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REVIEW ARTICLE

Prevention of Spinal Cord Ischaemic Complications After Thoracoabdominal Aortic Surgery

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Introduction

Spinal cord ischaemia remains the unsolved problem in operations on the thoracic and thoracoabdominal aorta. In contemporary elective operations, perioperative haemorrhage and clinically significant renal failure occur infrequently; however, ischaemic spinal cord injury remains a genuine threat. Perhaps the best barometer of the risk of this complication emanates from Crawford's monumental series of over 1500 patients, wherein a 16% overall risk of paraplegia or paraparesis was reported.[1] Over half of these complications resulted in complete paraplegia, which disallows any meaningful rehabilitation and is accompanied by excessive perioperative and late mortality.

Several contemporary reports suggests that the incidence of spinal cord injury is significantly less than that suggested by the original Baylor experience.[2–8] Indeed, those who have carried on Dr Crawford's work have reported the incidence of neurological complications to be 6%–8%,[4–6] figures consistent with our own experience.[8]

There is a general consensus that the clinical variables of aortic cross clamp duration, aneurysm extent, emergency operations, and chronic dissection increase the risk of spinal cord injury during thoracoabdominal aortic aneurysm (TAA) operations. For instance, Crawford *et al.* demonstrated that the risk of cord injury increased with aortic clamp duration for each type of aneurysm. Paraplegia was rare when clamp duration was <30 min but rose dramatically if >60 min.[1] Our own experience with 175 patients also emphasises the importance of these clinical factors. We found a significant association between neurological deficit and clamp duration >60 min, acute presentation/dissection, and particularly, ruptured aneurysms ($p = 0.001$).[8] Acher *et al.* incorporated most of the aforementioned clinical variables into a predictive model for neurological deficit after TAA repair,[2] and demonstrated excellent correlation ($r = 0.997$) between the predicted incidence of neurological deficits and those reported in 16 published series. This review will focus on clinically relevant strategies designed to decrease the risk of ischaemic spinal cord injury.

Review of spinal cord blood supply

Even in the non-pathological state, human spinal cord circulation is extremely variable, and in the presence of an aneurysm, additional variability may be introduced by mural thrombus or dissection. Thus the risk of cord injury varies even among patients with equivalent aneurysm extent, owing to the vagaries of the spinal cord circulation.

Spinal cord circulation can be divided into two interconnected parts: the intrinsic and the extrinsic circulation. The intrinsic circulation comprises a single anterior and paired posterior spinal arteries which

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travel in the anterior median sulcus and on the posterior columns, respectively. There are multiple interconnecting anastomoses along the lateral components of the cord from these vessels, but the most important branches are the perforating central arteries from the anterior spinal artery (ASA). These perforating central arteries of the ASA supply 75% of the spinal cord substance, while the paired posterior spinal arteries supply the remainder.

The extrinsic circulation comprises the radicular and medullary arteries and can be considered the "in-flow" for the intrinsic circulation. Radicular arteries travel with the nerve roots, and may or may not continue on as medullary arteries which ultimately contribute to the intrinsic circulation. For example, posterior branches of the intercostal arteries do contribute radicular arteries at each segmental level, but most of these supply only the nerve roots and do not actually contribute to spinal cord blood flow.[9] Also, the medullary arteries are not equally distributed. Most arise from the left, and more connect with the posterior spinal arteries than the ASA. Therefore, the circulation of any particular region of the cord will vary depending on how many radicular arteries actually contribute medullary components. In fact, only seven or eight radiculomedullary arteries supply the entire intrinsic circulation of the human spinal cord.[9]

The principal extrinsic blood supply in the cervical and upper thoracic region is provided by the vertebral arteries. The thoracolumbar cord is supplied by the intercostal and lumbar arteries, and the conus is supplied by the lateral sacral branches, which are terminal branches of the hypogastric vessels.

The cervicothoracic territory has at least four genuine radiculomedullary arteries. Although the middle thoracic segment has only one or two radiculomedullary arteries, the ASA in this region is well-perfused and well-developed. Experienced surgeons will recognise that with a proximal descending thoracic aortic clamp, the intercostal artery ostia in the T4 to T7 region are generally vigorously back-bleeding when the aorta is opened, indicating adequate collateral circulation in this region of the upper thoracic aorta. Alternatively, the thoracolumbar territory is at significant risk for ischaemic injury because this region is mostly supplied by a single radiculomedullary artery. This largest radiculomedullary artery, which is critical to the circulation of the thoracolumbar cord, was originally described in 1882 by Adamkiewicz.[10] It is commonly referred to as the arteria radicularis magna (ARM), the great radiculomedullary artery (GRA), or alternatively the artery of Adamkiewicz. An additional important concept to appreciate is the variability in both the size and continuity of the ASA itself. Although it is true that this is largely a continuous vessel travelling in the central sulcus, the vessel itself becomes extremely narrow in the middle thoracic region and often shows one or more breaks in continuity.[9,11] The calibre of the ASA just cephalad to the anastomotic point of the ARM is extremely small, whereas just caudal to the entry of the ARM it is relatively wide. This unique anatomic configuration, along with the acute angle at which the ARM enters the ASA, actually facilitates cephalocaudal blood flow.[12] The ARM enters the vertebral canal between the ninth to twelfth thoracic vertebral segments in 75%–78%[11,13] of cases. Angiographic studies have shown that one or more intercostal arteries can contribute to the ARM.[11] It is also clear that in the circumstance of extensive obliteration of intercostal vessels in the T9–T12 level, as might be seen in mural thrombus in a degenerative aneurysm, collateral vessels are available to maintain the integrity of the ARM. In an animal model in which the intercostal arteries were divided at the aorta, Giglia *et al.* demonstrated that the internal thoracic (mammary) arteries were able to maintain spinal cord viability during a double thoracic aortic clamp.[14]

Pathogenesis of ischaemic injury to the spinal cord

In the presence of a proximal descending aortic clamp, spinal cord perfusion will depend on the calibre and continuity of the ASA, the presence of patent critical segmental vessels distal to the clamp, and the relative spinal cord perfusion pressure. The latter is defined as the difference between the spinal artery and CSF pressure, and is therefore inversely related to CSF pressure. Proximal thoracic aortic clamping can result in increased CSF pressure presumably secondary to the abrupt increase in cranial bloodflow.[15,16] Our experience has been that this response is variable. Elevation of CSF pressure can be seen in very proximal aortic (i.e. arch) clamping, but a majority of patients exhibit only modest changes with clamping.[16–18] Furthermore, CSF pressure thresholds for compromise of cord blood flow in the human are unknown. The assumption that spinal cord perfusion pressure is equivalent to the distal (i.e. distal to the clamp) aortic pressure has been challenged.[19,20] Furthermore, Kazama *et al.* noted that cord blood flow was compromised by thoracic cross-clamping only when CSF pressure was four times greater than baseline.[17]

Ultimately, cord injury after aortic replacement results from an ischaemic insult that is caused by temporary or permanent interruption of spinal cord

blood supply. However, there continues to be debate about the relative importance of the initial ischaemic insult, and the secondary reperfusion or hyperaemic phase which may cause cord swelling and delayed neurological events. Dramatic individual case reports of reversal of postoperative neurological deficits with administration of naloxone[21] or CSF drainage[22] have been reported. More commonly, neurological deficits which occur in the hours and days after surgery correlate with haemodynamic instability and suggest that cord circulation may be in a delicate balance in the initial postoperative period. Postoperative hypotension with its decrease in spinal cord perfusion pressure has been the most important variable in the development of these delayed deficits. Crawford *et al.* reported that 10 out of 31 neurological deficits in a series of 98 prospectively studied patients occurred in delayed fashion and that these deficits were correlated with postoperative hypotension.[23] We have observed hypotension-induced deficits in the setting of postoperative bleeding and haemodialysis, as have others.[2] These observations strongly suggest that the blood supply to the cord is in a fragile balance for days to even weeks after surgery, and every effort should be made to maintain adequate perfusion pressure in the days following TAA resection. Other mechanisms such as thrombosis of reconstructed intercostal arteries and microembolisation may also contribute to the development of delayed deficits.

On a cellular level, many components of neuronal injury and death are similar to the pathophysiology of other ischaemic tissues, with the important exception that neural tissue is exquisitely sensitive to ischaemic insults. Experimental studies indicate that free radical formation and lipid peroxidation lead to failure of ATP-dependent membrane-bound ion channels which maintain cellular ionic homeostasis and the resting membrane potential.[24] The release of excitatory neurotransmitters such as L-glutamate have been shown to exacerbate this loss of membrane potential via a toxic influx of calcium.[25] The loss of membrane-dependent enzyme systems results in the inability of the cell to regulate its internal environment.

Clinical strategies for prevention of ischaemic spinal cord injury

Strategies for spinal cord protection during the course of thoracic and TAA repair can be divided into two major categories (Table 1). The first general class of these are methods designed to preserve relative spinal cord perfusion pressure. Preoperative (angiographic) and intraoperative (evoked potentials or polarographic) localisation techniques act as guides for the surgeon to preserve or reconstruct critical intercostal arteries. Distal aortic perfusion with shunt or bypasses and CSF drainage are designed to maintain maximal relative spinal cord perfusion pressure during the critical period of aortic clamping. Finally, intercostal and lumbar vessel reattachment is designed to preserve segmental arteries in that region of the cord where the origin of the ARM is most likely to be found (T9–T12).

The second general approach to spinal cord protection is to increase the ischaemic tolerance of the cord during the critical period of aortic clamping. A variety of neuroprotective adjuncts and pharmacological agents have been used for this purpose with variable clinical success.

Preservation of spinal cord perfusion

Preoperative angiographic localisation. With precise anatomic information of both the segmental level and the relative intercostal contribution to the ARM, a surgeon can reconstruct or preserve the appropriate vessels with either bevelled suture lines or with the inclusion button technique. Kieffer *et al.* demonstrated that risk of neurological deficit is highest when the aortic segment from which critical intercostal vessels arise is encompassed in the resection.[26] Williams *et al.* reported a trend towards decreased neurological complications when intercostal vessels which contributed to the ARM could be preserved in proximal or distal suture lines.[13] In a report from the same institution, Savader *et al.* identified the ARM by preoperative spinal arteriography in 65% of patients in whom this technique was attempted, with no difference between type I, II, or III TAA aneurysms.[11] Their angiographic findings were consistent with prior anatomic studies with respect to the level of origin of the ARM. In 78% of the patients studied, the ARM originated between the T9 and T12 levels, and in most of these patients the arteries ultimately supplying the ARM were left intercostals. Consistent with Kieffer's data, in patients where the critical intercostals were not included in the aneurysm resection no neurological morbidity was noted, compared to 50% in those whose resection involved the critical aortic segment. However, except for predicting risk of cord injury, clinical benefit from accurate preoperative localisation of the critical intercostals was not demonstrated in the Johns Hopkins experience. Frequent arguments against routine spinal angiography are that it is very time consuming, labour

Table 1. Strategies to prevent spinal cord ischaemia during thoracoabdominal aneurysm repair.

Maintenance of spinal cord blood supply
Identification of critical segmental (intercostal) vessels
Preoperative selective angiography
Intraoperative H_2 ion method
Intraoperative evoked potential monitoring
Shunts and bypasses – distal aortic perfusion
Passive internal (Gott) or external (axillofemoral) shunt
Atriofemoral or femoral-femoral bypass (partial CP bypass)
Complete cardiopulmonary bypass (w/w/o circulatory arrest/profound hypothermia)
Cerebrospinal fluid drainage
Intercostal/lumbar vessel re-anastomosis
Intrathecal vasodilators
Neuroprotective adjuncts
Hypothermia
Systemic
Passive (moderate)
Active (moderate or profound – with CP bypass)
Regional (moderate)
Epidural or intrathecal infusion (closed or drained)
Isolated aortic segment perfusion
Pharmacological agents
Neurotransmitter inhibition (naloxone)
Non-specific neuroprotective agents (steroids, barbiturates)
Calcium channel blockers
Oxygen free radical scavengers
Artificial O_2 delivery (fluosol-DA)

intensive, and is potentially morbid. However, in the Johns Hopkins study there was only a single case of transient lower extremity paraparesis and no permanent complications. Other reports of spinal angiography have also shown the risk of permanent spinal cord injury to be less than 1%.[27]

Intraoperative polarographic identification. Svensson *et al.* described the use of an intrathecal platinum electrode to identify critical segmental arteries. Briefly, a saturated hydrogen solution injected into isolated aortic segments resulted in an electric current detected by an intrathecal electrode if the segment was in continuity with the ostia of a critical segmental artery.[28] In a series of porcine experiments, they demonstrated that there was a highly significant reduction in paraplegia when intercostals in the aortic segment identified to be contributors to spinal cord blood supply were preserved. The authors applied this technique clinically and were able to identify the critical intercostal segment in six of eight patients. While there was good correlation with this technique and postoperative spinal arteriography, one patient out of five with an identified critical segment and intercostal reanastomosis did sustain a spinal cord ischaemic insult. While this elegant study correlates nicely with the available information concerning critical intercostal segments, its application in the clinical setting appears cumbersome and potentially wasteful of precious aortic clamp time. Subsequent clinical evaluation of this technique has not been published.

Intraoperative evoked potential monitoring. Evoked potential monitoring evaluates the ability of the long tracks of the spinal cord to conduct an impulse during the cross-clamp period. There are two basic techniques: the more commonly applied somatosensory evoked potential (SSEP) monitoring, and motor evoked potential (MEP) monitoring. SSEP utilises a stimulating electrode placed over a peripheral lower extremity nerve and a recording electrode placed over the appropriate cerebral hemisphere. MEP uses stimulation of the motor cortex or motor neurons and records from a peripheral muscle. Variations in the latency and amplitude of the recorded potentials imply ischaemia in the intervening spinal cord for both techniques. A concomitant upper extremity electrode acts as a control for systemic factors such as anaesthetic agents and temperature.

SSEP monitoring has been criticised because it assesses the dorsal (sensory) columns rather than the more sensitive and more clinically relevant ventral (motor) columns. In addition, lower extremity peripheral nerve ischaemia will affect SSEPs in most

patients if no distal perfusion methods are used. More recently, direct spinal cord stimulation with epidural electrodes (scSSEP) has been applied to overcome some of the shortcomings of conventional SSEP monitoring.[29–33]

MEP alterations have shown good correlation with cord injury in experimental systems, but until recently have required open access to the CNS which is not clinically applicable.[34] The use of transcranial stimulation of the motor cortex to detect intraoperative spinal cord ischaemia has recently been reported.[35] The authors used this technique to identify critical intercostal arteries and to modify intraoperative management when ischaemia was detected: however, postoperative paraplegia was still 15% in this series. As with SSEP, MEP mandates that distal perfusion be used because of clamp-induced lower extremity ischaemia.

Cunningham *et al.*[36] and Schepens *et al.*[37] have classified the spectrum of SSEP responses that can occur after aortic clamping and have shown a correlation with postoperative cord injury. Grubbs *et al.* reported 33 patients with an overall incidence of paraplegia of 15% compared to >70% when the SSEP signal was absent for more than 30 min.[38] These authors correlated loss of SSEPs and risk of neurological injury with distal aortic pressure <60 mmHG, and failure to reimplant critical intercostals in <30 min. They acknowledged, however, that their results and recommendations largely applied to those patients in whom the critical aortic segment could be protected with distal aortic perfusion. Therefore, their findings may not be applicable to patients with aortoiliac occlusive disease, distal dissections, or extensive TAA where the T9–L1 region is encompassed in the resection. Subsequently, Crawford *et al.* performed a prospective study wherein two groups of nearly 100 patients each were randomised to either distal perfusion with SSEP monitoring or neither of these adjuncts.[39] Although the incidence of paraplegia was highest in those patients with complete and permanent loss of potentials, there was no statistically significant difference in the incidence of spinal cord complications between the two study groups. Matsui *et al.* noted an overall paraplegia/paraparesis rate of 9% in a series of 68 patients treated with distal aortic perfusion and direct scSSEP recording.[31] These authors correlated decreased femoral artery pressure, increased aortic clamp time and type II TAA with increased risk. These data are similar to the earlier Cunningham study in that patients with lesions limited to the descending thoracic aorta wherein potentials were maintained with distal perfusion had a negligible incidence of cord injury. However, the neurological deficit rate in patients with type I and type II TAA was 16%, no better than with previously employed methods. Similar findings were reported by Shiiya *et al.*[33] who found that scSSEP monitoring could detect ischaemia and guide reconstruction of critical intercostal arteries. Despite such monitoring, 41% of 12 patients with type I, II or III TAA sustained neurological injury, whereas none of nine patients with isolated thoracic aortic aneurysms were paraplegic.

The largest clinical series with scSSEP was reported by Grabitz *et al.* using two electrodes placed directly in the epidural space, one at the L1–2 level for stimulation and one at the T5–6 level for recording.[32] This system proved to be safe and technically successful in 167 of the 172 patients (97%) in which it was attempted. Eighty percent of their patients had type I, II or III TAA (i.e. likely to have resection of the critical aortic segment), and bypass and distal perfusion techniques were not used. Approximately one-third of their patients had no diminution in scSSEP after aortic clamping and there were no neurological deficits in this group. Another third of the patients experienced an intermediate response with normal scSSEPs which began to dissipate 15 min after placement of the aortic clamp. Overall, neurological deficits were 16% in this group. In the group of patients who experienced loss of scSSEPs within 15 min of aortic clamping, neurological deficit was 26%. The overall rate of lower extremity neurological deficit in the entire series was 15%. Not surprisingly, absence of scSSEP loss after aortic clamping varied with the extent of aneurysm; 75% of patients with type IV aneurysms had no change in potentials with clamping, with the corresponding figure for type III aneurysms being 45%. However, only 25% of patients with the more extensive type I and type II aneurysms had no loss of scSSEPs with clamping. Loss of potentials in less than 15 min was seen in at least one-third of patients with type I, II and II aneurysms. Neurological outcome for each group of scSSEP response was correlated with the ability to achieve rapid return of scSSEP with early intercostal vessel re-implantation. While the rapidity of onset of scSSEP loss did not necessarily predict neurological outcome, total time of scSSEP loss and time until scSSEP regeneration as well as total aortic clamp duration were highly significant variables predictive of neurological deficit. Prompt reversal of scSSEP changes after intercostal vessel re-anastomosis provides strong evidence of the worth of this manoeuvre in many patients, if it can be accomplished in a timely fashion. It is likely that earlier studies using SSEP monitoring with peripheral nerve stimulating electrodes are subject to a higher degree of false-negative and false-positive recordings when

compared to the direct scSSEP recording method of Grabitz *et al.*[32] Furthermore, it is important to emphasise that the overall incidence (16%) of neurological deficit in this large series is nearly identical with Crawford's benchmark series of over 1500 patients.[1] Both of these reports utilised the clamp-and-sew technique with selective intercostal vessel re-anastomosis.

Cerebrospinal fluid pressure monitoring and drainage. The rationale for CSF pressure monitoring and drainage for spinal cord protection relates to the theory that perfusion of the spinal cord is related to the difference between spinal artery and CSF pressure. Early investigation by Miyamoto *et al.*[40] and Blaisdell and Cooley[41] demonstrated that CSF pressure would rise with proximal thoracic aortic clamping and attenuating the rise by drainage of CSF could abrogate neurological complications in a dog model. Thoracic aortic clamping is felt to result in an abrupt increase in intercerebral blood flow, which leads to an increase in CSF pressure[15] and subsequently a decrease in spinal cord perfusion pressure. There is evidence that nitroglycerin and nitroprusside can aggravate this decrease and may lead to a worse functional result.[42–46] However, Kazama *et al.* found that CSF drainage favourably influenced spinal cord blood flow only when CSF pressure was experimentally elevated to four times baseline values.[17] Furthermore, spinal artery pressure will vary depending on the position or presence of a distal aortic clamp, the use of distal aortic perfusion, and whether or not the aortic segment supplying the critical intercostal vessels arises caudal to the distal aortic clamp or whether it is open to atmospheric pressure. Bower *et al.*, using a canine double thoracic aortic clamp model, demonstrated a protective effect for CSF drainage even after 60 min of such aortic clamping and correlated increases of CSF pressure with decreased regional spinal cord blood flow.[47] McCullough *et al.* demonstrated nearly complete protection from paraplegia in an animal study when preclamp CSF drainage was performed.[48] This protective effect was presumably due to the significantly higher spinal cord perfusion pressure which was noted in those animals who underwent CSF drainage. In the same article the authors introduced clinical CSF drainage ($n=24$), and reported no neurological deficits when CSF pressure was kept less than 10 mmHg. Subsequently, Crawford and colleagues performed the only randomised, prospective study designed to assess the benefits of CSF drainage.[23] One hundred patients with type I, II and III TAA were randomised but there was no difference in either the incidence (30% vs. 33%), severity, or time course of neurological deficits after TAA resection. However, this study has been criticised because the volume of CSF withdrawn was limited. It is worthwhile to point out that in Crawford's study, a rather aggressive posture towards intercostal vessel re-implantation was also employed. In addition, a retrospective study from the Mayo Clinic compared the incidence of neurological deficit in 50 patients with CSF drainage, and demonstrated no benefit when compared to historical undrained controls.[49] Hill *et al.* reported dramatic reversals of immediate total paraplegic deficits in two patients who underwent emergency TAA resections and in whom prompt early postoperative CSF drainage was used.[22] In both of these patients, initial opening CSF pressures were exceedingly high and deficits totally reversed. However, Grabitz *et al.* studied the effect of CSF pressure monitoring and drainage in a subset of 27 patients who were monitored with scSSEP.[32] CSF drainage alone never restored scSSEP attenuated by aortic clamping in any of these patients. Continuous postoperative monitoring of CSF pressure has been suggested by some as a means to potentially counteract delayed oedema of the cord, thought by some to be important in the pathogenesis of delayed deficits. This has been our policy for several years, although we have yet to observe significant postoperative elevations in CSF pressure. Furthermore, CSF pressures are approximately twice baseline values during clamping with our method of epidural cold infusion and we have not observed postoperative deficits of the thoracolumbar cord.[50] We concluded from this experience that the neuroprotective effect of the epidural cooling outweighed any potential disadvantage of elevation of CSF pressures.

While there is little evidence that CSF drainage alone is protective, it is simple and safe to perform and continues to be used in combination with a variety of other manoeuvres such as distal aortic perfusion,[4] as a component of the so-called multi-modality therapy reported by Hollier *et al.*,[3] and in combination with naloxone.[2] The influence of CSF drainage on cord blood flow is controversial, as reviewed above,[16–18] and will vary in accordance with the level of proximal aortic clamping, the presence and level of a distal aortic clamp, proximal and distal mean arterial pressures, and whether or not critical intercostal vessels are patent and contained in aortic segments undergoing resection.

Intercostal vessel re-anastomosis. Sacrifice of critical intercostal vessels which supply the ARM and/or the ability to reperfuse these arteries in timely fashion are acknowledged by most to be central to the pathogenesis of ischaemic cord injury. From a practical standpoint, re-anastomosis of intercostal vessels can

be technically difficult or even impossible in circumstances where excessive atheroma or an acute dissection surrounds intercostal ostia. Furthermore, even with attempts at re-anastomosis by the inclusion button method, postoperative angiographic studies have suggested that these reconstructions fail in a significant percentage of patients.[28] Early studies from Crawford's group actually suggested that the performance of intercostal vessel re-anastomosis was associated with a worse neurological outcome, although this was attributed to the practical reality that the surgeon will usually expend previous clamp time in an effort to reconstruct intercostal vessels. It is the authors' opinion that there is now sufficient angiographic evidence in humans indicating that the ARM originates between T8 and L1 in nearly all patients and that attempts at intercostal vessel re-anastomosis should be directed towards this region. It is our practice to expeditiously oversew intercostal vessels between T4–T8 and to balloon occlude those vessels in the critical zone selected for subsequent reconstruction. The studies of Wadouh[20] and Dapunt[19] give credence to the theory that freely back-bleeding or intercostal vessels exposed only to atmospheric pressure can create a steal phenomenon and actually decrease relative spinal cord perfusion. It must be acknowledged, however, that intercostal vessel re-anastomosis is usually a "blind" manoeuvre unless one of the aforementioned methods of preoperative or intraoperative localisation of critical intercostal vessels is applied. Scheinin *et al.* even suggested that intercostal vessels should be allowed to freely back-bleed so as to potentially decrease pressure in the spinal canal during the period of aortic clamping, although this viewpoint appears counterintuitive and unsupported by either clinical or investigative data.[51] Acher *et al.* suggested that expending aortic clamp time for intercostal vessel re-anastomosis was a worthless manoeuvre and routinely oversewed all intercostal vessels with the adjunctive use of CSF drainage and intravenous naloxone, and reported an overall neurological deficit rate of 3%.[2] However, these authors must be considered in the minority and most agree that sacrifice of critical intercostal vessels is the single most important factor in the development of postoperative spinal cord injury and therefore believe such vessels should be re-anastomosed. Svensson *et al.* reported the most detailed study of specific level of intercostal vessel management available.[52] These investigators prospectively mapped the number and level of patent intercostal vessels and whether or not such vessels were reattached. They reported a 32% rate of overall spinal cord injury, half of which were devastating paraplegia. There was no difference in the incidence of neurological deficit among these who underwent lumbar or intercostal vessel reattachment versus those who did not. However, these authors did demonstrate that those patients who had sacrifice of patent intercostal vessels at the T8–L1 level had a much higher incidence of spinal cord injury compared to those who did not have sacrifice of vessels at this level. There was a statistically significant improvement in neurological injury rate for those patients who had re-anastomosis of vessels in this critical region compared to those who did not. While these investigators concluded that intercostal re-anastomosis at this level was an important adjunct, an equally valid conclusion would be that intercostal vessel re-anastomosis alone was insufficient to prevent cord injury, as there was still a 30% deficit rate in patients who underwent reconstruction of vessels in the critical zone. Such intercostal re-anastomosis may be inadequate simply because it cannot be performed quickly enough. This conclusion is suggested by the observation of Grabitz *et al.* with direct scSSEP. In patients who had loss of scSSEP with aortic clamping, neurological outcome was much better in the subgroup in whom return of potentials could be achieved by rapid restoration of flow into critical intercostal vessels, for example, by preservation of these vessels in a bevelled proximal anastomosis of a type III aneurysm.[32] Similar conclusions were reached by Dapunt *et al.* in a swine study where localisation and restoration of flow in critical intercostal vessels identified by direct scSSEP improved neurological outcome.[19] These studies also reinforced our opinion that ischaemia during the period of aortic clamping is the single most important event in the pathogenesis of cord injury and that intercostal vessel re-anastomosis will generally need to be supplemented by some neuroprotective manoeuvre, such as regional hypothermia, during the period of clamping in order to be successful.

Distal aortic perfusion with shunts and bypasses. Retrograde distal aortic perfusion to that aortic segment caudal to a distal occluding clamp is intuitively logical when distal occlusion is at or more proximal to the T8–T9 level, the rationale being that the aortic segment from which critical intercostal vessels are likely to arise can be continuously perfused during the course of operation. In fact, there is reasonable evidence that in surgery confined to the proximal thoracic aorta, distal perfusion can decrease the incidence of neurological deficit, particularly as clamp times exceed 30 min.[4,53,54] In the circumstances of type I, II, or III TAA repair, the critical aortic segment will generally be encompassed by the resection and cannot be continuously perfused. Furthermore, the critical aortic

segment with respect to intercostal origin lies topographically in proximity to the visceral vessels so that these cannot be separated with use of a sequential clamping technique.

A wide array of shunts and bypasses have been described for thoracic aortic resection. These include internal passive shunts such as the Gott shunt which requires insertion either into the left ventricle, proximal thoracic aortia or left subclavian artery and the femoral artery or the aorta caudal to the distal clamp.[55] While some have reported continued excellent results with respect to paraplegia after thoracic aortic aneurysm resection using this method,[53,55] few centres utilise this technique in contemporary practice mainly because of: (1) the morbidity related to the proximal and distal insertion sites, and (2) the questionable amount of distal aortic perfusion and pressure delivered.[56] Since the Gott shunt was formulated from non-thrombogenic polymers (tridodecylmethylammonium chloride–heparin-coated polyvinyl), systemic heparin was not necessary.[55] A similar principle employing an externally placed shunt was reported by Comerota and White, who utilised a temporary axillo-femoral bypass.[57] Other variations on the theme of external or extra-anatomic bypass have included temporary ascending to descending thoracic aortic shunt and axillary to iliac artery bypass. Among the varieties of partial cardiopulmonary bypass techniques used to accomplish the same end, femoral-femoral bypass has the advantage of an in-line heat exchanger and oxygenator, but has the distinct disadvantage of requiring full doses of heparin.

Partial left heart bypass with use of an atrial-femoral bypass and a simple motorised centrifugal pump was an important advance because this required little or no intraoperative heparin.[58] The majority of surgeons who prefer distal aortic perfusion currently use this method. Sequential reports from a number of institutions[4,59,60] are available, indicating an evolution of surgeons' preference to the atrial-femoral bypass technique. Often these methods are supplemented with other adjuncts such as cerebrospinal fluid drainage.[4] Safi *et al.* reported that adoption of atrial-femoral bypass had a statistically significant impact on neurologic deficit after type II thoracoabdominal aneurysm compared to institutional historical controls. However, the incidence of neurological deficit in the control group was 38.9%.[4] Table 2 summarises the results of contemporary series reporting experience with approximately 100 or more patients undergoing TAA repair with either distal perfusion or a clamp and sew technique.[1–5,8,32,59,61] While a variety of other adjuncts are used in most of these series including our own, when examining the variable of atrial-femoral bypass versus a clamp-and-sew technique, no significant difference is evident in the incidence of postoperative neurological deficit, postoperative renal failure, or operative mortality.

Neuroprotective adjuncts for prevention of spinal cord ischaemia

Hypothermia. Hypothermia has been used throughout the evolution of cardiac and central aortic surgery. Although the neuroprotective effect of hypothermia is presumed to be secondary to decreased tissue metabolism and to a generalised reduction of energy requiring processes in the cell, the mechanism may be more complex involving membrane stabilisation and reduced release of excitatory neurotransmitters.[62] Oxygen requirements in neural tissue are known to decrease 6–7% for each degree decrement in cord temperature.[63] Hypothermia for purposes of cord protection during TAA surgery can be either regional (i.e. confined to the spinal cord) or systemic (see Table 1). In a model of spinal cord ischaemia, systemic hypothermia has been shown to blunt the hyperaemic response after cross-clamping and reperfusion injury.[64] Profound hypothermia (15°–18°C) and circulatory arrest have been used successfully for many years in circumstances of correction of complex cardiac and/or aortic arch disease. However, enthusiasm for extending this philosophy to TAA resection has been limited, principally related to the threat of coagulopathy, pulmonary complications, and massive fluid shifts. Kouchoukos *et al.* have used this approach specifically for spinal cord protection during TAA resections.[65] They reported use of this technique in 51 patients undergoing a variety of central aortic operations. Overall, 30 days' mortality was 9.8% and spinal cord injury occurred in 6.5%. Among the 27 patients with type I, II and III TAA, neurological deficit occurred in 7.5% of those who survived operation. We believe maintenance of near normal temperature homeostasis is an important component of the operative management of TAA. This view is supported by Bush *et al.*, who reported that hypothermia to a level of 34.5 °C was significantly and independently associated with the development of complications after elective abdominal aortic operations.[66]

Variations of systemic hypothermia include so-called passive moderate hypothermia, where core temperature is allowed to drift to the 32–34 °C range by merely lowering the room temperature and allowing heat evaporation from the large surgical field. Active

Table 2. Operative complications in major series of thoracoabdominal aneurysm repair.

Series	n	Clamp and sew technique Paraplegia/Paresis # (%)	Renal failure # (%)	Mortality # (%)
Cambria *et al.*[8]	160	11 (6.9)	16 (10)	15 (9.4)
Acher *et al.*[2]	110	12 (11)	3 (2.7)*	8 (7.3)
Coselli[5]†	309	23 (7.4)	22 (7.1)	19 (6.1)
Grabitz *et al.*[32]	260	39 (15)	27 (10.4)*	37 (14.2)
Hollier *et al.*[3]	150	6 (4)	14 (9.3)	11 (7.3)
Mauney *et al.*[61]	91	9 (9.9)	10 (11)	12 (13.2)
Svensson *et al.*[1]†	1251	178 (14.2)	235 (18.8)	100 (8)
Totals	2331	278 (11.9)	327 (14)	202 (8.7)
Series	n	Bypass/distal perfusion technique Paraplegia/Paresis # (%)	Renal Failure # (%)	Mortality # (%)
Coselli[5]†	63	1 (1.6)	7 (11.1)	2 (3.2)
Safi *et al.*[4]§	94	8 (8.5)	20 (21.3)	9 (9.6)
Svensson *et al.*[1]†	258	56 (21.7)	34 (13.2)	23 (8.9)
Schepens *et al.*[59]	50	5 (10)	5 (10)*	4 (8)
Totals	465	70 (15)	66 (14.2)	38 (8.2)

* Only those patients who required dialysis.
† These reports detail separate results with the two techniques.
§ Includes only type I and II TAA.

moderate systemic hypothermia can be achieved with use of an in-line exchanger with atrial-femoral or femoral-femoral bypass. The degree of hypothermia achieved with this method is limited by the potential for cardiac arrhythmias. Two variations of regional hypothermia have been reported. These include the direct installation of cold perfusate into the epidural or intrathecal space or into isolated thoracic aortic segments, with the intention that cold perfusate will be delivered to the spinal cord via the intercostal arteries. The latter technique was originally reported by Coles *et al.*[67] These investigators showed in dog experiments that isolated aortic segments between two clamps when perfused with cold Ringer's lactate would rapidly diminish cord temperature to 20 °C and was 100% effective in preventing paraplegia. Colon *et al.* added continuous perfusion to an isolated aortic segment in a swine model using the Bio-Medicus® pump and cooled blood perfusate.[68] No animal so treated developed neurological deficits. Ueno *et al.* showed a similar benefit of hypothermic perfusion in a rabbit model, although no verification of levels of hypothermia achieved in the spinal cord were reported.[69,70] Clinical experience using a variation of this approach was reported by Fehrenbacher *et al.*, who employed atrial-femoral bypass and passive perfusion of isolated aortic segments in the course of a sequential clamping technique.[71] There was no verification of the level of hypothermia achieved at the level of the spinal cord, and in the clinical setting this method will be limited by the number and size of patent intercostal vessels. The authors used their technique in 23 patients with type I and II TAA, and reported a 4.3% incidence of both paraplegia and operative mortality. Given our experience with the volumes of direct epidural cold infusate required to achieve moderate cord hypothermia (see below), and the aforementioned anatomic limitations of intercostal–radiculomedullary arteries in the human, it appears unlikely that isolated aortic segment perfusion could achieve meaningful levels of cord hypothermia in patients.

Experimental work with regional hypothermic perfusions delivered directly to the epidural or intrathecal space and achieving profound (less than 20 °C) hypothermia have demonstrated a 100% protective effect against cord injury in several animal models.[72–75] To achieve this degree of hypothermia, however, has generally required open laminotomy techniques not applicable to the clinical setting. It remained for Marsala *et al.* to demonstrate that a clinically applicable closed epidural infusion system which achieved moderate (~27 °C) levels of cord hypothermia could be 100% effective against spinal cord ischaemia induced by double thoracic aortic clamping.[76] We adapted this strategy and have used it clinically since 1993. The mechanics of the epidural infusion system have been

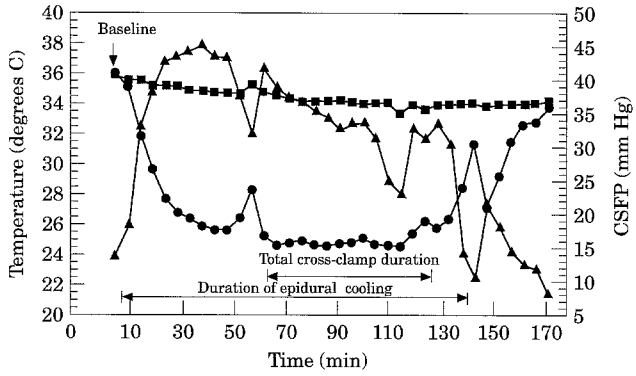

Fig. 1. Graphic display of mean data for CSF temperature and pressure, and core temperature in 70 patients undergoing repair of type I, II and III TAA with use of epidural cooling. Total cross-clamp duration refers to interval until reperfusion of legs. Note mean CSF temperature of 25 °C during clamp interval and rapid return of same to baseline after discontinuation of epidural cooling. (reprinted with permission.[50]) (■) Core temp.; (●) CSF temp.; (▲) CSF pressure.

described in detail.[77] Briefly, a 40 cm epidural catheter placed at the T11–12 level and advanced cephalad 4–5 cm is used for both administration of local anaesthetics and infusion of iced (4 °C) saline. A second 4–French thermistor catheter is placed 4 cm into the subarachnoid space at the L3–4 level, permitting both continuous recording of CSF temperature and pressure. No drainage catheter is used as the infusate rapidly runs out along nerve roots. The infusion is begun well in anticipation of aortic clamping, such that CSF temperatures in the range of 23–25 °C (in the thoracolumbar segment) are achieved at the time of aortic clamping. We have also demonstrated that the effect is regional by SSEP monitoring from the lower and upper extremity in a small series of patients. We could demonstrate that potentials from the thoracolumbar cord are ablated as anticipated because of the hypothermia, but those recorded after median nerve stimulation are preserved, demonstrating that the hypothermic effect did not reach the upper thoracic or cervical cord.[78] CSF temperature and pressure and core temperature for 70 patients undergoing resection of type I, II and III TAA with use of epidural cooling are displayed in Fig. 1. CSF pressure can rise dramatically during initiation of the infusion and averages twice the baseline value during the period of aortic clamping. The average volume of infusate used in our 70 patients was just over 1400 ml, and the mean CSF temperature at the point of aortic clamping was 25 ± 1°C. Other relevant intraoperative data included a visceral ischaemic time which averaged 48 min and an aggressive posture towards re-anastomosis of patent intercostal vessels in the T8–L1 region. Fifty per cent of patients had patent intercostal vessels in this zone either preserved in bevelled proximal or distal anastomosis or reconstructed with separate inclusion buttons. Neurological outcome in these 70 epidural cooling patients was significantly better than a historical control group from our institution who underwent operation in the 3 years immediately prior to adoption of the epidural cooling system[50] (Table 3). Furthermore, there was a highly significant reduction in the predicted incidence of neurological deficits using the Acher model.[2] The rationale for regional hypothermia relates to protection of the cord during the critical period of aortic clamping. Failure of intercostal vessel re-anastomosis to impact significantly on the complication of paraplegia may in part be related to the fact that revascularisation simply cannot be performed rapidly enough to prevent ischaemia. The data of Grabitz *et al.* with scSSEP monitoring of critical intercostal re-anastomosis suggested that the ischaemic window for return of potentials was less than 20 min.[32] Our data have led us to the conclusion that in those patients at high risk for paraplegia (i.e. resection of T8–L1 with patent intercostal vessels) some neuroprotective manoeuvre during the interval of aortic clamping must be added to intercostal vessel re-anastomosis to prevent cord ischaemic complications.

Pharmacological. A wide variety of pharmacological agents have been utilised in clinical and laboratory studies to increase the ischaemic tolerance of the spinal cord to aortic clamping. While many of these agents have shown a protective benefit, there is difficulty in interpreting their clinical utility. Interpretation of the clinical literature is hampered by evolution in surgical and anaesthetic techniques, and the use of other adjuncts including distal aortic perfusion, CSF drainage, and hypothermia. Animal studies have varied ischaemic insults which do not always allow conclusions to be drawn concerning clinical utility. However, several neuroprotective agents have shown promise in various settings and are worthy of review.

Corticosteroids have been investigated for nearly 30 years as a way to reduce spinal cord injury following trauma.[79–81] Similar salutary effects have been seen after ischaemic spinal cord injury.[82] A 21-aminosteroid (U-74006F, Upjohn) devoid of glucocorticoid or mineralocorticoid side effects,[83] has also been shown to have protective effects in models of spinal cord ischaemia, presumably via inhibition of reperfusion-associated lipid peroxidation and hydrolysis.[84] Free excitatory amino acids, especially glutamate, are elevated following spinal cord ischaemia, and are felt to be involved in the cascade which results in neuronal death.[85] Blockade of N-methyl-D-aspartate (NMDA) excitatory neurotransmitter receptors by $Mg^{2}+$, dextrorphan, and other compounds decreases ischaemic

spinal cord injury.[86–90] Naloxone, an opiate antagonist, has been shown to be neuroprotective in a variety of laboratory and clinical studies.[2,21,91] While its mechanism of action is not completely known it also appears to affect lipid peroxidation and cell membrane stabilisation via an attenuation of the inactivation of $Na+-K+Mg^2+$ ATPase.[92] An integral part of the cascade is the eventual influx of calcium. In experimental models of spinal cord ischaemia calcium channel antagonists have been found to preserve function,[93,94] and to reduce infarct size.[95] Barbiturates have been shown to be protective in spinal cord ischaemia either by reducing metabolic demand or by acting as an oxygen free radical scavenger.[96,97] Other oxygen free radical scavengers, such as deferoxamine, U-74006F (Tirilazad, Upjohn) and superoxide dismutase have also been shown to decrease reperfusion related injury.[98–101] Antibody mediated blockade of activated neutrophils, another source of oxygen free radicals, failed to ameliorate ischaemic injury in at least one experimental study.[102] Perfluorocarbons have been perfused intrathecally and systemically in experimental models of spinal cord ischaemia, with near complete prevention of neurological deficits.[103,104]

Few clinical series are available to corroborate the experimental studies. Hollier *et al.* used systemic barbiturates as a component of "multimodality therapy" and reported excellent results in elective TAA resection.[3] Acher *et al.* used naloxone infusions with CSF drainage and noted significant improvement in neurological deficits when compared to historical controls,[2,21] even though the naloxone dose was much lower than those suggested by animal studies.[91]

Summary

Since the publication of prior reviews on this topic, substantial clinical experience with a variety of operative strategies to prevent ischaemic cord complications has been reported. The available data on angiographic localisation of critical intercostal vessels,[11,13,26] and, in particular, the evoked potential response to cross-clamping in patients[31–33,36] indicates that risk of paraplegia varies considerably even among patients with equivalent TAA extent. Factors such as individual development of the ASA, patent critical intercostals, and the particulars of collateral circulation when intercostal aortic ostia are already occluded likely account for this variability. Information available from SSEP monitoring relative to the dynamic course of cord ischaemia with cross-clamping, and the parallel, if not, frustrating experience with angiographic localisation and intercostal vessel reconstruction indicates that a narrow temporal threshold of cord ischaemia with clamping is present in many patients. This reinforces the importance of both expeditious clamp intervals, critical intercostal re-anastamoses, and the desirability of neuroprotective manoeuvres during cross-clamp induced cord ischaemia. As suggested in compelling experimental work[73–76] our contemporary clinical experience,[50] and predicted by prior reviewers,[105] regional cord hypothermia provides significant promise for limiting or eliminating, in particular, immediate perioperative deficits. Avoidance of postoperative hypotension, spinal cord oedema, and preservation of critical intercostal vessels are additional strategies necessary to impact the development of delayed deficits favourably.

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