Spinal Cord Protection for Thoracic Aortic Surgery: Bench to Bedside

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This article summarizes the anatomically driven pathophysiology of spinal cord injury, the impact of ischemia reperfusion on the cellular level, current research in developing neuronal ischemic tolerance, and promotion of collateralization. It addresses neuroprotective strategies in modern clinical practice, current pharmacologic interventions, and continued challenges in the management of complex aortic disease. The pathophysiology of spinal cord injury includes disruption and recovery of collateral blood flow and the effects of malperfusion on the spinal cord. The optimal approach to spinal cord protection is to employ an integrated and protocolized set of strategies to simultaneously maximize spinal cord blood flow, improve ischemic tolerance, and promote collateralization. In the laboratory setting, investigation should continue to pursue a more granular understanding of ischemic injury and seek to translate protective therapies to clinical practice.

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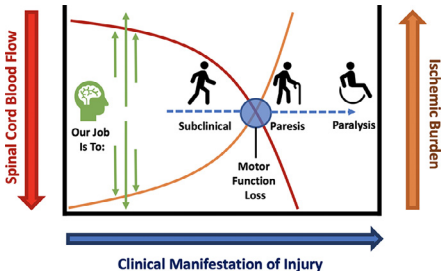

Preventing spinal cord injury: Maximize blood flow and increase ischemic tolerance.

Central Message

Approach to spinal cord protection: Maximize spinal cord blood flow, improve ischemic tolerance, and promote collateralization.

INTRODUCTION

Spinal cord injury (SCI) remains a devastating complication following descending thoracic aortic (DTA) and thoracoabdominal aortic (TAA) intervention. Improved understanding of the pathophysiology of SCI, implementation of neuroprotective strategies, and advances in surgical technique have led to a decreased incidence of SCI, however paraplegia persists. The incidence of SCI ranges from 2.9% to 16% in large series of open TAA operations[1,2] and 3% to 13% of endovascular DTA/TAA repairs.[3]

SCI clinically manifests as lower extremity paraparesis or paralysis, and the extent of neurologic injury ranges from temporary motor deficits to complete paralysis. Permanent neurologic deficits are associated with increased morbidity, increased short- and mid-term mortality,[4–6] increased healthcare costs,[7] and decreased quality of life.[8] In a retrospective analysis of 224 open DTA and TAA operations, patients with SCI had a mortality of 39% compared to 14% without SCI.[5]

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As experience has grown so has the understanding of factors that influence the occurrence of SCI. These risk factors (summarized in Table 1) include surgical acuity, dissection etiology, extent of aortic replacement or coverage, prior operation on any portion of the thoracoabdominal aorta, extent of segmental artery (SA) sacrifice, loss of collateral blood flow – particularly from the internal iliac and subclavian arteries, duration of cross clamping, hypotension, and anemia.[9,10]

Although embolization and permanent segmental perfusion disruption can occur, they are not reversible. The most common SCI is primarily precipitated by temporary interruption of spinal cord blood flow (SCBF) during intraoperative aortic clamping or longer term reduction of flow in the setting of SA sacrifice. This leads to an initial ischemic insult in watershed regions and is followed by a delayed inflammatory response after reperfusion that causes a secondary insult. While collateral perfusion is thought to recover relatively quickly, the extent of neuronal damage depends on the timeliness of collateral recovery relative to the neuronal ability to tolerate malperfusion. Embolic ischemic injury has been suggested to play a role,[10] but the low-flow state is the dominant mechanism. Therefore, clinically, our purpose is to prevent ischemia from occurring in the watershed region at all. On the cellular level, our goal is to improve ischemic tolerance. Figure 1 illustrates the relationship between SCBF, increasing ischemic burden, and clinical manifestations of SCI.

Table 1. Risk Factors for Spinal Cord Ischemia

Preoperative	• Surgical acuity
	• Dissection etiology and associated malperfusion
	• Prior operation on any portion of the thoracoabdominal aorta
	• Age, diabetes, renal dysfunction, or COPD
Intraoperative	• Extent of aortic replacement or coverage
	• Extent of segmental artery sacrifice
	• Loss of collateral blood flow from the subclavian or internal iliac arteries
	• Duration of cross clamping
	• Hypotension, hypoxia, or anemia
Postoperative	• Hypotension, hypoxia, or anemia

COPD, chronic obstructive pulmonary disorder.

In this article, we will review the anatomically driven pathophysiology of SCI, the impact of ischemia reperfusion on the cellular level, current research in developing neuronal ischemic tolerance, and promotion of collateralization. We will then discuss neuroprotective strategies in modern clinical practice, current pharmacologic interventions, and continued challenges in the management of complex aortic disease.

BASIC SCIENCE

Anatomy of Spinal Cord Perfusion

Segmental arterial blood flow to the spinal cord originates from branches of the subclavian arteries (vertebral, ascending cervical, and deep cervical), intercostal arteries, lumbar arteries, and lateral sacral arteries which arise from the internal iliac arteries (Fig. 2). Three longitudinal arteries run along the spinal cord and are directly responsible for supplying its flow: the anterior spinal artery and 2 posterior spinal arteries. The anterior spinal artery gives off sulcal arteries which supply the ventral two-thirds of the cord and the posterior spinal arteries supply the dorsal third (Fig. 3).[11] Superiorly, the longitudinal arteries initiate their course from vertebral artery branches and are reinforced by anterior and posterior segmental medullary arteries, which are formed by spinal branches of the SAs. The largest of the anterior segmental medullary arteries is the great anterior segmental medullary artery (artery of Adamkiewicz), arising at the level of T8-L1 in a majority of individuals, and provides a significant proportion of flow to this region of the spine.[12,13] Historically, bias was to focus on finding and preserving this artery, but an evolving understanding of SCBF has shifted our paradigm to a more global collateral recovery approach.

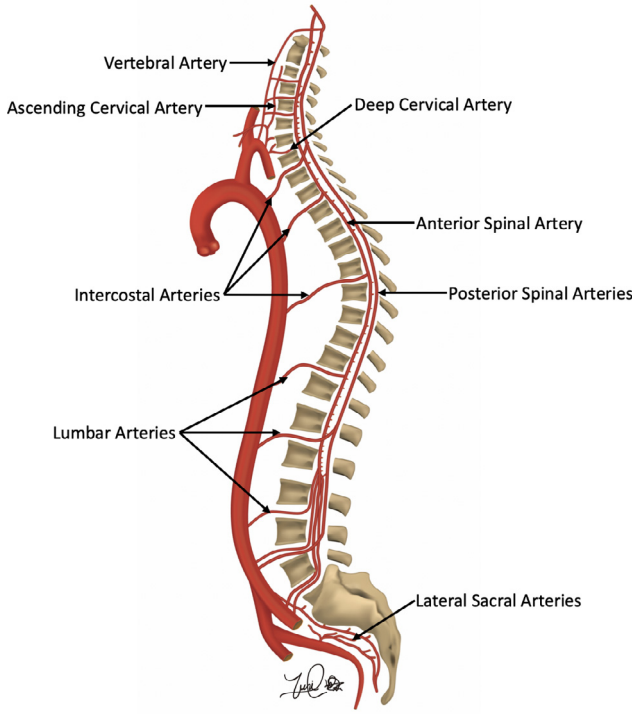

Figure 2. Global blood flow to spinal cord.

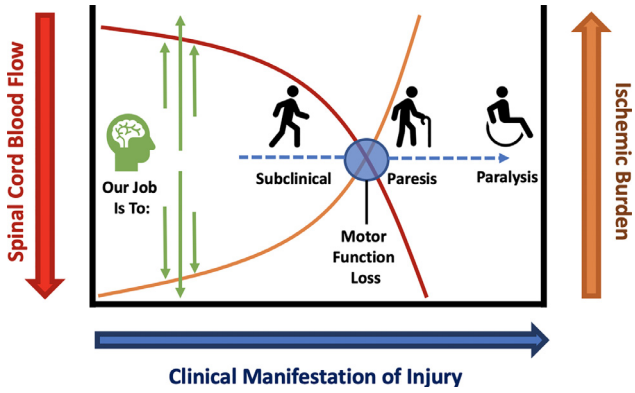

Figure 1. Decreasing spinal cord blood flow and increasing ischemic burden lead to clinical manifestations of spinal cord injury, ranging from paraparesis to complete paralysis. Our job is to maximize spinal cord blood flow and minimize ischemic burden/bolster ischemic tolerance to prevent spinal cord injury.

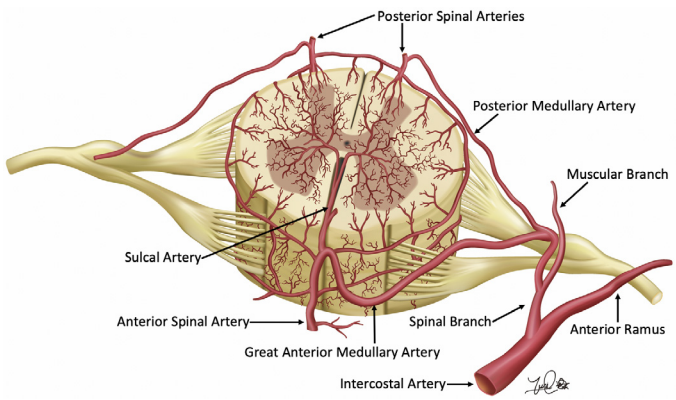

Figure 3. Spinal cord blood flow at the level of the distal thoracic or proximal abdominal aorta where the artery of Adamkiewicz can be found in a majority of patients. Rendering inspired by figure from Martirosyan et al.[11]

Griepp's Collateral Network Concept

In the last 2 decades, Dr. Griepp has fundamentally changed the way we understand the anatomy and physiology of spinal cord perfusion. Anatomic studies demonstrated that there is a dense network of collaterals between the vasculature of the paraspinous muscles and the adjacent spinal cord. Arteries within the spinal canal form multiple anastomoses cranially and caudally, and this network forms connections to the subclavian arteries, internal iliac arteries, and internal thoracic arteries through the intercostals. Notably, the volume and density of the collateral network is far greater than that of the SAs directly supplying the spinal cord.[14] Physiologic studies showed that spinal cord perfusion pressure (SCPP) is approximately 80% of systemic mean arterial pressure prior to intervention and falls to 25% with the sacrifice of all SAs. SCPP steadily increases postoperatively and returns to baseline within 5 days regardless of the presence of SCI.[14,15] Another study of staged SA sacrifice demonstrated that SCPP fell to only 50−70% in the staged group with significantly decreased incidence of SCI.[16] These findings suggest that the low-flow state precipitated by SA sacrifice leads to a recruitment of flow through existing collaterals and development of new collateralization.[14]

A study measuring SCBF prior to, during, and after total SA sacrifice using microsphere injection in a porcine model lends further insight to the timing of SCI. SCBF settles at a lower baseline during mild hypothermia and anesthesia than in the awake and normothermic state. Control animals mount a hyperemic response in the first 5 hours postoperatively and then return to their awake baseline within 24−72 hours. Among animals with total SA sacrifice, those that did not develop SCI were able to recover SCBF to their awake baseline by the 5-hour mark, though they were unable to sustain the hyperemic response seen in the controls. Animals that developed SCI were not able to recover SCBF to the awake baseline by 5 hours postoperatively.[17]

The conclusions drawn from these studies emphasize the importance of supporting SCBF during the immediate postoperative period while collateralization develops and indicate that SCI may have a belated presentation (1−5 hours after SA sacrifice) if an adequate hyperemic response is not achieved.

Ischemia Reperfusion Injury, Excitotoxicity, and Cell Death

Both open and endovascular interventions can result in regional cord ischemia. The days of clamp and sew are long gone so the pure ischemia reperfusion injury has become less obvious. This most likely has lessened the incidence of dense paraplegia with most injuries resulting from a period inadequate collateral flow in excess of the metabolic tolerance to malperfusion. Inadequate SCBF leads to an imbalance between spinal cord metabolic demand and oxygen supply. Once an ischemic burden is reached, neuronal oxidative phosphorylation is halted, and the cells' ATP stores are consumed. This leads to an inability to maintain normal cell electrochemical homeostasis, since ATP-dependent sodium/potassium (Na^+/K^+) pumps are responsible for moving Na^+ to the extracellular space and preserving a normal electrical gradient.[13,18]

Consequently, Na^+ is built up in the cell, which causes membrane depolarization and osmotic swelling. Membrane depolarization activates voltage-sensitive calcium (Ca^+) channels, driving massive Ca^+ influx. This is compounded by glutamate release, which activates *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor dependent ion channels, further increasing the intracellular Ca^+ concentration. The cascading response to neuronal ischemia causing excessive NMDA and AMPA receptor stimulation is known as excitotoxicity. This phenomenon is thought to further exacerbate cellular damage and may represent the ultimate cause of neuronal demise.[13,18]

Damaged and apoptotic neurons release inflammatory mediators and recruit microglia and neutrophils. In a murine model of ischemia reperfusion, Smith et al showed that local spinal cord inflammatory chemokine concentrations have a bimodal temporal distribution.[19] The initial wave of inflammatory markers is likely driven by the damaged neurons and activated local inflammatory cells. This inflammation further damages the surrounding tissue and endothelium, causing tissue swelling, which may diminish SCPP and produce a secondary ischemic insult. In this study, the second wave of inflammatory mediator release corresponded with delayed motor dysfunction in the mice. These findings highlight the fact that the drivers of SCI are not limited to the initial ischemic insult, but are also driven by excitotoxic, inflammatory, and oxidative processes.

In the clinical setting, we tend to view SCI as a binary outcome based on patient motor function. Ultimately this is a crude approach that underestimates the prevalence of ischemic injury. Bell et al analyzed the spinal cords of mice that were exposed to 3 minutes of ischemia, followed by reperfusion. Histologic analysis demonstrated significant cytoarchitectural changes and neuronal degeneration even in mice with preserved motor function. The severity of microscopically evident damage increased with motor manifestations in a stepwise manner.[20] Etz et al and Bischoff et al found similar changes in the spinal cords of pigs with preserved motor function after total and segmental SA sacrifice respectively, while paralyzed pigs had frank necrosis.[16,17] These studies indicate that SCI occurs on a continuum and that even in the absence of motor dysfunction, short periods of ischemia cause damage at the cellular level. This should stress the importance of continuing to seek therapies and strategies to preserve neuronal viability.

Approach at the Bench

Contemporary understanding of the pathophysiology of SCI provides us with a number of targets in our research. We currently employ 3 different models in the study of SCI: (1) Surgical manipulation of spinal cord blood supply in pigs allows us to study collateralization. (2) We use an in vivo murine spinal cord ischemia-reperfusion model to augment neuronal

ischemic tolerance and excitotoxicity, and observe the impact on motor outcomes. (3) We also culture murine spinal cord neurons in vitro and aim to improve their ischemic tolerance; ischemia-reperfusion is simulated by oxygen-glucose deprivation followed by re-exposure to a normally oxygenated environment and glucose-rich medium.

Erythropoietin and Diazoxide — A Synergistic Effect

Erythropoietin (Epo) is known to play an anti-inflammatory and antiapoptotic role in the setting of tissue injury, hypoxia, and metabolic stress. Epo receptor (EpoR) is either expressed as a homodimer EpoR-EpoR or as a heterodimer EpoR-beta common receptor (βcR), which was thought to mediate its tissue protective properties.[21,22] Epo has been shown to improve functional outcomes and reduce neuronal loss in animal models of spinal cord ischemia-reperfusion, including our murine model.[23] We also showed that Epo treatment in vitro preserves neuron viability after oxygen-glucose deprivation. However, the role of the βcR was yet unclear. Foley et al demonstrated that βcR subunit expression in spinal cord tissue is upregulated after ischemic exposure and that Epo-mediated neuronal preservation was lost in βcR viral-knockdowns.[21,22] Next, we sought to pharmacologically increase the expression of βcR to optimize Epo protection.

Diazoxide (DZ) is an activator of mitochondrial ATP sensitive potassium (K^+-ATP) channels and it is well recognized for its neuroprotective effects by mimicking cellular ischemia.[24] Yamanaka et al demonstrated that DZ treatment induces βcR expression; optimal βcR upregulation occurs at 36 hours after DZ administration in vivo.[25] We also found that the combination of treatment with DZ prior to ischemia and Epo at the time of ischemia reperfusion significantly preserved mouse motor function when compared to DZ alone. Histologic analysis of spinal cords from these mice had significantly decreased levels of apoptosis. In future studies, we will pursue a better understanding of the mechanism of βcR upregulation and the synergistic effect between DZ and Epo.

Inducing Metabolic Tolerance

The concept of ischemia-induced metabolic tolerance is predicated on the idea that brief periods of spinal cord ischemia stimulate a systemic response that leads to an increased tolerance to a subsequently greater ischemic insult. This has been well supported by experiments in animal models. In a rat model, Liang et al found that short ischemic exposure improved local SCBF, spinal cord tissue oxygenation, motor outcomes, and histopathologic results.[26] Herajarvi et al studied this in a porcine model and demonstrated significantly preserved spinal cord function after SA sacrifice as measured by motor evoked potentials in pigs subjected to brief ischemia prior to intervention. Molecular study of harvested spinal cords also suggested improved protection against oxidative stress.[27] In the experimental setting, the enhanced tolerance to spinal cord ischemia associated with prior ischemic exposure is noteworthy, but its clinical application poses challenging questions and has yet to be elucidated.

Pharmacologic Agents

Many pharmacologic agents have been evaluated for neuroprotective properties in the experimental setting. The theoretical framework for the selection of agents is the pathophysiology of SCI as described above. Overall, the literature regarding pharmacologic protection can be confusing as both agonists and antagonists of certain receptors appear to both be efficacious. For instance, blood flow modulators can preserve perfusion when either increasing the systemic pressure or decreasing collateral vascular resistance. Increasing the driving mean arterial pressure to improve watershed perfusion has become the clinical standard of care for both prevention and treatment of spinal malperfusion.[9] In a retrospective analysis of 398 patients who had undergone TAA repair, the Cleveland Clinic demonstrated that intrathecal administration of the vasodilator papaverine led to significantly lower incidence of permanent paraplegia (3.6% vs 7.5%; $P < 0.01$) compared to those who had not.[28]

Other pharmacologic options include anti-inflammatories, antioxidants, antiapoptotic agents, drugs that reduce neuronal excitotoxicity, drugs that mimic ischemic preconditioning, medications that reduce metabolic demand, and osmotic agents to reduce tissue swelling. Table 2 lists multiple agents that are used clinically or have shown promising results in animal experiments.[10,13,29] Importantly, while many drugs have a theoretical and anecdotal benefit clinically, or in animal models, there is a paucity of randomized clinical trials to robustly evaluate their utility.

CLINICAL PRACTICE

Clinically, our purpose is to protect SCBF on a macro level and augment spinal cord ischemic tolerance on a micro level. Protocolized neuroprotective strategies are based on these principles. The first step is determining the perceived risk of injury as it relates to modifiable factors, which depends on previous injury, extent of coverage, and collateral status (risk factors described in Table 1). In practice, most open procedures will undergo preemptive lumbar drain placement. For endovascular procedures, drains will be placed in high-risk patients.

Plan of Reconstruction

In most centers, a serial approach will be utilized when possible. This means that for extensive anatomic reconstructions, attempting to reduce the degree of collateral recovery required at any single operation may be beneficial. For instance, if a proximal TEVAR can augment an extent 2 repair to an extent 3, the collateral recovery may be less burdensome metabolically than an initial extent 2 operation. Similarly, optimizing collateral inflow through inflow revascularization such as subclavian or internal iliac bypass can be beneficial in the perioperative period.

Table 2. Pharmacologic Agents for Spinal Cord Protection

Drug Category	Agent	Evidence	Used Clinically?
Blood flow modulators - Systemic HTN	Vasopressors	Strong	Yes
Local vasodilatation	Papaverine	Retrospective	Yes
Anti-inflammatory	Steroids	Retrospective	Yes
	Prostaglandins	Experimental	No
Antioxidant	Allopurinol	Experimental	No
	Superoxide dismutase	Experimental	No
Antiapoptotic	Erythropoietin	Experimental	No
	Minocycline	Experimental	No
	Dexmedetomidine	Experimental	No
Antiexcitotoxic	Naloxone	Retrospective	Yes
	Magnesium	Retrospective	Yes
	Lidocaine	Theoretical	Yes
	Riluzole	Experimental	Yes
	Ketamine	Experimental	Yes
	Gabapentin	Experimental	Yes
Preconditioning	Anesthetic gases	Experimental	Yes
	Diazoxide	Experimental	No
Antimetabolic	Barbiturates	Experimental	Yes
	Adenosine	Experimental	No
	Narcotics	Theoretical	Yes
Osmotic	Mannitol	Theoretical	Yes

Distal Perfusion

Open DTA/TAA repairs are unique compared to their endovascular counterparts, because they involve mandatory cessation of SCBF during aortic cross clamping and circulatory arrest. When the aorta is clamped distal to the subclavian artery, SCBF is absent below the level of T10.[14] While the most important risk factor for the development of SCI is total ischemic time, it can be mitigated by establishing distal aortic flow via left heart bypass. In retrospective analyses, left heart bypass with distal perfusion decreased incidence of adverse neurologic outcomes.[30,31] Further minimalization of ischemia can be achieved with sequential aortic clamping if anatomically feasible.[10]

Optimizing Spinal Perfusion

Augmentation of systemic blood pressure intraoperatively and in the first 48 hours postoperatively is a broadly accepted strategy in the prevention of SCI. This is intended to counteract the significant reduction in SCPP after extensive SA sacrifice, while neovascularization occurs and SCPP returns to noncritical levels. There is also good evidence for pressing systemic blood pressure if patients develop SCI intra- or postoperatively.[9]

Cerebrospinal fluid (CSF) drainage can improve spinal cord perfusion by reducing the intrathecal pressure and thus increasing the spinal parenchymal perfusion pressure. A meta-analysis performed by Khan et al demonstrated a significant SCI reduction among patients with CSF drain placement in the pooled analysis. SCI reduction remained significant in the subgroup analysis for open TAA repairs. Results were conflicting regarding endovascular operations. This led to the conclusion that there is moderate quality evidence for the use of CSF drainage in open TAA repair, but no conclusions could be drawn for its application in endovascular surgery.[32] In a position paper of the European Association for Cardio-Thoracic Surgery, Etz et al recommended that CSF drainage should be considered in high-risk patients undergoing endovascular aortic repairs, based on consensus of opinion.[33]

SA reimplantation can also be considered to improve SCBF. Historically, SA reimplantation was prioritized because it was believed this would be the most effective approach to preventing SCI. The data are conflicting though and suggest more nuanced consideration is needed. If a SA is easily visualized and it does not show any evidence of back bleeding, then reimplantation should be considered. Alternatively, if SAs are not easily identified or if dissection prior to reimplantation would significantly prolong ischemic time, the risk of SCI from circulatory arrest would likely outweigh the benefit of SA reimplantation. Furthermore, if a SA is identified and there is significant back bleeding, even with reimplantation, this may lead to a steal phenomenon which would increase the likelihood of SCI. In this case, over sewing such a SA would be the most time-effective and protective approach.[33]

Maximize Ischemic Tolerance

Hypothermia is the most reliable adjunct to increase spinal cord ischemic tolerance. At normothermia, the spinal cord may tolerate up to 20 minutes of circulatory arrest. For every 10°C of cooling, the cellular metabolic rate is decreased by half. Therefore, the time-window within which a safe operation

may be performed is doubled. A majority of surgeons utilize moderate hypothermia (30–32°C).[14] Unfortunately, maximizing neuronal ischemic tolerance pharmacologically is not well developed. So at this time, the utilization of pharmacologic protection remains local voodoo without definitive evidence of efficacy.

Intraoperative Neuromonitoring

Neurophysiologic intraoperative neuromonitoring (NIOM) is utilized for the early diagnosis of SCI. It includes peripheral somatosensory evoked potentials and motor evoked potentials. In a meta-analysis, Tanaka et al found that NIOM has a summary sensitivity of 89.1% (95% confidence interval 47.9–98.6%) and a summary specificity of 99.3% (95% confidence interval 96.1–99.9%) for the detection of SCI.[34] This suggests that NIOM is an extremely useful tool. Prompt recognition of SCI can allow for timely interventions such as hemodynamic stabilization, blood pressure optimization, CSF drainage, and operative interventions to restore SCBF that may reverse early SCI.

Promote Collateralization

For patients who are appropriate candidates, a staged TAA repair should be considered. In a porcine model, Bischoff et al demonstrated significantly better motor outcomes and preserved SCPPs in pigs that underwent staged SA sacrifice.[16] Etz et al showed similar findings in a retrospective analysis comparing 35 staged vs 55 complete TAA repairs — patients in the staged group had significantly lower incidence of SCI (0% vs 15%).[35] These findings are likely due to the fact that partial SA sacrifice does not result in a large enough ischemic burden and because interval collateralization develops with a return of SCPP to baseline. Larger clinical studies are needed,

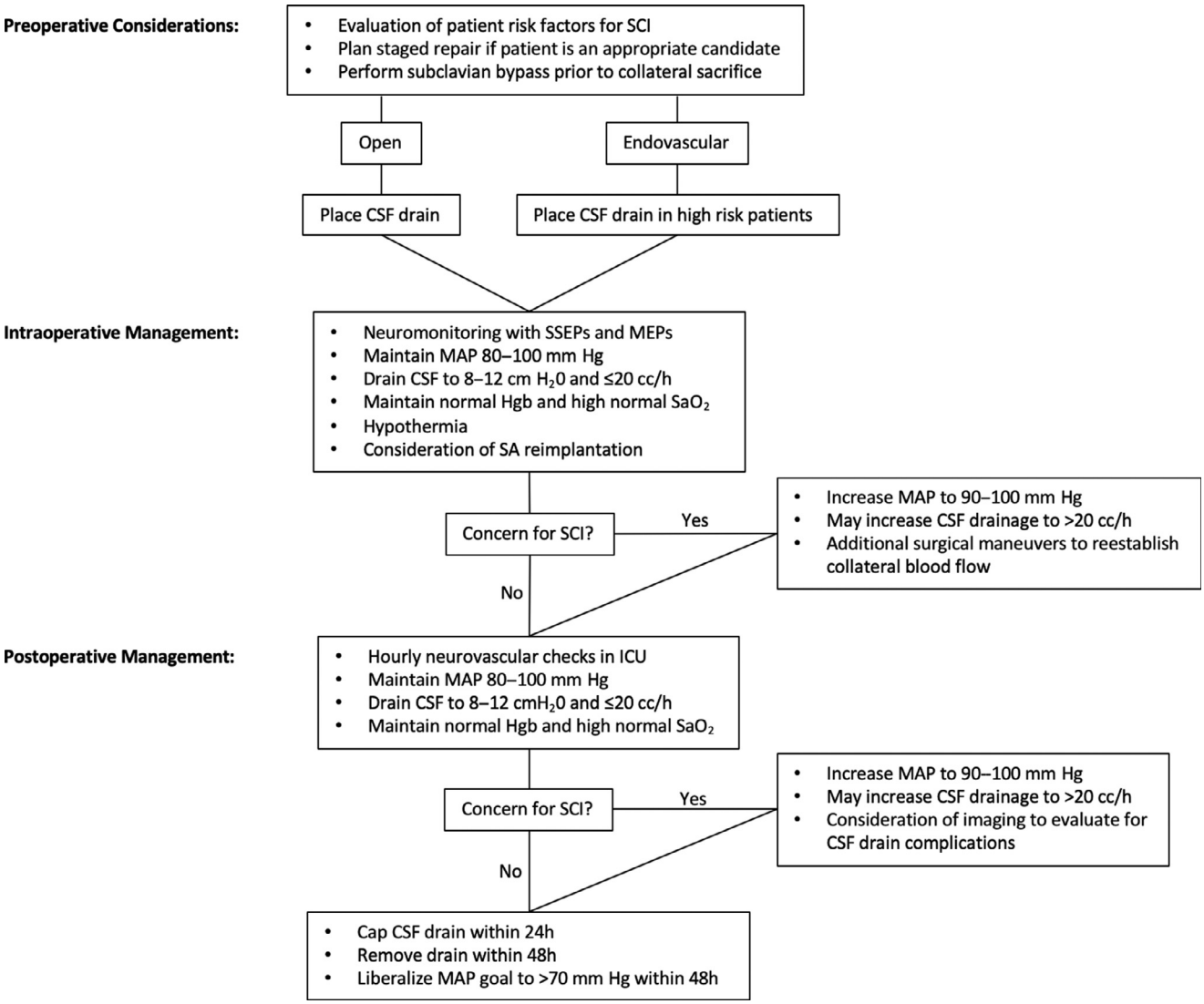

Figure 4. Spinal cord injury prevention algorithm adapted from Lindsay et al and Parotto et al.[9,10] CSF, cerebrospinal fluid; Hgb, hemoglobin; MAP, mean arterial pressure; MEP, motor evoked potential; SA, segmental artery; SaO_2, oxygen saturation; SCI, spinal cord injury; SSEP, somatosensory evoked potential.

but early results have spurred a European randomized trial on segmental embolization prior to definitive repair.

Postoperative Care

In the immediate postoperative period, patients after DTA/TAA operations should be monitored in the intensive care unit. Hourly neurologic exams should be performed and strict hemodynamic stability maintained. Concerns about SCI should prompt more aggressive CSF drainage as allowed by protocol, increased blood pressure goals, and consideration of spinal imaging studies. Imaging studies are not helpful in SCI alone, but can demonstrate complications of lumbar drain placement. This is particularly relevant when there are questions of a bloody tap on insertion or unilateral symptoms more likely to be epidural hematoma related than the bilateral ischemic SCI.

Figure 4 delineates our proposed algorithm for prevention of SCI. It is important to note that despite compelling laboratory research in spinal cord protection and a growing, complex understanding of SCI on the cellular level, the tenets of SCI prevention in clinical practice are simple: evaluate patients' risk factors for SCI, stage repairs when possible, maximize SCBF with collateral preservation/augmentation and systemic vasopressor use, CSF drainage, and hypothermia.

CONCLUSIONS/MOVING FORWARD

In conclusion, the pathophysiology of SCI includes disruption and recovery of collateral blood flow and the effects of malperfusion on the spinal cord. The optimal approach to spinal cord protection is to employ an integrated and protocolized set of strategies to simultaneously maximize SCBF, improve ischemic tolerance, and promote collateralization. In the laboratory setting, we should continue to pursue a more granular understanding of ischemic injury and seek to translate protective therapies to clinical practice.

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