

Prevention of Spinal Cord Ischaemia During Descending Thoracic and Thoracoabdominal Aortic Surgery

Recommendations

Primary Suggestions

1. Hemodynamic Stability- obvious avoidance of extremes but important to:
 - a. Avoidance of hypotension- maintain MAP within 20% of baseline and at least 65-70 mmHg (adjust accordingly)
 - b. Consider higher MAP if shunt in use or history of hypertension
 - c. Avoidance of tachycardia (i.e. cardioprotective strategy)
2. Spinal drain for 48 hrs keeping the CSF pressure < 7-10 cmH₂O
3. Keep spinal cord perfusion pressure (Distal aortic MAP- CSF pressure) > 60-70 mmHg
4. Regional hypothermia- Use of cold saline either by intermittent boluses or infusion into epidural and/or subarachnoid space (target is CSF temp 25-28°C). Remember to safeguard against the potential deleterious effects of CSF pressure elevation that occurs coincident with the epidural infusion .

Considerations

1. Preoperative identification of artery of Adamkiewicz using MRA or angiogram to allow preservation and/or reimplantation intraoperatively.
2. Femoral arterial line or arterial cannula in distal part of the axillo-femoral graft to measure MAP below the clamp.
3. Monitoring of spinal cord function by MEP and/or CSF lactate.
4. Intrathecal papaverine in selected cases.

One of the most feared complications of thoracoabdominal aneurysm repair is paraplegia following seemingly successful surgery. Neurological injury after conventional open repair occurs in up to 22% of patients after type II repair¹. Paraplegia rates are often diluted into a wider group of patients such as thoracic repair² and type IV³ repair in whom the risk is reduced. Paraplegia results not only in severe physical disability, but is also associated with decreased survival rates⁴. There is much debate over the best methods to reduce the rate of paraplegia

With advances in anesthetic and surgical techniques, the incidence of intractable neurological complications has declined, but the rate of paraplegia or paraparesis still ranges from 5 to 40%⁵

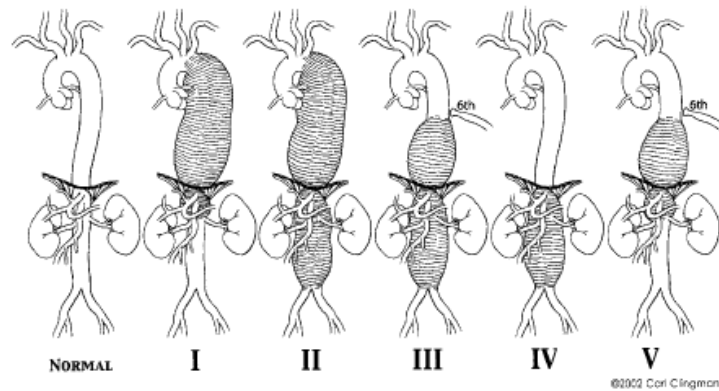


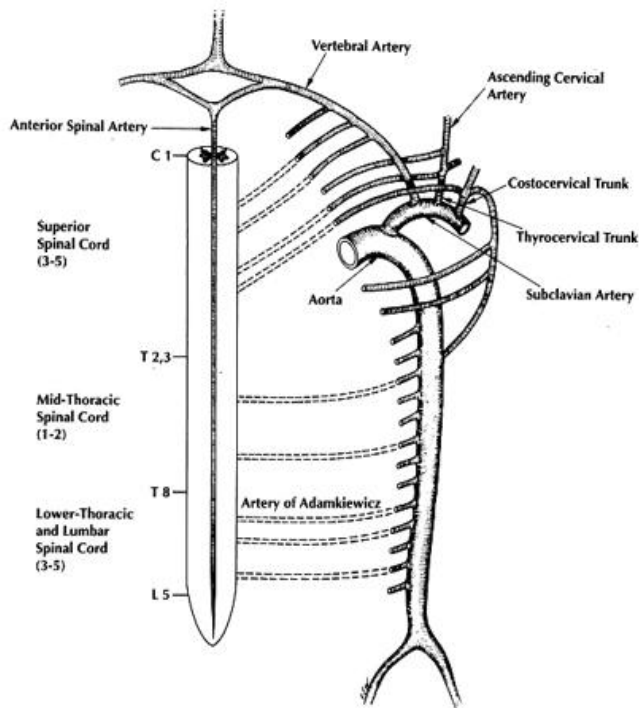
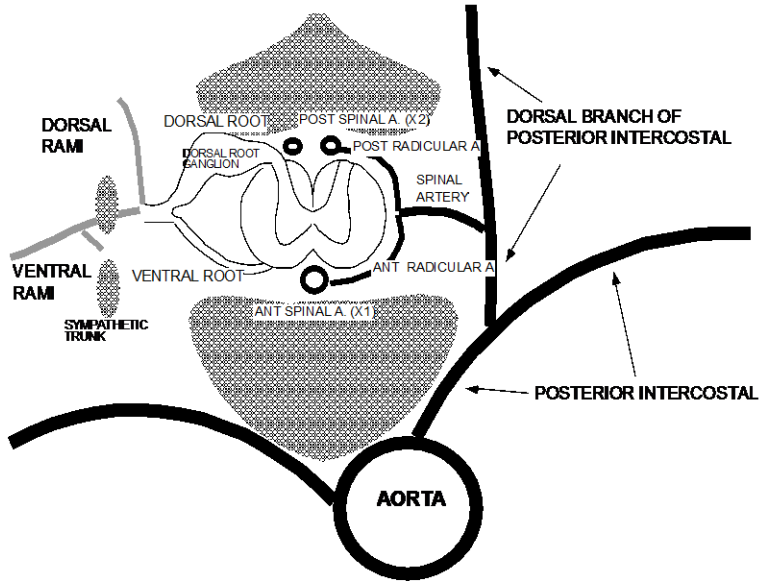
FIGURE 1. Normal thoracoabdominal aorta and aneurysm classification. Extent I, distal to the left subclavian artery to above the renal arteries. Extent II, distal to the left subclavian artery to below the renal arteries. Extent III, from the sixth intercostal space to below the renal arteries (total abdominal aortic aneurysm). Extent V, below the sixth intercostal space to just above the renal arteries.

BLOOD SUPPLY TO THE SPINAL CORD

In the human embryo, there are paired radicular arteries that supply the spinal cord.⁶ With growth, these radicular arteries involute, and as a result, there are only a few radicular arteries remaining in adults.⁷ These radicular arteries are linked together by the longitudinal arteries of the spinal cord, namely the paired posterior spinal artery and the single anterior spinal artery (AnSA), which supplies the anterior two third of the spinal cord.⁸

Among the radicular arteries at different levels, there is one which is exceptionally large called the artery of Adamkiewicz (ARM).⁷ It has a characteristic hairpin bend that perfuses the spinal cord distal to its junction with the AnSA. An interesting finding is that the AnSA above the ARM is considerably smaller in diameter compared with that below the ARM.⁷ The level at which the ARM arises from the aorta varies amongst individuals but arises from T9 to T12 in 75% of individuals (Varying in position from T7 to L4).^{9,10}

The AnSA is fed by different inputs. If most of these inflow tracts are disconnected from the aorta, there will be a decrease in the pressure in the ASA and retrograde flow of blood through the opened intercostal and lumbar vessels to the operating field instead of going through the ASA due to a steal mechanism.¹¹ This explains the clinical observation that the more extensive the aortic involvement and resection, the higher will be the rate of paraplegia.¹²



PATHOGENESIS OF SPINAL CORD ISCHAEMIA

Immediate neurological complications are considered a direct result of hypoperfusion of the spinal cord and secondary in hypoxic damage. Delayed complications can develop between 1 and 21 days following surgery.¹³ This has been postulated to be the result of reperfusion hyperaemia and free radical generation leading to edema of the cord with

regional hypotension and reduced perfusion of the vascular plexus.¹⁴ The major causes of spinal cord injury, during and after aortic surgery are:¹⁵

- (I) the duration and degree of ischaemia;
- (II) Failure to re-establish blood flow to the spinal cord after repair;
- (III) Biochemical mediated reperfusion injury.

I-Duration and degree of ischaemia

Effect of aortic cross-clamping:

Clinical studies have demonstrated that the duration of aortic cross-clamping is a major determinant of postoperative paraplegia.¹² The rate of paraplegia increases from 0% when the cross-clamp time is less than 15 min, to 25–100% when the time exceeds 60 min.^{16,17} The application of the aortic cross clamp will lead to hypertension proximal to the clamp which increases the afterload of the heart resulting in heart failure and causes hypotension distal to the clamp.¹⁸ The other effect of aortic cross clamping is an increase in CSF pressure.¹⁹ Both the increase in CSF pressure and hypoperfusion of cord may contribute to significant neurological complications.

Experimental studies demonstrated that the CSF pressure rose significantly after 60 min of cross clamping. If the CSF pressure was uniformly raised to, or exceeded that in the distal aorta, the incidence of paraplegia was 100%.²⁰ This has led to the concept of ‘*relative spinal cord perfusion pressure*’ which is equal to the distal mean arterial pressure minus the CSF pressure.²¹

II-Failure to re-establish spinal cord blood flow: monitoring techniques

Failure to re-establish blood flow to the spinal cord after repair will lead to spinal cord ischemia. Based on cadaver dissections examining the spinal cord blood supply in humans, as well as on the use of hydrogen mapping, the critical vessels to be reattached during surgery are those from T6 down to L2.

In 98 patients undergoing type I or type II thoracoabdominal aneurysm repairs Svensson et al²² found that If patients had intercostal or lumbar arteries between the T10 and L1 segments that were not reattached during the time of the aortic repair, the incidence of paraplegia/paresis postoperatively was 63%, in contrast to a 25% incidence rate in patients in whom these vessels were present and reattached ($p = .05$). Similarly, studies by Ross and colleagues and by Safi and colleagues show a higher incidence of paraplegia/paresis when patent intercostal or lumbar arteries were not reattached at the time of surgery in these segments.^{23,24}

III-Reperfusion injury: mechanism

Reperfusion injury has been postulated as one of the etiologies of delayed spinal cord injury. Reperfusion is the restoration of blood flow to the organ after a period of ischaemia. Reperfusion of ischaemic neuronal tissues leads to release production of oxygen derived free radicals, produced as a result of incomplete oxygenation during the period of ischaemia.¹⁵

Superoxide on its own is not highly reactive, however, when it reacts with transition metal such as iron, superoxide and its metabolite, hydrogen peroxide, can be converted into iron oxygen complexes and hydroxyl radicals. These are extremely reactive and can cause considerable cellular damage. Neural tissue is very vulnerable to iron related free radical injury. Efforts have been made to discover free radical scavengers so as to reduce ischaemic cellular damage.²⁵

MONITORING OF SPINAL CORD ISCHEMIA

Techniques have been developed to monitor the function of the spinal cord during surgery so that surgeons can obtain information concerning the adequacy of blood supply to the spinal cord after repair.

1. Somato-sensory Evoked Potential monitoring:

The primary injury to the spinal cord during surgery and aortic cross clamping is hypoxic damage to the neurons. Nerve conduction is highly sensitive to hypoxia. A peripheral electrical stimulation is elicited and the signal amplitude and conduction time along the spinal cord are recorded at the cortical projection on the contralateral postcentral gyrus.

SSEP amplitude decreased by 40% after cross clamping with hypotension for 3–4 min. If this was allowed to persist, a flat-line SSEP response would be observed indicating the absence of conduction.^{26,27} Practically, SSEP is obtained by stimulation of the posterior tibial nerve at the medial malleolus by a bipolar input channel. The SSEP waveforms can be recorded by electrodes placed on the scalp. Measurements are made before aortic cross clamping which serve as baseline. Tracings are recorded at 2-min intervals during the rest of the operation.²⁸ A 10% increase in signal latency usually precedes a decrease in the amplitude. This shift in latency is directly related to the decrease in perfusion pressure of the spinal cord. The duration of ischaemia required to shift the latency 10% from its baseline is defined as the L10 time, indicating the need to re-establish spinal cord perfusion in 4–6 min.²⁶ There are four classical types of SSEP response:²⁹

Type I responses are characterized by a decreased amplitude and increased latency 3–5 min after aortic cross-clamping. This indicates failure to provide adequate perfusion pressure of up to 60 mmHg distal to the clamp.

Type II responses, SSEP is maintained throughout the period of aortic cross clamping indicating adequate distal perfusion pressure. This indicates that the critical segmental arteries are not located within the segment of aorta between the cross-clamps.

Type III responses are represented by the sudden loss of sensory conduction after application of the proximal cross clamp indicating that the critical arteries are located within the excluded segment of the aorta. This is an indication for reimplantation and reperfusion of the excluded intercostal segments.

Type IV responses are characterized by gradual ‘fade out’ of normal SSEP tracings in 30–50 min. This indicates marginal or deficient distal perfusion even in the presence of proximal to distal bypass with acceptable distal perfusion pressure. This occurs in the presence of profound vasodilatation, extensive

aneurysmal disease and failure of retrograde perfusion distal to aortic clamp. The surgeon must react quickly to further re-establish distal perfusion at a higher perfusion pressure usually greater than 70 mmHg.

Clinical studies³⁰⁻³⁴ have shown that SSEP is sensitive and may offer an improvement in surgical strategy during thoracoabdominal aortic surgery. However, SSEP only records the activity of the posterior and lateral columns of the spinal cord. It fails to represent the function of the anterior spinal cord that is supplied by the single ASA. The specificity of SSEP measurement is low with a false positive rate of 67%.¹³

2. Motor Evoked Potential

MEPs are elicited either transcranially or by stimulation of the cord directly. Motor responses can be recorded at the level of the cord (spinal MEP), the nerve (neurogenic MEP) or the muscle (myogenic MEP). Experimental studies suggest myogenic MEP may be sensitive in predicting paraplegia.³⁵ Transcranially elicited MEP has been used clinically with detection of cord ischaemia within minutes, and no false positive or false negative results were observed.³⁶ However, preoperative anesthetic planning is necessary as most volatile anesthetic agents will depress myogenic responses.³⁷ Neuromuscular blocking agents can affect the amplitude of the MEP and the level of the drugs has to be maintained precisely. The other shortcoming of MEP is that axonal conduction is resistant to ischaemia and the disappearance of MEP is slow after spinal blood flow has been interrupted.^{38,39}

3. Cerebrospinal Fluid S100 and Lactate

There are strong correlations between C-S100 levels and C-lactate levels with time in patients with SCI. In patients with SCI C-lactate levels increased soon after aortic cross-clamping, whereas C-S100 levels did not become significantly elevated until 6 hours after cross-clamping.⁴⁰

STRATEGIES TO PREVENT SPINAL CORD ISCHEMIA

I- Reduction of the duration of ischaemia:

The duration of spinal cord ischaemia during aortic cross-clamping is of utmost importance as the rate of postoperative paraplegia increased with cross-clamping time. Large retrospective series have shown that the duration of aortic cross-clamping is intimately related to the risk of neurological complications.^{12,41} aortic cross-clamp time was the most important predictor of immediate post-operative neurological deficit along with the extent and type of aortic aneurysm repaired, the presence of aortic rupture, patient age, and renal dysfunction.¹² The incidence of paraplegia was noted to be 27% in those with an aortic cross-clamp time of over 60 min, falling to 8% with those that have expedient surgery and clamp times of less than half an hour.

II-Reduction of the severity of ischaemia:

a. Identification of critical segmental arteries (Preoperative angiography).

Preoperative angiography aimed at identifying the segmental arteries that give rise to the critical radicular arteries supplying the cord. The major problem of this method is the direct injection of toxic contrast agents via the ARM that may itself result in paraplegia.⁴² Preoperative angiography may identify the ARM in 85% of cases. With the ARM identified and that particular segment of aorta revascularized, the risk of paraplegia was 5%. If reimplantation was not carried out within the excluded segment bearing the ARM, the risk of paraplegia was 50%.⁴³ Recently, magnetic resonance angiography has been proposed as an alternative non-invasive method for studying of the ARM preoperatively.⁴⁴ It has been shown that the ARM could be demonstrated in 69% of the patients, however, the number of patients in this study is relatively small.⁴⁵

b. Intraoperative localisation of critical segmental arteries

The basis of this technique is that hydrogen is dissolved in solution with the production of a weak current when in contact with platinum. If hydrogen is injected into a radicular artery that supplies the spinal cord, it is carried to the ASA. The hydrogen will pass through the membrane and the wall of the artery that is then detected by a platinum electrode placed alongside the spinal cord.⁴⁶

c. Distal aortic perfusion techniques

It is important to maintain distal aortic perfusion pressures between 60 and 70 mmHg. As perfusion falls below 60 mmHg, the spinal cord blood flow falls in proportion to perfusion pressure.⁴⁷ With the use of distal perfusion techniques, a significant reduction in the risk of spinal cord ischaemia has been reported.

d. Passive Shunts

In the 1960s, temporary external conduits were used as shunts in thoracic aortic surgery. The most popular shunt was the one developed by Gott.⁴⁸ It was made of polyurethane polyvinyl plastic with internal diameter of 5–6 mm and the lumen was coated with a

heparin-bonded nonthrombogenic material (benzalkonium or methylamonium). The shunt was used to bypass the cross-clamped aorta. As the shunt has got a relatively small diameter, the resistance to the blood flow is quite significant which may compromise distal aortic perfusion, and the proximal aorta may not be adequately decompressed. The maximum flow through the shunt at a pressure gradient of 60 mmHg represents only 50% of the cardiac output.⁴⁹

Temporary passive axillary–femoral bypass can and are often used. Blood flow is dependent on the mean aortic blood pressure proximal to the cross-clamp for distal aortic perfusion.⁵⁰ The targeted MAP is debatable but should be kept at least 65-70 mmHg and possibly higher (see above).

e Left atrial to femoral artery bypass (LAFA)

With the use of LAFA bypass, the flow to distal aorta can be regulated by a roller or centrifugal pump. The centrifugal pump causes less haemolysis and it is relatively free of the complications of air embolism as any air being trapped in the pump will cause cessation of its function.⁵¹ Minimal heparinization is needed but it is recommended for patients with distal aortic perfusion or femoral occlusive disease. With the use of the pump, the distal aortic perfusion can be maintained at 60–70 mmHg.⁵¹ The distal perfusion technique is always used in conjunction with other adjunctive measures such as CSF drainage or hypothermia.

In situations where there is an absence of well developed collaterals, such as in the case of traumatic aortic injury, the role of distal aortic perfusion in preserving neurological function is more obvious.²² Coselli⁵² has reported a large group of over 1000 patients who had thoracoabdominal aneurysm repairs, comparing those where left heart bypass was employed with a historical cohort. In patients with type II thoracoabdominal aneurysms, those undergoing surgery with bypass had a incidence of paraplegia or paraparesis of 4.5%. This was significantly lower than the rate of 11.2% in those that did not.

f. Reestablishment of spinal cord blood flow

Griep et al⁵³ proposed stepwise sacrifice of intersegmental arteries the start of the procedure before the aneurysm was opened. At the same time, somatosensory evoked potentials were used to monitor spinal cord function with temporary occlusion before the segmental arteries were tied off permanently.⁵³ The concept of oversewing segmental vessels with appropriate monitoring of the spinal cord is based on the fact that many clinical studies showed that the rate of postoperative paraplegia increases with cross-clamping time. Time might be saved by not reattaching the non-critical segmental arteries.

Preischaemic conditioning by temporary occlusion before cross-clamping may provide a certain degree of protection for the spinal cord,⁵⁴ and the reattachment of segmental arteries especially from below T6 to L2, may be important even if the cross-clamping time is prolonged.⁵⁴ With the refinement of hydrogen mapping techniques, together with monitoring of evoked potentials, the goal of shorter cross-clamping time and selectively reattaching the critical segmental arteries may be achieved.⁵⁴

III- Cardiovascular stability

Clearly hypotension will decrease the spinal cord perfusion substantially and long periods may precipitate immediate neurological injury. The volume of blood lost is significantly related to spinal cord injury⁵⁸ presumably as a result of decreased spinal cord perfusion. Anaesthetic staff need to be well trained in the field of major thoracoabdominal aneurysm surgery to prevent large fluxes of blood pressure and end organ perfusion during the procedure. Equally an intensive care unit that is familiar with all aspects of post-operative care is invaluable in maintaining stability.

Safi¹⁰³ provide useful information of this subject in a study of patients who develop late onset spinal dysfunction. All patients in his study who developed spinal cord paralysis showed an acute rise in cerebrospinal fluid pressure before the onset of symptoms. Interestingly half of the patients who developed spinal symptoms had a period of blood pressure instability immediately beforehand. Kawanishi et al concluded that Perioperative hemodynamics stability is of vital importance for spinal cord protection during thoracoabdominal aortic surgery. In particular, the duration of hypotension after coming off bypass was an independent risk factor for paraplegia.¹⁰⁴

IV-Physiological and pharmacological adjuncts

a. Drainage of cerebrospinal fluid.

When CSF pressure equaled or exceeded distal aortic pressure, paraplegia uniformly occurred.²¹ The combined effects of decreased arterial pressure and an increase in CSF pressure during aortic cross-clamping resulted in decreased spinal cord perfusion pressure. The perfusion pressure can be maintained by decreasing the CSF pressure, i.e. by CSF drainage. The use of CSF drainage before aortic cross-clamping in experimental studies has shown that the incidence of paraplegia was lower when compared with a control group.⁵⁵

Three trials analyzed by Khan et al with a total of 287 participants operated on for Type I or II TAAA were included. In the first trial of 98 participants,⁵⁶ neurological deficits in the lower extremities occurred in 14 (30%) of CSFD group and 17 (33%) controls. The deficit was observed within 24 hours of the operation in 21 (68%), and from 3 to 22 days in 10 (32%) participants. CSFD did not have a significant benefit in preventing ischaemic injury to the spinal cord. A criticism of this study was the volume of CSF drainage was only 50 ml during the period of cross-clamping. CSF was not allowed to drain freely by gravity and drainage was not continued during the postoperative period.

The second trial of 33 participants⁵⁷ used a combination of CSFD and intrathecal papaverine. A statistically significant reduction in the rate of postoperative neurological deficit ($P = 0.039$), compared to controls. In this study, 20 ml of CSF was drained 20 min before cross-clamping and 3 ml of warmed preservative free papaverine solution was introduced. CSF was allowed to drain freely by gravity but stopped after unclamping the aorta. CSF was then allowed to drain freely during postoperative period if the CSF pressure exceeded 7–10 cmH₂O.

In the third trial⁵⁸ TAAA repair was performed on 145 participants. CSFD was initiated during the operation and continued for 48 hours after surgery. Paraplegia or paraparesis occurred in 9 of 74 participants (12.2%) in the control group versus 2 of 82 participants (2.7%) receiving CSFD (P = 0.03). Overall, CSFD resulted in an 80% reduction in the relative risk of postoperative deficits.

Neurological deficits attributable to the spinal drain itself including intracranial haemorrhage occurred in 1% of patients and patients with cerebral atrophy were found to be at increased risk.⁵⁹

Study	Cases	Control	CSFD vol/pressure	Postop drainage
Crawford ⁵⁶	14/46 (30%)	17/52 (33%)	50 mls only	No
Svensson ⁵⁷	2/17(11.8%)	7/16(43.8%)	7-10 cm H2O	Up to 48 hours
Coselli ⁵⁸	2/82(2.7%)	9/74(12.2%)	<10mm Hg	Up to 48 hours

b. Hypothermia

Hypothermia is one of the most effective methods in the protection of neural tissues during ischaemia.⁶⁰⁻⁶³ Experimental work has shown that during the periods of aortic cross-clamping, hypothermia conferred a protective effect on spinal cord function. Hypothermia increases the tolerance of neural tissue to ischaemia by decreasing oxygen demand and the metabolic rate, and can confer a marked protective effect on the spinal cord.⁶³ Other mechanisms may also account for the protective effect of hypothermia. The release of neurotransmitter has been implicated in the pathogenesis of ischaemic injury of the spinal cord.⁶⁴⁻⁶⁶ The inhibition of the synthesis and release of these neurotransmitters by hypothermia has been proposed as an additional factor that results in the protection of the spinal cord.^{67,68}

Profound systemic hypothermia carries with it the associated risks of coagulopathy and cardiac dysrhythmias, whereas moderate systemic hypothermia minimizes these risks.⁶⁹ The principal limitation of moderate hypothermia lies in its potential for the promotion of arrhythmias.⁷⁰ It is widely accepted that hypothermia is associated with morbid cardiac events.⁷¹

Apart from systemic hypothermia, regional hypothermia has been used for spinal cord protection. Experiments showed that regional hypothermic perfusion applied to the epidural or intrathecal space may protect the spinal cord during cross-clamping of the aorta⁷²⁻⁷⁵. However, open laminectomy has to be performed if such a degree of hypothermia (15–18°C) is to be achieved. Davison et al.⁷⁶ demonstrated regional hypothermia of the spinal cord with an infusion of iced (4°C) saline solution. This was administered into an epidural catheter while monitoring cerebral spinal fluid (CSF) temperature, that reached 25°C during cross-clamping and returned to near core temperature levels by the end of the procedure. A standard 4F 40-cm epidural catheter for administration of local anesthesia and infusion of iced (4°C) normal saline was inserted at the T10 to T12 level and advanced cephalad 4 to 5 cm. A second 4F thermistor catheter was placed 4 cm into the subarachnoid space at the L3-4 interspace, permitting continuous recording of CSF temperature and pressure. An arbitrary 30 to 40 mm Hg gradient was maintained between the mean arterial and CSF pressures, particularly during

the early stages of the infusion, to safeguard against the potential deleterious effects of CSF pressure elevation that occurs coincident with the epidural infusion⁷⁷.

A strategy that combines the neuroprotective effect of regional cord hypothermia, preservation of spinal cord blood supply, and postoperative adjuncts (eg, avoidance of hypotension, CSF drainage) appears necessary to minimize SCI after TAA repair. Cambria⁷⁸ has reported good results with regional hypothermia. In his series of 334 thoracoabdominal aneurysm repairs, neurological injury to some degree occurred in 11.4%. Epidural cooling reduced the risk in patients with types I-III TAA from 19.8% to 10.6%.

c. Pharmacological agents

Several pharmacological agents with different mechanisms of action have been suggested as being effective in protection of the spinal cord during the period of hypoperfusion.

1. Increasing Spinal Cord Tolerance to Ischemia

i. Intrathecal papaverine- The use of intrathecal papaverine and CSF drainage has been described. Experiments in baboons showed that even with 60 min of cross-clamping, the use of CSF drainage and intrathecal papaverine prevented the development of paraplegia.⁷⁹ The role of papaverine is as an arterial dilator that helps to increase regional spinal cord perfusion.

ii. Opiate antagonist naloxone- During aortic cross-clamping in dogs, the level of β -endorphin in the CSF was increased. The opiate antagonist naloxone has been shown to improve neurological outcome following ischaemic insults to neural tissue.^{80,81} The combination of CSF drainage and naloxone has been studied in 61 patients compared with 49 patients as a control group, and significant protection from neurological deficits demonstrated.⁸²

iii. Anesthetic Agents- Barbiturates like thiopental block synaptic transmission and relax vascular smooth muscle, and have been reported to be neuroprotective in animals.⁸³ Kirshner and co-workers⁸⁴ however, found no benefit provided by thiopental alone, but did find a moderate amount of protection conferred by the combination of thiopental, hypothermia, and superoxide dismutase.

iv. Calcium channel blockers- Calcium-channel blockers augment cerebral blood flow and neurologic recovery after cerebral ischemia.⁸⁵ Schittek et al⁸⁶ observed almost complete protection from spinal cord injury afforded by the intravenous administration of nimodipine after 30 minutes of spinal cord ischemia in pigs. In a rabbit model of spinal cord ischemia, however, Lyden et al⁸⁷ found no protective effects conferred by three calcium-channel blockers selective for the cerebrovascular system. They proposed that calcium enters the injured neuron by way of channels other than those blocked by these drugs.

v. Excitatory amino acid antagonists- Recent attention has been focused on the excitotoxic neurotransmitter theory of spinal cord injury. Administration of the NMDA receptor antagonists MK801⁸⁸ and LY233053⁸⁹ have been found to provide some degree of spinal cord protection in rabbit models of spinal cord ischemia.

2. Decreasing Reperfusion Injury

i. Free radical scavengers- A large body of research has been focused on limiting free radical-induced injury during the reperfusion of ischemic tissue. The intravenous administration of the endogenous free radical scavenger superoxide dismutase (SOD) just before and after termination of aortic occlusion in animals was found to protect against ischemic periods of 30 minutes or less.⁹⁰ However, it was found that SOD alone is not protective against periods of ischemia of 40 minutes or more.^{85,90} With the conjugation of SOD to polyethylene glycol, the half-life of SOD is increased from minutes to hours.⁸⁹ It was found that this form of SOD alone effects partial but not complete prevention of neurologic injury after 40 and 60 minutes of spinal cord ischemia.⁹¹ Despite success in limiting myocardial reperfusion injury, the xanthine oxidase inhibitor allopurinol has been shown to be of no benefit in animal models of spinal cord ischemia.⁹²

ii. Steroids- Laschinger et al⁹³ reported that ischemic spinal cord injury was prevented in animals receiving methylprednisolone intravenously. The protective effects of corticosteroids were thought to be related to their ability to stabilize membranes, modulate the immune system, and scavenge for free radicals. The 21-aminosteroids lack any mineralocorticoid or glucocorticoid activity and are potent scavengers of superoxide and lipid peroxy radicals, as well as extremely potent inhibitors of iron-dependent lipid peroxidation under in vitro conditions.⁹⁴ Fowl et al⁹⁵ reported a decreased rate of spinal cord injury in rabbits given the 21-aminosteroid U74006F intravenously.

iii. Immune system modulation- Immune system modulation is a relatively new technique for attenuating reperfusion injury. Giulian and Robertson⁹⁶ were able to inhibit the phagocytic and secretory functions of mononuclear phagocytes with chloroquine and colchicine, and demonstrated that the clinical and histopathologic outcomes were improved after 20 minutes of spinal cord ischemia in rabbits treated with these agents. Clark et al⁹⁷ studied the effects of an antibody to the surface glycoprotein CD18, a substance required for leukocytes to adhere to the endothelium, and found a significant reduction in neurologic deficits after 30 minutes of spinal cord ischemia in rabbits given the antibody.

iv. Adenosine- An expanding body of literature has documented the neuroprotective effects of adenosine and its analogues.⁹⁸⁻¹⁰⁰ Adenosine-1 receptors are primarily located in the neural tissue, whereas adenosine-2 receptors reside in the smooth muscle and endothelium of the vasculature. The activation of adenosine-1 receptors decreases neuronal and membrane excitability, thereby limiting the damaging influx of calcium through voltage-gated channels. Aspartate and glutamate release is inhibited.^{98,99} Adenosine-2 receptor activation promotes vasodilation, inhibits platelet aggregation, and inhibits neutrophil activation and subsequent free radical production, thus theoretically reversing the tendency toward the no-reflow phenomenon.¹⁰⁰ Recently, in a gerbil model of cerebral ischemia, von Lubitz and Marangos¹⁰¹ demonstrated significant neuroprotective effects from an exogenously administered adenosine analogue that was given after reperfusion. On the basis of these findings, regional infusion of hypothermic adenosine into the excluded infrarenal aorta of the rabbit provides complete protection from spinal cord injury after 40 minutes of spinal cord ischemia, as shown by both clinical and histologic evidence.¹⁰²

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