who had received the drug within 8 hours after their injury.8-9 As a result, this 24-hour, high-dose methylprednisolone infusion, if started within 8 hours after injury, quickly became an implied standard of care despite considerable criticism of the validity of such a post hoc analysis.10

Subsequent clinical trials have provided conflicting evidence about steroid treatment in acute spinal cord injury. A Japanese study attempted to replicate the results seen in the 8-hour subgroup from NASCIS II and reported improved function at 6 months in a larger number of muscles and sensory dermatomes among subjects who received high-dose methylprednisolone infusion than among those who received only low doses of the drug or no drug.12 However, the study lacked detail about randomization and outcome measures, and it included only 74% of the enrolled subjects in the outcome analysis. Conversely, an underpowered prospective randomized trial that used a methylprednisolone regimen similar to that used in NASCIS II found no improvement in motor and sensory scores at 1 year.13,14 NASCIS III compared a 48-hour infusion of methylprednisolone with a 24-hour infusion started within 8 hours after injury and found no benefit from extending the infusion beyond 24 hours. Again, only post hoc analysis showed a benefit from extending the infusion to 48 hours when treatment was started between 3 and 8 hours after injury. No other study has verified the primary outcome of 48 hours versus 24 hours or the post hoc conclusion of benefit from starting treatment between 3 and 8 hours after injury.

A meta-analysis of all of the trials concluded, on the basis of the controversial subgroup post hoc analyses in NASCIS II and III and the data from the Japanese study, that a 24-hour high-dose methylprednisolone infusion within 8 hours after injury is efficacious.15 Despite this meta-analysis, the efficacy of such a regimen remains uncertain and will require further study. The controversy about the post hoc analyses of NASCIS data continues,16-23 and unfortunately the studies that could have clarified the efficacy of such a regimen have lacked the rigour to do so.

Steroid therapy is not without risk. Most patients with acute spinal cord injury are treated in intensive care units, have polytrauma, have impaired lung capacity and are vulnerable to sepsis. In all 3 NASCIS studies and other, smaller studies, the incidence of sepsis and pneumonia was higher in the high-dose methylprednisolone groups than in the placebo or other treatment groups;6-11,24-26 the differences were not significant except in NASCIS III. Hyperglycemia and gastrointestinal complications were also reported following high-dose methylprednisolone treatment.11,24 Therefore, it has been proposed that, without compelling evidence for its efficacy, methylprednisolone should be used with caution and may even be harmful, particularly if infusion goes beyond 24 hours.17

The cost of a 24-hour methylprednisolone infusion is not prohibitive, and a gain of antigravity strength in one or more muscles below a spinal segment can provide an impor-
tant functional gain, especially for patients with cervical spinal cord injuries. Therefore, even the small improvement observed in the NASCIS subgroups could be viewed as a benefit in cases of complete or incomplete cervical cord injury. Despite the risk of complications and as long as the outcomes in the NASCIS subgroups remain a possibility, physicians may still opt to administer a high-dose methylprednisolone infusion within 8 hours after injury. However, they should no longer feel compelled to do so. Physicians who conduct the initial triage and resuscitation of patients with acute spinal cord injury should consult their specialist colleagues who will be continuing the care of these patients regarding their preference for methylprednisolone infusion.

The Canadian Neurosurgical Society, the Canadian Spine Society and the Canadian Association of Emergency Physicians have adopted the committee’s recommendation that a high-dose, 24-hour infusion of methylprednisolone started within 8 hours after an acute closed spinal cord injury is not a standard treatment nor a guideline for treatment but, rather, a treatment option, for which there is very weak level II and III evidence.27

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Dr. Hugenholtz is with the Division of Neurosurgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS.

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References


Correspondence to: Dr. Herman Hugenholtz, New Halifax Infirmary, Rm. 3808, 1796 Summer St., Halifax NS B3H 3A7; fax 902 473-8912

Members of the Committee of the Canadian Spine Society and the Canadian Neurosurgical Society to Review the Role of Methylprednisolone in Acute Spinal Cord Injury: Herman Hugenholtz (chair), Division of Neurosurgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS; Nirmala D. Bharatwal, Toronto Rehabilitation Institute, Toronto, Ont.; Dan E. Cass, Director of Emergency Services, St. Michael’s Hospital, Toronto, Ont.; Marcel F. Dvorak, Medical Director, Combined Spine Program, Vancouver Hospital and Health Sciences Centre, Vancouver, BC; Derek Fewer, Section of Neurosurgery, University Health Network, Toronto, Ont.; Richard J. Fox, Department of Neurosurgery, Walter C. Mackenzie Health Science Centre, University Hospital, Edmonton, Alta.; Dennis M.S. Izukawa, Department of Neurosurgery, Trillium Health Centre, Mississauga, Ont.; Joel Lexchin, Emergency Department, University Health Network, Toronto, Ont.; Christine Short, Nova Scotia Rehabilitation Centre, Halifax, NS; and Sagun Tuli, Department of Neurosurgery, Brigham and Women’s Hospital, Boston, Mass.
Pathogenesis of spinal cord injury during spinal surgery

Patients at risk for persistent neurological injury following spinal surgery are those with preoperative neurological deficit (tumour, spinal stenosis, disc herniation). Operative procedures associated with greater risk for spinal injury include the passage of sub laminar wires, thoracic pedicle screws, distraction derotation manoeuvres, osteotomies, segmental vessel ligation, and combined anterior-posterior fusion. For example, an inappropriately sized laminar hook or the osteotome may cause direct contusion to the spinal cord. Sub laminar wires can cause direct cord trauma. The risk of neurological damage with pedicle screw placement increases the higher up in the spinal column surgery is performed. Furthermore, rotational deformities make placement of pedicle screws more difficult. During scoliosis surgery the application of corrective forces is another potential cause of cord damage. Furthermore, neurological complications are more likely in longer cases and those with large blood losses. Large time-temperature integrals are linked to complications, suggesting that it is the quantity of hypothermia rather than the nadir temperature that is a risk factor.

In summary, mechanisms of spinal cord injury include ischaemia, compression and over distraction / rotation. Nerve root injury (C5 injury has an incidence as high as 12.9% after laminectomy) is attributed to posterior migration and expansion of the spinal cord and oedema of the affected root.

Anatomy relevant to spinal cord monitoring

Figure 1: Motor and sensory pathways of the spinal cord.
The lateral and anterior corticospinal tracts subserve voluntary movement. From the primary motor cortex the upper motor neuron axon descends via the internal capsule to the medulla oblongata. 85% of the motor fibres cross the midline at the pyramidal decussation to descend contralaterally as the lateral corticospinal tract. 15% do not cross the midline and descend ipsilaterally as the anterior spinal tract. A functional corticospinal tract is necessary for recording motor evoked potentials (MEPs) and the Stagnara wake-up test.

The dorso-medial sensory tracts subserve touch, proprioception and vibration. From the dorsal root ganglion the primary sensory neuron runs ipsilaterally in the dorsal aspect of the spinal cord to the medulla oblongata. After synapsing the second order neuron crosses the midline and projects to the thalamus. From here the third order neurons project to the primary somatosensory cortex. This path must be intact to record somatosensory evoked potentials (SSEPs).

**Figure 2: Transverse section through spinal cord at T6.**

The blood supply of the spinal cord is from the anterior spinal artery (formed by the union of a branch from each vertebral artery), which supplies the anterior two thirds of the cord including the corticospinal tracts (unshaded area *fig 2*). The posterior spinal arteries (derived from the posterior cerebellar arteries) supply the posterior third of the cord including the dorsomedial columns (shaded area *fig 2*). These arteries are reinforced by a variable number of medullary feeding arteries from the vertebral arteries in the cervical region, and vessels from the aorta in the thoracic and lumbar regions (including the Artery of Adamkiewicz).

**Spinal cord monitoring**

The incidence of motor deficit or paraplegia after scoliosis surgery without spinal cord monitoring is between 3.7 and 6.9% [1, ii, iii, viii, ix]. This figure may be reduced to 0.5% when intraoperative monitoring (IOM) is used. [x]

Ideally, IOM should detect changes in spinal cord function early, allowing the surgeon and anaesthesiologist to take action to prevent irreversible damage. The disturbing fact is that the time between onset of changes in electrophysiological recordings and permanent ischaemic damage of the cord with over distension is only 5 – 6 minutes in animal studies. [xi]
A. Clinical tests

1. Ankle clonus test

This test is performed during emergence at the end of surgery or during the wake-up test. The foot is sharply dorsiflexed at the ankle joint. Spinal cord injury is indicated by complete absence of clonus. The test is based on a number of physiological principles: In the awake individual, higher cortical centres have a descending inhibitory influence on the reflex, and clonus is not elicited on ankle joint dorsiflexion. During anaesthesia there is a loss of this descending inhibition, and clonus can be elicited during emergence in the neurologically intact individual. Spinal cord injury results in a period of spinal shock with a loss of reflex activity and consequently a flaccid paralysis – no ankle clonus can be elicited. Obviously neuromuscular paralysis must be completely reversed before performing this test.

Although this test has both a high sensitivity (100%) and specificity (99.7%) xii, there are a number of problems. The test can only be performed intermittently. Advances in surgical methods have changed the period of neural risk from one identifiable event (distraction) to multiple, potentially deleterious events (sub laminar wires, multiple hooks, pedicle screws). A more continuous form of monitoring has become mandatory. Furthermore, the absence of clonus has other causes besides cord damage: inadequate or too great a depth of anaesthesia. xiii

2. Stagnara wake-up test

In 1973 this test was described by Vauzelle and Stagnaraxiv and evaluates the functional integrity of the motor pathways (lower + upper motor neurons and muscles). Integrity of peripheral sensory function is not assessed. Preoperatively the patient is told that he will be woken and asked to perform a motor function. Usually they are instructed to first perform an action involving muscle groups above the level of potential cord damage e.g. grip the anaesthesiologist’s fingers. Following a positive response, the patient is subsequently instructed to move his legs. If the patient is unable to respond corrective measures are instituted immediately.

The technique has a number of disadvantages. It requires the patient’s cooperation and poses risks to the patient of falling from the operating table and of tracheal extubation. It requires skill from the anaesthesiologist. As with the ankle clonus test, it does not allow continuous IOM of motor pathways. The onset of a change in electrophysiological recordings and permanent neurological injury can occur more than 20 minutes after the last corrective force is applied to the spine.xv

Because of the limitations of the wake-up test, neurophysiologic monitoring of the spinal cord has become a preferred method of optimising safety during spinal surgery. If reliable monitoring is in place, the wake-up test can be omitted.xv
B. Neurophysiologic monitoring

Neurophysiologic monitoring methods are based on evoking electrical potentials and quantifying these potentials as an assessment of an otherwise silent neural tract. These evoked electrical potentials are extremely small, necessitating digital signal averaging to resolve them from the much longer EEG and ECG activity. This method entails repeatedly stimulating the nervous system and measuring the response for a set window of time (needed to resolve the evoked neural activity from other electrical activity). The evoked response becomes apparent because this unwanted background activity is unrelated to the stimulus and thus averaged out. The peaks and valleys of the evoked response are thought to arise from specific neural generators (often more than one neural structure per peak) and therefore can be used to follow the response at various points along the stimulated tract. 

Several studies have confirmed the efficacy and cost effectiveness of intraoperative monitoring. The American Academy of Neurology has concluded that “considerable evidence favours the use of monitoring as a safe and efficacious tool in clinical situations where there is a significant nervous system risk, provided its limitations are appreciated.”

1. Somatosensory evoked potentials (SSEP)

This is the electrophysiological technique that is probably used most extensively for spinal cord monitoring. SSEP are elicited by stimulating electrically a mixed peripheral nerve (usually post. tibial, peroneal, ulnar or median), and recording the response from electrodes at sites cephalad to the level at which the surgery is performed. Dermatomal, rather than mixed nerve stimulation is less frequently used. In these cases, electrodes are applied that stimulate the sensory fibres innervating the skin surface, or alternatively the underlying muscle groups. In theory, proper placement of electrodes will monitor responses mediated by a single nerve root.

With mixed nerve SSEP stimulation sites are chosen because of easily identifiable anatomical landmarks. To stimulate the median nerve, the cathode of the stimulating pair of electrodes is placed 2 – 4 cm proximal to the wrist crease between the tendons of flexor carpi radialis and palmaris longus. The anode is placed 2 – 3 cm distal to cathode to avoid anodal block. For ulnar nerve stimulation the cathode is placed 2 – 4 cm proximal to the wrist crease on either side of the tendon of flexor carpi ulnaris. Stimulation of the posterior tibial nerve is done at the ankle between the medial malleolus and the Achilles tendon. To stimulate the peroneal nerve the cathode is placed distal to the lateral aspect of the knee and slightly medial to the head of the fibula.

Typically the stimulus is applied to the peripheral nerve on the left and the right limb alternately as a square wave for 0.1 – 0.3 ms, at a rate of 3 – 5 Hz. The intensity varies, depending on the electrodes and quality of skin contact, a current of 25 – 40 mA is used.
Recording electrodes are placed in the cervical region over the spinous processes or over the somatosensory cortex on the scalp, or are sited during surgery in the epidural space. Baseline values are obtained after skin incision to ensure a stable plane of anaesthesia as anaesthetic agents affect SSEPs.

Responses are recorded repeatedly during surgery and the functional integrity of the somatosensory pathways is determined by comparing amplitude and latency changes of the responses obtained during surgery to baseline values. A significant response is considered one in which a 50% reduction in amplitude and 10% increase in latency is recorded.

The pathways involved in the recorded responses include a peripheral nerve, the dorsomedial tracts of the spinal cord, and the cerebral cortex (when cortex electrodes are used). It is currently thought that upper limb SSEP represents primarily the activity in the spinal pathways of proprioception and vibration (posterior column) The response from the lower limbs probably includes a contribution from the antero-lateral spinal cord (pain + temperature) dorsal spino cerebellar pathways in addition to posterior column activity. Because of the close proximity of the dorsomedial sensory tracts with the motor tracts in the cord, it is assumed that when using SSEPs, any damage to the motor tracts will be signalled by a change in SSEPs. THIS CANNOT BE GUARANTEED. Furthermore, the blood supply of the anteriorly situated corticospinal tracts comes from the anterior spinal artery, while the posteriorly situated dorsomedial tracts are supplied by the posterior spinal arteries. It is, therefore, possible to have normal SSEP recordings throughout surgery, but have a paraplegic patient postoperatively. Another limitation is that in patients with pre-existing neurological disorders reliable data can only be collected in 75 – 85% of patients.

For monitoring purposes TIVA is the best choice. When SSEP’s alone and no motor evoked potentials are monitored, an alternative is inhalational agent at <0.5 MAC without N₂O.

*Effectiveness of SSEP*

A large retrospective study including over 51 000 cases, showed SSEP to have a sensitivity of 92% and specificity of 98.9% The false negative rate was 0.127% (normal SSEP throughout the procedure but neurological deficit post op) The false positive rate was 1.5% (SSEP changed, but no new neurological deficit post op).

SSEP is currently the “gold-standard” of spinal cord monitoring with a proven record. It is a reliable technique with a high sensitivity and specificity for early detection of neurological deficit.

**2. Motor evoked potentials (MEP)**

MEPs are neuroelectric events elicited from descending motor pathways: corticospinal tracts → spinal cord interneurons → anterior horn cells →
peripheral nerves → skeletal muscle innervated by alpha motor neurons. In contrast to the white matter-mediated sensory neurons monitored with SSEP, the corticospinal axons that originate in the motor cortex enter the spinal cord grey matter. In the grey matter corticospinal tract axons interact with spinal interneurons that synapse with alpha motor neurons that innervate skeletal muscles.

**MEP monitoring techniques are subdivided according to:**

**Site of stimulation:**
- Motor cortex or spinal cord

**Method of stimulation:**
- Electrical potential
- Magnetic fields

**Site of recording:**
- Spinal cord
- Peripheral mixed nerve
- Muscle

The principles of all the above techniques are similar: Stimulation cranial to the site of surgery causes prodromic stimulation of motor tracts in the spinal cord, and of peripheral nerve and muscle caudal to the site of surgery. A compromised motor pathway results in a reduction in amplitude and an increase in latency of the recorded response.

The motor cortex can be stimulated by electrical or magnetic means. Magnetic stimulation equipment is bulky but has the advantage of not being affected by the quality of electrode contact.

Recorded responses may be either myogenic or neurogenic. Myogenic responses result from the summed EMG activity in a muscle in response to stimulation. Neurogenic recordings result from the summed electrical activity in a peripheral nerve or the spinal cord. Responses recorded from the spine consist of a direct or D wave representing the direct activation of the corticospinal tract cells by the transcranial stimulus. In awake or lightly anaesthetised patients, the D wave is followed by a series of I waves (indirect waves) generated by cortical synapses.

The advantage of recording EMG responses is their large amplitude, but the main disadvantage is the variable morphology of EMG waves. When EMG recording is done, the depth of neuromuscular relaxation is critical: if too deep no response is obtained; if residual block only, violent movement in response to stimulation could cause injury. It is therefore recommended that neuromuscular blocking agents be administered by continuous infusion. The depth of blockade should be maintained at first twitch of train-of-four at 10 – 20% of control.

Neurogenic responses are not affected by neuromuscular blockade, and are more reliable in terms of morphology.
Spontaneous EMG (spEMG) can be used to monitor for injury to spinal nerve roots. In this case the stimulus is involuntary: decompression, hook / screw insertion, removal of bony fragments, tumour resection or traction on a spinal root will provoke ion depolarisation, and the resultant motor unit potential can be recorded from the muscle innervated by that specific nerve root. These events are observed as discrete EMG “bursts”.

Stimulus evoked electromyography (stEMG) is another useful technique during pedicular screw placement. The technique involves applying an electrical stimulus to the pedicle screw and recording EMG activity from muscles innervated by the nerve root adjacent to the pedicle. If the pedicle wall is fractured, the nerve root will depolarise at a much lower current (< 7mA) compared with an intact pedicle.

A TIVA technique using propofol and an opioid (fentanyl or remifentanil) has been advocated for providing adequate MEP recording in 7% of cases when multiple pulse stimulation is used.

**Effectiveness of MEPs**

MEP monitoring is less reliable in patients with preoperative neurological deficit. Sensitivity of MEP is not 100%, especially when neurogenic MEPs are used. Neurogenic spinal evoked potentials are mediated through pathways that are responsible for SSEPs, thus measuring sensory rather than motor function, and offering an explanation for the false negative cases.

MEP is complementary to SSEP, rather than a replacement. The wake-up test is reserved for situations where neurophysiological monitoring is not available / possible, or responses are significantly compromised.

**Conclusion**

The detection of emerging injury through intraoperative neurological monitoring is the best way to prevent neurologic injury during spinal surgery. Intraoperative care in the ideal setting should include neurological monitoring and interpretation by a team comprising the anaesthesiologist, neurophysiologist and surgeon.

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SPINAL CORD MONITORING AND PROTECTION DURING SPINAL SURGERY

A. Travers

Pathogenesis of spinal cord injury during spinal surgery

Patients at risk for persistent neurological injury following spinal surgery are those with preoperative neurological deficit (tumour, spinal stenosis, disc herniation). Operative procedures associated with greater risk for spinal injury include the passage of sub laminar wires, thoracic pedicle screws, distraction derotation manoeuvres, osteotomies, segmental vessel ligation, and combined anterior-posterior fusion. For example, an inappropriately sized laminar hook or the osteotome may cause direct contusion to the spinal cord. Sub laminar wires can cause direct cord trauma. The risk of neurological damage with pedicle screw placement increases the higher up in the spinal column surgery is performed. Furthermore, rotational deformities make placement of pedicle screws more difficult. During scoliosis surgery the application of corrective forces is another potential cause of cord damage. Furthermore, neurological complications are more likely in longer cases and those with large blood losses. Large time-temperature integrals are linked to complications, suggesting that it is the quantity of hypothermia rather than the nadir temperature that is a risk factor.

In summary, mechanisms of spinal cord injury include ischaemia, compression and over distraction / rotation. Nerve root injury (C5 injury has an incidence as high as 12.9% after laminectomy) is attributed to posterior migration and expansion of the spinal cord and oedema of the affected root.

Anatomy relevant to spinal cord monitoring

Figure 1: Motor and sensory pathways of the spinal cord.
The lateral and anterior corticospinal tracts subserve voluntary movement. From the primary motor cortex the upper motor neuron axon descends via the internal capsule to the medulla oblongata. 85% of the motor fibres cross the midline at the pyramidal decussation to descend contralaterally as the lateral corticospinal tract. 15% do not cross the midline and descend ipsilaterally as the anterior spinal tract. A functional corticospinal tract is necessary for recording motor evoked potentials (MEPs) and the Stagnara wake-up test.

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**Figure 2: Transverse section through spinal cord at T6.**

The blood supply of the spinal cord is from the anterior spinal artery (formed by the union of a branch from each vertebral artery), which supplies the anterior two thirds of the cord including the corticospinal tracts (unshaded area fig 2). The posterior spinal arteries (derived from the posterior cerebellar arteries) supply the posterior third of the cord including the dorsomedial columns (shaded area fig 2). These arteries are reinforced by a variable number of medullary feeding arteries from the vertebral arteries in the cervical region, and vessels from the aorta in the thoracic and lumbar regions (including the Artery of Adamkiewicz).

**Spinal cord monitoring**

The incidence of motor deficit or paraplegia after scoliosis surgery without spinal cord monitoring is between 3.7 and 6.9%\(^I, ii, iii, viii\),\(^ix\). This figure may be reduced to 0.5% when intraoperative monitoring (IOM) is used.\(^x\)

Ideally, IOM should detect changes in spinal cord function early, allowing the surgeon and anaesthesiologist to take action to prevent irreversible damage. The disturbing fact is that the time between onset of changes in electrophysiological recordings and permanent ischaemic damage of the cord with over distension is only 5 – 6 minutes in animal studies.\(^{xi}\)
A. Clinical tests

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Although this test has both a high sensitivity (100%) and specificity (99.7%) \( \text{xii} \), there are a number of problems. The test can only be performed intermittently. Advances in surgical methods have changed the period of neural risk from one identifiable event (distraction) to multiple, potentially deleterious events (sub laminar wires, multiple hooks, pedicle screws). A more continuous form of monitoring has become mandatory. Furthermore, the absence of clonus has other causes besides cord damage: inadequate or too great a depth of anaesthesia. \( \text{xiii} \)

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