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"Late spinal cord ischemia after thoracoabdominal aortic aneurysm repair"

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Chapter I: Introduction

Definition

A thoracoabdominal aortic aneurysm (TAAA) is an increase in aortic diameter at least 50% greater than physiologic size and with involvement of the aorta at the diaphragmatic hiatus. Physiologic aortic diameter varies according to age, sex and body surface area and it is diverse at different aortic segments, with a decreasing trend from the ascending aorta to the iliac bifurcation.

Figure 1: Thoracoabdominal aortic aneurysm 3D CT-scan reconstruction

Etiology

Cause of TAAA development can be classified into four major groups. The most common is medial degeneration of the aortic wall, followed by dissection, genetic disorders involving connective tissue composition, and infections of the aortic wall.

Medial degeneration is the result of destruction of elastin fibers and loss of smooth muscle cells within the medial layer of the vessel wall.

Aortic dissection is the second cause of TAAA. Aortic dissection is a separation of the laminae of the medial layer caused by blood flowing through an entry tear in the intima. One or more distal re-entry tears can be present along the aorta. Classification is based on timing from onset: dissections are defined as acute in a time-span <14 days from initial tear, after that they are considered chronic.

Borst and al have suggested to refer to dissection in between 2 to 6 weeks from onset as subacute, as in this time-period the vessel wall and dissection lamella is still fragile and not fully sclerotic and thick as in chronic dissections.

Two different classifications are available according to extent of dissection and site of proximal entry tear. In the DeBakey classification, type I dissections involve the ascending aorta onwards to the descending thoracic aorta and the abdominal aorta (Figure 2). Type II dissections involve the ascending aorta alone. Type III dissections originate in the descending thoracic aorta and are divided into IIIa, if the dissection extends to the abdominal aorta, and IIIb if it is limited to the thoracic aorta.

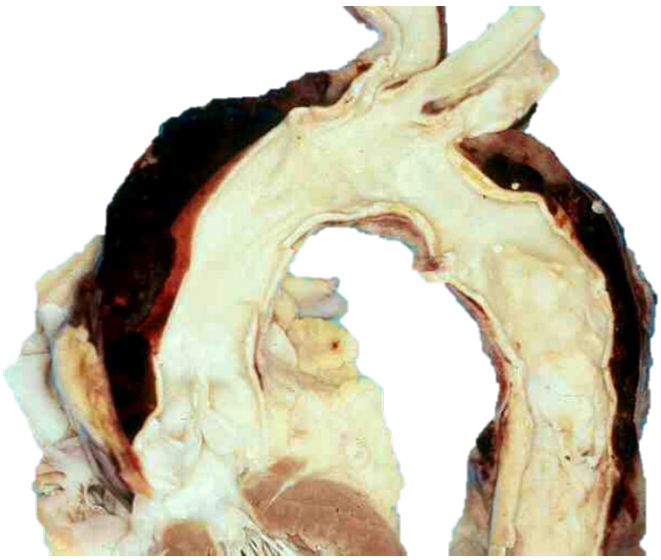

Figure 2: gross anatomy picture of Type 1 aortic dissection showing extensively dissected media filled with blood

Stanford classification refers to dissections involving the ascending aorta as Type A, dissections, and to those that spare the ascending aorta as Type B. This distinction is important because it is the main determinant of clinical and surgical management.

Genetic connective tissue disorders are frequently associated with TAAA development: Marfan, Loeys-Dietz and Ehlers-Danlos syndromes are the most predominant. In Marfan syndrome, a mutation in the fibrillin-1 gene determines abnormal transforming growth factor-beta (TGF-β) activity, leading to degeneration and weakening the aortic wall matrix. Loeys–Dietz syndrome is caused by alterations in TGF-β receptors genes, with a plethora of clinical presentations including aneurysms. Ehlers-Danlos has a high variability in terms of presentation and genetic pattern, but it is caused by deficits in collagen synthesis due to mutations in genes coding for fibrous proteins or enzymes.

Infections of aortic wall can cause mycotic aneurysms. They mostly present as sacciform aneurysms rather than fusiform and usually occur in the region of the visceral vessels. Staphylococci, Salmonella and Streptococci are the most common microorganism known to cause mycotic aneurysms although historically syphilis used to be a predominant infectious etiology of aortic aneurysms. But since the diffusion of screening and pharmacological therapy the incidence has decreased drastically and is mostly limited to third world countries.

Classification

To stratify operative risk and standardize studies on the pathology in 1986 Crawford proposed the first TAAA classification based on aneurysm extent, and divided them in four types or extents (Figure 3).[1]

Type I: extends from the left subclavian artery (LSA) downwards, until the origin of visceral arteries. Type I TAAA differs from descending thoracic aortic aneurysms (DTA), as the latter do not involve the celiac axis.

Type II: is the most extensive TAAA, originating at the level of the LSA and involving the whole abdominal aorta. In type-B dissections and Marfan patients the aneurysm can involve also the iliac arteries.

Type III: affects the lower part of the descending thoracic aorta, from T6 level, and the abdominal aorta.

Type IV: involves the abdominal aorta from the diaphragm to the bifurcation.

This classification aids in understanding disease extent and procedure planning.

The extent of the aneurysm is strictly correlated with peri-operative complications like paraplegia, renal failure and lung failure.

Safi et al.[2] suggested a variation to the original Crawford classification to include a type V TAAA, extending from below T6 to above the renal arteries, thus including the aortic segment from which, according to some authors, the most critical intercostal arteries arise.

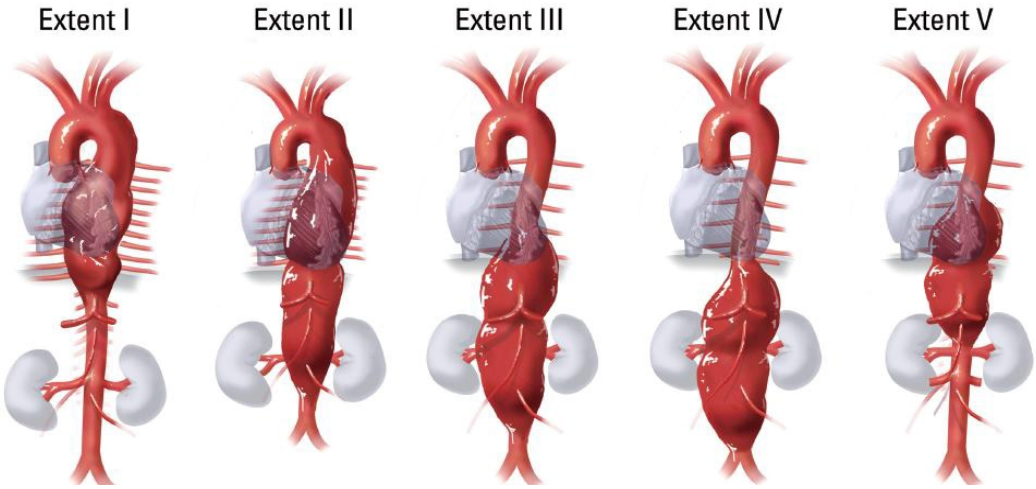

Figure 3: Classification of thoracoabdominal aortic aneurysms, including Safi variation

Surgical procedure

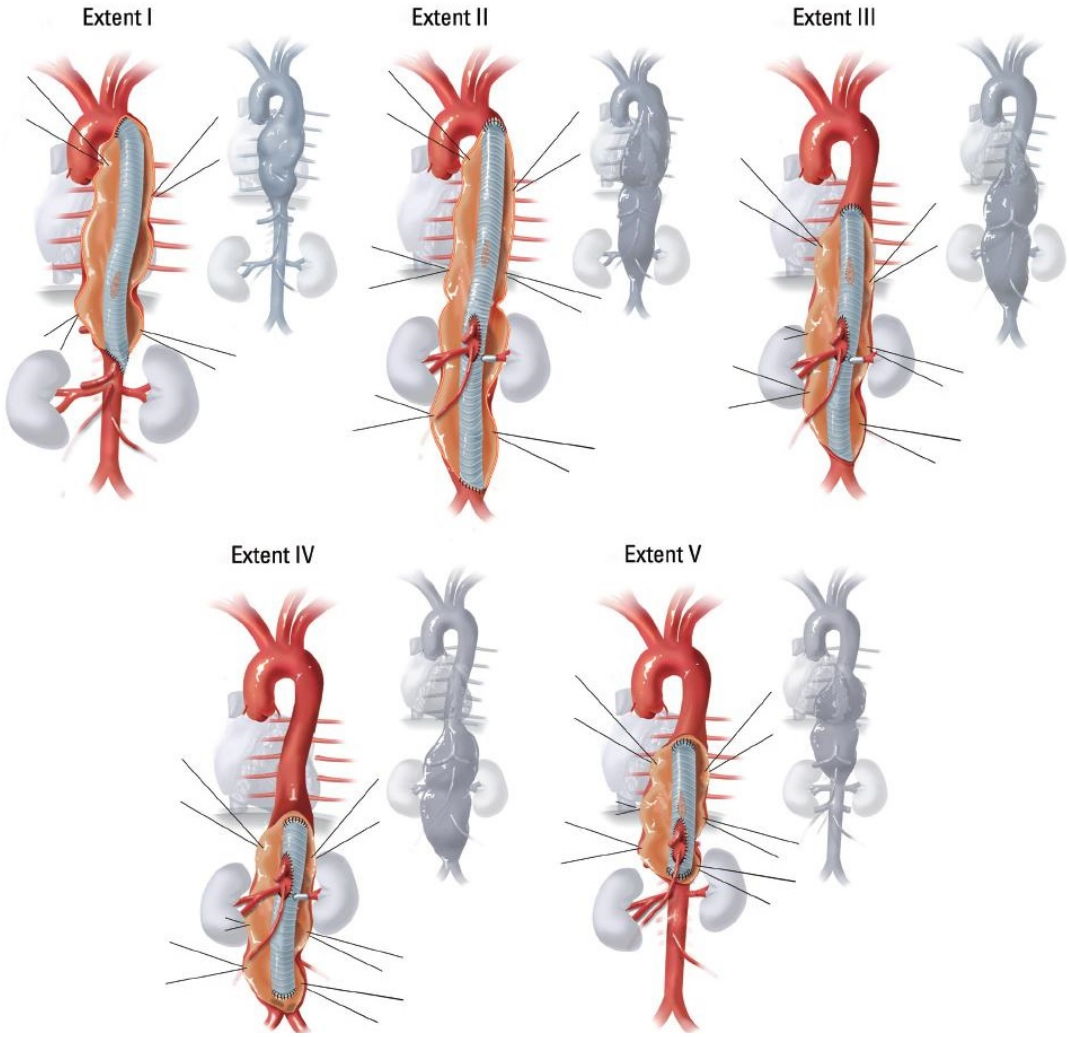

Figure 4: Different repair extents according to aneurysm type

Surgical access to the thoracoabdominal aorta

For surgical access the patient is placed in right lateral decubitus. The shoulders are rotated 15° posteriorly and the pelvis is rotated 50° posteriorly, to allow femoral artery access if needed. Left thoracotomy is performed to gain access to the DTA. Different intercostal spaces can be approached according to different pathology extent. A higher intercostal space (4^{th}/5^{th}) allows better exposure of distal aortic arch and proximal DTA while a lower intercostal space can be incised for type 3 and 4 TAAA. The thoracotomy incision is continued through the costal margin caudally to a paramedian laparotomy. Following fascial and muscular layer incision blunt

dissection and medial rotation of abdominal content is performed to gain retroperitoneal access. The diaphragm is incised circumferentially avoiding injury to the central tendon, site of innervation. The diaphragmatic crus can be spared to minimize post-operative dysfunction or incised for better aortic exposure.

Repair of the thoracic aortic segment

After isolation of clamping sites (proximal and distal aneurysm necks, and intermediate sites for sequential clamping) a variable amount of heparin is administered IV and cannulae for left heart or cardiopulmonary bypass are put in place and the pump is started. In Type II TAAA the distal arch can be mobilized by carefully dividing the ligamentum arteriosum, avoiding injury to the vagus and recurrent laryngeal nerves.

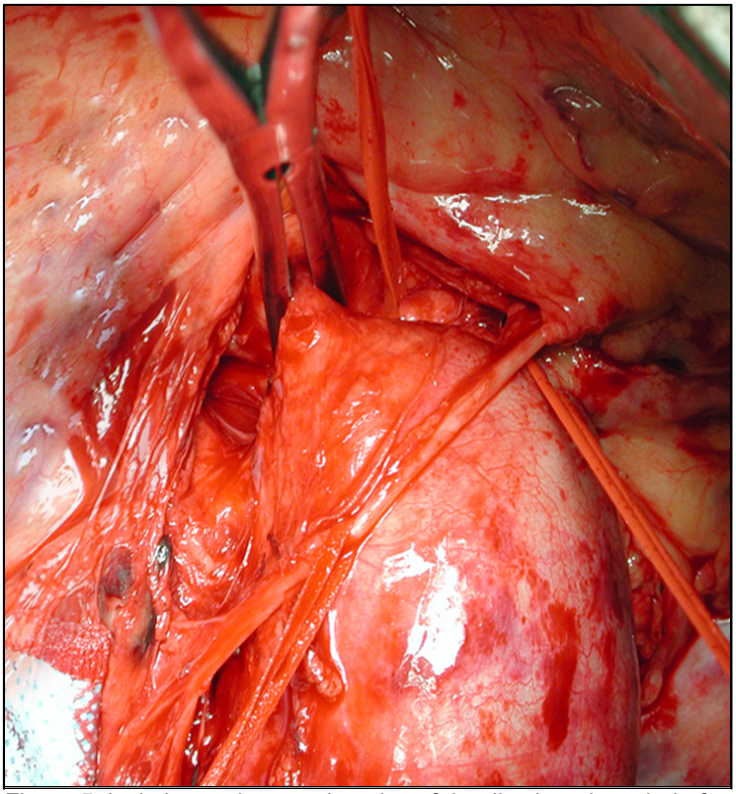

Figure 5: Isolation and cross-clamping of the distal aortic arch. Left subclavian artery is visible just distally to the clamp and recurrent laryngeal nerve is evident on top of the descending thoracic aorta.

The proximal clamp can be placed between the left common carotid and LSA origins if the extent of the aneurysm doesn't allow a more distal clamping. In very complex aortic aneurysms, where no safe proximal clamping site is available, deep hypothermic circulatory arrest is a valid option. Location of distal clamping varies according to surgical technique, it can be placed in the mid-DTA if sequential clamping is employed to decrease ischemic time, or at the distal aneurysm neck if a more expeditious surgery is planned. The aneurysm sac is then opened and non-reimplantable intercostal and lumbar arteries are oversewn. A Dacron graft is selected according to aortic neck size, and the proximal anastomosis is performed using a running 2-0 polypropylene suture. At suture completion the clamp is moved to the graft to check for

anastomosis hemostasis and decrease clamping damage to the aortic wall. Reimplantation of some intercostal arteries on the graft is possible if deemed necessary by the surgeon.

In patients with concurrent untreated ascending or arch aneurysm, a reverse elephant trunk technique can be considered by infolding the proximal portion of the Dacron graft to facilitate the future distal anastomosis during subsequent arch repair.

Repair of the abdominal aortic segment

At the abdominal level, once the aneurysm is opened, the origin of the visceral and renal arteries is identified and endarterectomized if necessary. Selective perfusion with normothermic blood or cold solutions is performed for organ protection. Visceral and renal arteries can be reimplanted on the graft as an aortic wall button or individually with different techniques. Subsequently the clamp is moved distally on the graft to allow reperfusion while distal anastomosis is performed.

Many variations exist on surgical technique and organ protection devices employed according to TAAA extent. For instance, Type I aneurysms can usually be repaired with a beveled anastomosis to the abdominal aorta just above the visceral segment.

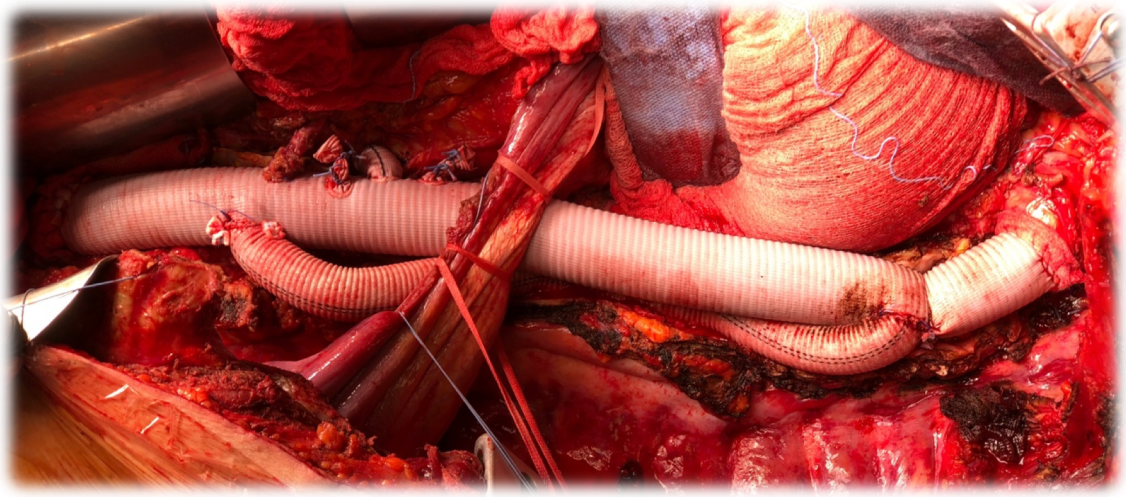

Figure 6: final result of type 2 TAAA reconstruction with multi-branched Dacron graft

Chapter II: Spinal cord

Vasculature

Blood is supplied to the spinal cord by one anterior spinal artery (ASA) and two posterior spinal arteries. The former supplies the anterior portion of the spinal cord where corticospinal, lateral spinothalamic, and autonomic inferomedial pathways are located. Consequently, a severe ischemic lesion involving the territory of the ASA would present with paraplegia, loss of pain and temperature sensation, and autonomic dysfunction.

The posterior spinal artery provides blood flow to the dorsal columns.

Historically, spinal cord perfusion was thought to be dependent principally upon a single prominent branch of the descending thoracic aorta the so-called artery of Adamkiewicz, or Arteria Radicularis Magna, which supplied the anterior spinal artery (ASA).

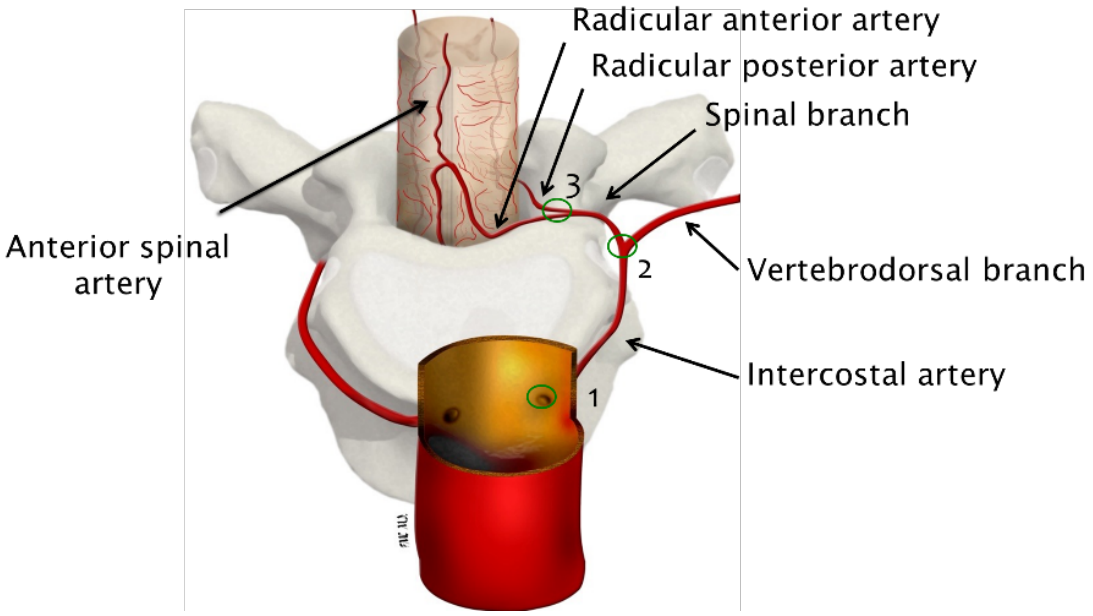

Figure 7: Pictorial representation of the spinal cord vascularization.

The earliest anatomical studies reported were conducted both by post-mortem dye injection in the vertebral artery and by infusion in the abdominal aorta. At necropsy examination, the ASA was a continuous vessel present without interruption along the spinal cord in all studied cases.[3]

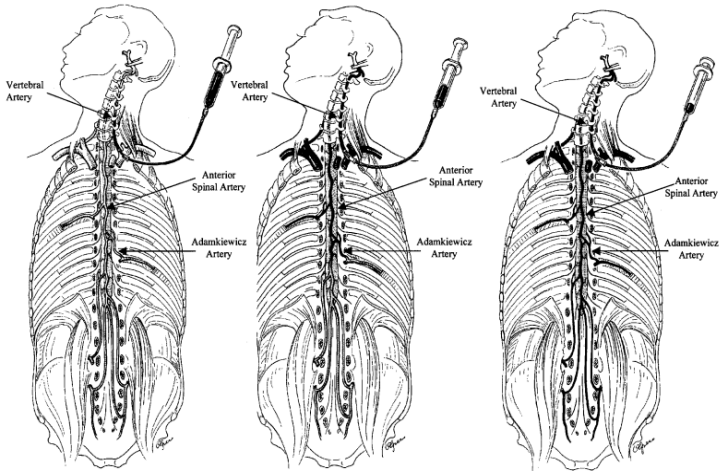

Figure 8: Drawing of the investigational technique used to identify critical intercostal arteries, feeding the ASA, by retrograde dye injection through the vertebral artery.

Nowadays instead a novel view on spinal cord blood supply is being validated, also thanks to improving non-invasive imaging techniques and functional tests which highlighted the existence and importance of an extensive collateral circulation.

This collateral network is composed of all segmental arteries (SA), both intercostal and lumbar, feeding the ASA. In addition, the ASA can potentially receive input from the epidural arterial network, and can be connected to the multitude of small vessels supplying the intercostal and paravertebral musculature.

Figure 9: Post-mortem vessel plastination revealing the much more complex nature of spinal cord vascularization

The whole system is interconnected, and form anastomoses with the subclavian arteries cranially, and the hypogastric arteries caudally (Figure 10).[4]

This extensive network, in theory, would allow compensatory flow to the spinal cord when some of the tributaries are lost temporarily or permanently during repair of TAAAs.

Intra-operative findings of back-bleeding from patent intercostal arteries at aneurysm sac opening further supports the collateral network idea.

To prove the relative importance of each supplier of the collateral network a series of experiments have been carried out in animal models.

A study demonstrated in a swine model that the subclavian and median sacral arteries (equivalent of the human hypogastric arteries) are important feeders of the collateral network as well. Indeed, if any of those are ligated, fewer SAs can be sacrificed before spinal cord ischemia onset.[5]

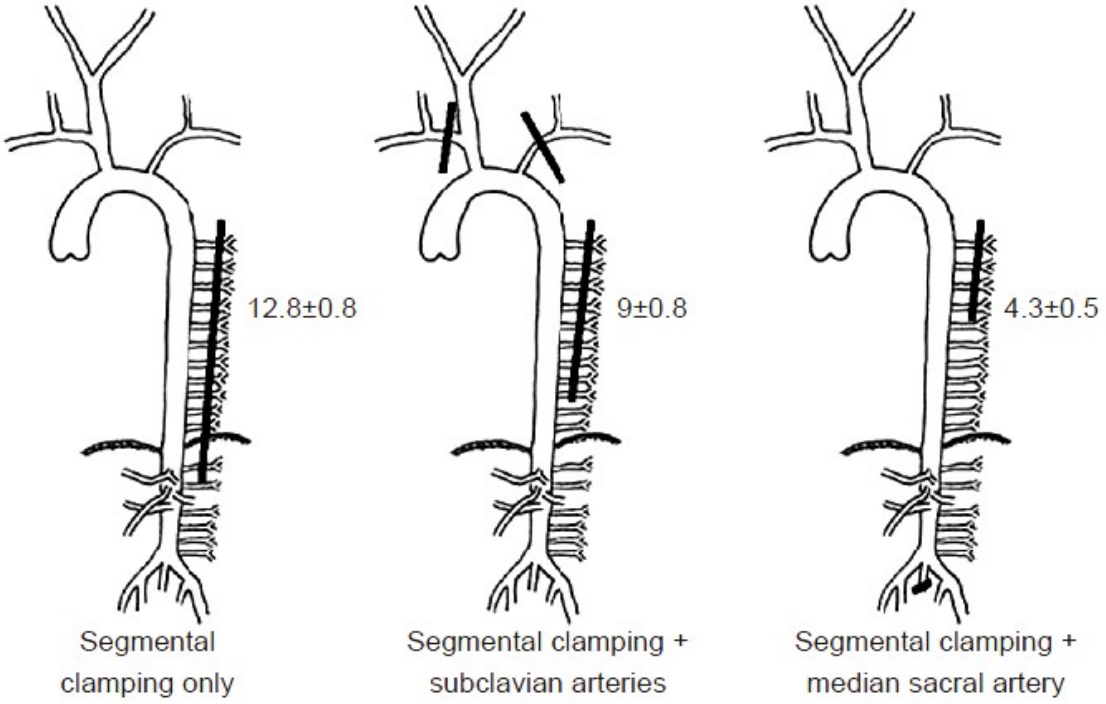

Figure 10: Number of segmental feeders which can be closed before SCI onset according to subclavian and median sacral arteries patency status.

Also mammary arteries may play a role in the network, as suggested by Giglia et al.[6]

While during embryonic stage the spinal cord supply relies on 31 bilateral segmental feeders most of them physiologically regress in the adult human and, furthermore, in degenerative thoracoabdominal aneurysms many of the remaining segmental arteries are occluded by mural thrombus or atherosclerotic plaques. This again suggests that, in these patients, spinal cord perfusion deeply relies on an extensive collateral network.

Pathophysiology of spinal injury

Spinal cord injury during and after thoracoabdominal aortic aneurysm (TAAA) surgery remains one of the most dreaded complications. The cause of such damage is multi-factorial.

Arterial etiology

During open TAAA repair aortic cross-clamping determines an obvious decrease in the perfusion pressure of the spinal cord.

In a baboon model, Svensson and Loop have demonstrated a 90% fall in thoracic and lumbar spinal cord blood flow to 1.8ml/100g of tissue/minute after aortic occlusion for 60 minutes, and consequent paraplegia onset. In the same experiment a flow of 10 ml/100g tissue/minute determined no paraplegia. Conversely, whenever blood flow was reduced to 4 ml/100g tissue/minute paraplegia was the common end-point.[7] This is just one of the many studies supporting the idea of a minimum blood flow requirement for paraplegia prevention.

Truly, regardless of the mechanism, any decrease in spinal cord perfusion results in neuronal death.

In normothermic conditions mitochondrial oxidative phosphorylation stops after 3-4 minutes resulting in depletion of the adenosine triphosphate (ATP) stores, and failure of the ATP-dependent membrane pumps, which regulate intracellular calcium homeostasis. Increasing intracellular calcium activates the release of cytoplasmic enzymes that damage DNA and structural proteins, and also results in production of xanthine oxidase, which mediates free radical production during reperfusion and release of neurotoxic amino acids aspartate and glutamate.[8]

The free radicals further damage DNA, degrade cellular structural elements, cause a loss of membrane integrity, and increase the ratio of vasoactive prostaglandins. Prostaglandins further exacerbate the ischemia by inducing vasospasm and microvascular thrombosis.

Since the spinal motoneuronal system has a high metabolic rate it is especially vulnerable to ischemia.

Furthermore, proximally to the clamp the aortic pressure rises. The proximal aortic hypertension results in an increase in cardiac afterload and an increase in CSF pressure which, associated to the spinal cord edema due to membrane disruption, can result in paraspinal compartment syndrome, thus worsening perfusion.

A third pathway leading to spinal cord ischemia is represented by thrombus embolization into critical spinal arteries. Most thoracoabdominal aneurysms indeed are characterized by abundant parietal thrombus and wall atherosclerotic plaques which at aortic isolation and clamping can be disrupted and dislodged with consequent embolization to peripheral, visceral and spinal vessels.

Several authors also proposed that, because of the collateral network, segmental arteries back-bleeding into the opened aneurysm sac may determine significant blood flow steal from the ASA further worsening spinal cord perfusion.[9–11] This was emphasized by Svensson et al. who demonstrated that patients who had limited back-bleeding from segmental arteries during TAAA repairs, had a significantly decreased risk for neurologic deficits.[12]

Venous etiology

Tobinick and Vega described the vertebral venous system as a large-capacity, valveless network in which flow is bidirectional. The system spans from the suboccipital intracranial veins to the sacral and pelvic veins and it includes the vertebral venous plexuses.

It is important for intracranial pressure regulation and it is related to central venous pressure (CVP). An increased CVP can thus determine vertebral venous plexus increase in pressure and can impair spinal cord outflow.

If we consider that arterial pressure in the spinal cord collateral network is much lower than aortic pressure, and can fall to 20 mmHg for several hours after SAs sacrifice (Figure 11), we can understand how high venous pressure could considerably influence spinal cord perfusion.[13]

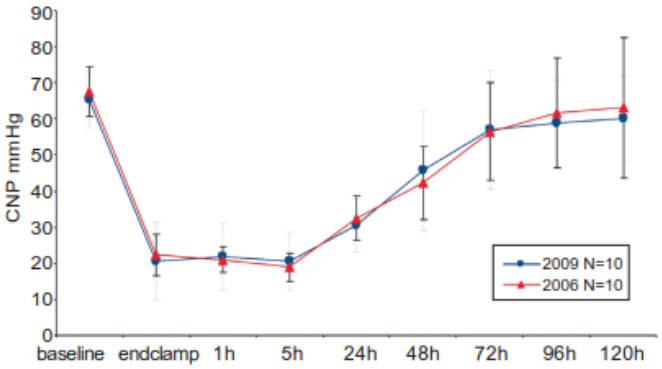

Figure 11: Drop in spinal cord perfusion pressure at cross-clamping and following intercostal arteries sacrifice.

The overall risk of spinal cord ischemia (SCI) secondary to thoracoabdominal aortic surgery is determined by the combination of four independent processes: intra-operative spinal cord perfusion; spinal cord metabolic rate; post-ischemic reperfusion injury and post-operative blood flow.

A number of techniques have suggested and tested to lower the risk of SCI. These adjuncts address one or more factors associated to spinal cord injury.

Presentation of spinal injury

Despite the several protective measures employed, spinal cord ischemic injury remains the most devastating complication of open thoracoabdominal aneurysm repair. Clinical presentation of such injuries include lower limbs flaccid paralysis (paraplegia), weakness (paraparesis) and neurologic bladder (due to loss of autonomic control), with an incidence ranging from 3 to 15% in experienced centers.

Despite paraplegia being a cumbersome complication by itself, the consequent delay in patient mobilization and recovery further increase the rate of many other complications. Indeed, decreased mobility and compliance from these patients increases the rate of pulmonary complications (pneumonia and pulmonary embolism), the rate of deep vein thrombosis and associated risks, and the rate of GI complications (occlusion) with consequent infections and sepsis in the early post-operative period. Neurologic bladder can result in incontinence and/or recurrent urinary infections.

Furthermore, wound dehiscence and bed sores are more common in the spinal cord complication group than in control, with increased risk of wound and graft infection.

Even after successful patient discharge paraplegia has a great impact on patient outcome: mortality rate is significantly higher in plegic patients with respect to ambulatory ones at mid-term follow-up (Figure 12).[14]

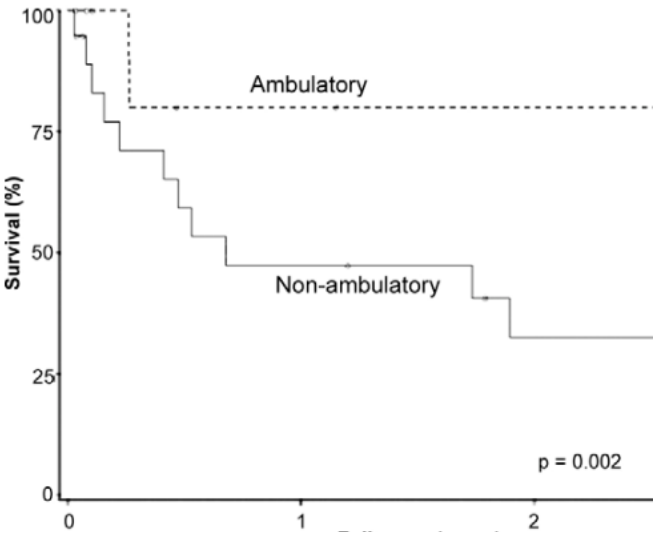

Figure 12: Kaplan-Meier survival curve showing impact of post-operative paraplegia on mid-term survival

Neurologic symptoms can manifest immediately after surgery (immediate SCI) or can have a delayed presentation. Wong DR et al. also reported high variability in the timing of onset of delayed SCI: ranging from 13 hours to 91 days post-operatively.[14]

In a study by Desart et al. on SCI after TEVAR not only immediate SCI patients had a poorer survival at follow-up, but also delayed SCI patients had a considerably higher mortality with respect to neurologically intact ones (Figure 13).[15]

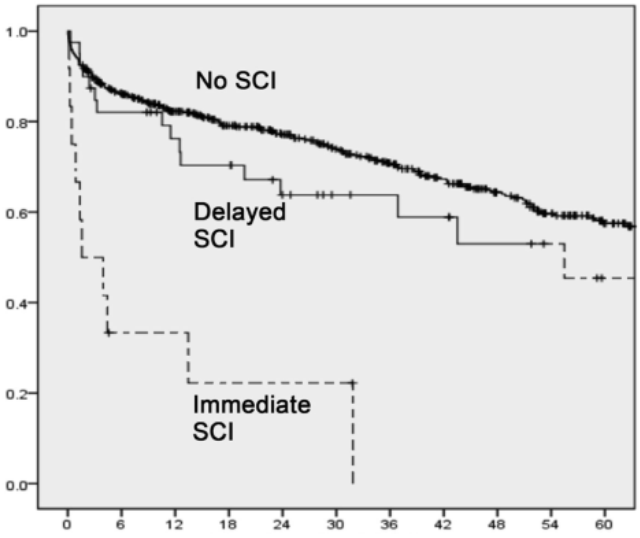

Figure 13 :Kaplan-Meier curves showing impact on survival according to SCI time of onset

Findings of paraplegia at awakening from anesthesia indicates a likely intra-operative irreversible ischemic injury to the spinal cord. On the other side, initially normal neurologic findings suggest that the vascular supply to the spinal cord was intact after the operation and delayed-onset deficits, therefore, are probably the result of a state of malperfusion which could be reversed with appropriate interventions.

While episodes of hypoperfusion are obvious mediators of delayed SCI, most cases occurred without such events, suggesting that development of this complication is multifactorial as well.[16] Indeed another reported cause of post-operative fall in spinal cord perfusion is the occlusion of reattached segmental arteries.[17]

Reperfusion injury may also play a role in the pathophysiology of delayed neurologic deficit. When spinal cord ischemia is followed by abrupt reperfusion a variable degree of neuronal damage may result from liberation of oxygen free radicals, cytotoxic actions of leukocytes and microglia, and prostaglandins-induced vasospasm.

Pre-operative management

Regardless of the operative approach, an extensive pre-operative workup is mandatory. Aneurysm extent and anatomical considerations help to stratify risk of SCI. Previous aortic surgery and/or chronic occlusion of vertebral or hypogastric arteries significantly increase risk of post-operative neurologic complications.

Imaging

Computed tomographic angiography (CTA) of the aorta with 3D reconstruction is nowadays the gold standard for pre-operative imaging. This modality is truly valuable in pre-operative planning to aid in selection of appropriate repair strategies: from surgical access site to repair extent and approach to visceral and spinal arteries reimplantation.

Selective spinal cord angiography would be a logical method to asses in detail blood supply. However, this procedure is not 100% safe as manipulation within an atherosclerotic ostium or in a partially thrombosed aneurysm sac could trigger embolization in SAs with resulting neurologic deficits. Incidence of angiography complications, including paraplegia, ranging 0% to 4.6% are reported. Furthermore, the success rate of actually identifying the Adamkiewicz artery is only 55%% to 69%, and it isn't associated with improvements in post-operative paraplegia rate.[18,19]

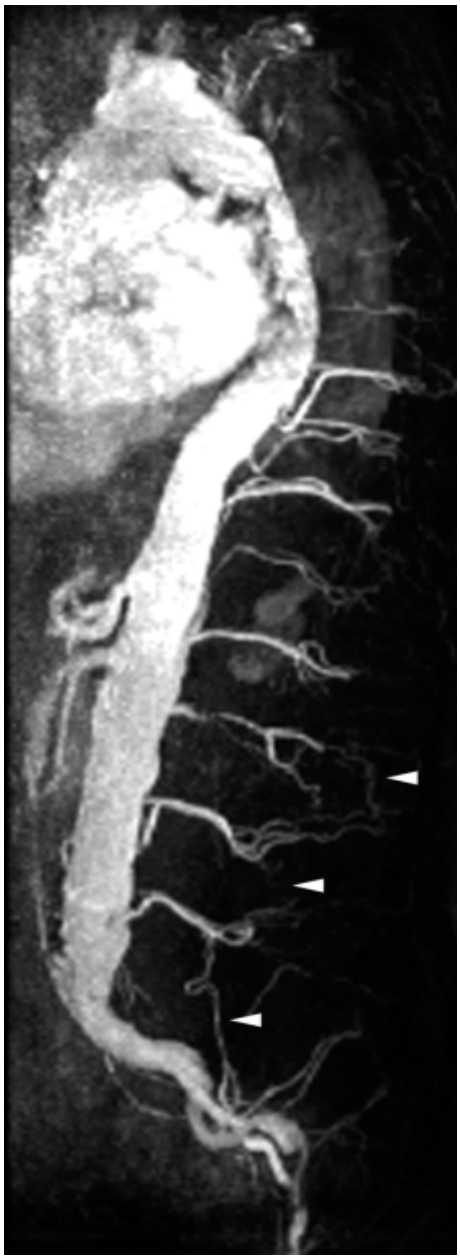

Figure 14: Magnetic resonance angiography of the thoracoabdominal aorta showing extensive anastomotic network among segmental arteries.

One study by Backes WH et al. investigated whether presence of collateral vascularization detected by magnetic resonance angiography (MRA) at baseline was linked to neurologic status during intra-operative exclusion of the SAs supplying the Arteria Radicularis Magna. 1.5 Tesla spinal cord MRA was used to localize the ARM and its feeders in 85 patients scheduled for open surgery. A statistically significant ($p < 0.0015$) correlation was found between the presence of collaterals and intra-operative spinal cord function. Pre-operatively identified collateral network was 97% predictive of unchanged spinal cord function at intra-operative motor evoked potentials evaluation. Alternatively, patients in whom no collaterals had been identified at pre-operative MRA were at increased risk of post-operative spinal cord dysfunction.[20]

Ischemic preconditioning

Taking into consideration the collateral network concept of spinal cord vascularization, segmental arteries (SAs) occlusion would stimulate and recruit redundant intraspinal and paraspinal vessels and eventually trigger angiogenesis, resulting in spinal cord perfusion restoration within 96 to 120 hours. This principle is already exploited in staged approaches to

endovascular TAA/A repair, and has led to a drastic fall of paraplegia rates both in experimental and clinical practice.[21]

Considering the impossibility of a staged open treatment due to redo-access complications, and the poor results of staged hybrid approaches[22], ischemic pre-conditioning could be a safe and effective way of spreading SA sacrifice along two or more procedures. Selective minimally invasive SA coil embolization (MISACE) could provide safe staging of SAs exclusion in elective open TAAA repair inducing angiogenic preconditioning and allowing recruitment of otherwise redundant, hypotrophic arterial collaterals. This technique has already been employed in human as pre-operative management of patients undergoing complex endovascular TAAA treatment, and unpublished results confirmed the theoretical advantage provided by such preconditioning.

Selective, transarterial MISACE might lead to a dramatic reduction of SCI also in open TAAA repair in the future.[23]

Intra-operative polarographic identification

Svensson et al. described the use of an intrathecal platinum electrode to identify critical segmental arteries. Briefly, a saturated hydrogen saline solution is injected in aortic segments between two clamps. If a SAs supplying the spinal cord arises from such segment an electric current can detected by this intrathecal platinum electrode. Although this technique is very reliable in identifying critical intercostal arteries, its application in the intra-operative setting is time-consuming and potentially dangerous as it prolongs cross-clamping time. Clinical studies on the impact on neurological outcome of this technique are yet to be carried out.[24]

Intra-operative and post-operative management

Being spinal cord injury the most dreaded complication of open thoracoabdominal aortic surgery many centers have been trying to reduce their SCI rates with a vast array of devices and operative techniques. Unfortunately, as there is no single mechanism causing SCI, there is no single intervention that can decrease the rate of neurologic complications to zero. The best approach must indeed be multi-modal to try and compensate for the different pathways leading to SCI.

Cerebrospinal fluid drainage

To fight the deficit in spinal cord perfusion secondary to rise in cerebro-spinal fluid (CSF) pressure and fall in arterial pressure within intercostal arteries at aortic clamping, many authors have suggested the use of a CSF drain peri-operatively.

As for the brain, the perfusion pressure (CPP) in the spinal cord is given by the difference between systemic mean arterial pressure (MAP) and intracranial/intrathecal CSF pressure (ICP). Thus to increase CPP we can act both on increasing MAP and on decreasing ICP, by means of a CSF drain.

Different techniques of lumbar CSF drainage (CSFD) have been employed both intra-operatively, and post-operatively.

While the rationale behind CSFD is clear, high variability in management is found among different centers: some centers drain CSF manually according to CPP, others use pressure dependent passive CSF drainages, while some others use flow and pressure dependent CSF active draining machines (i.e. LiquoGuard).

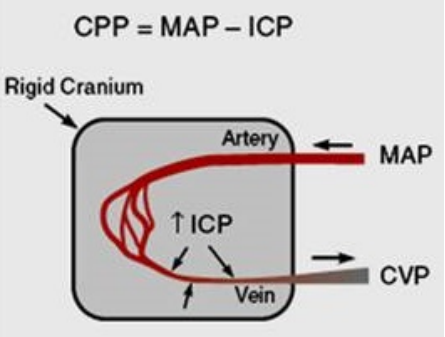

Figure 15: Equation of cerebral perfusion pressure, how ICP and MAP affect spinal cord perfusion

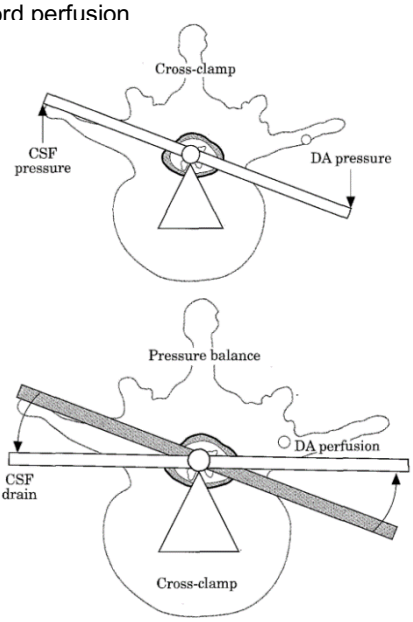

Figure 16: How cerebrospinal fluid drain and distal aortic perfusion re-equilibrate the perfusion pressure

A recent metanalysis based on 3478 publication demonstrated that cerebrospinal fluid drainage decreases SCI in TAAA patients by nearly 50% (relative risk 0.42, 95% confidence interval 0.25–0.70; p = 0.0009).[25]

Coselli et al. demonstrated a drop in paraplegia rate in extensive TAAA repair from 13% to 2.6% using CSFD to maintain cerebrospinal fluid pressure below 10 cmH_2O.[26]

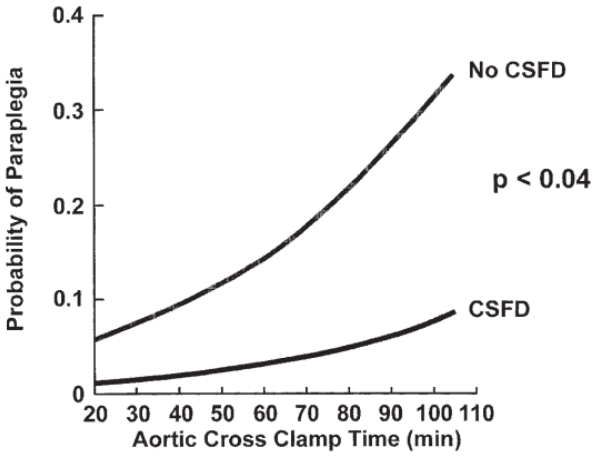

Figure 17: Graph showing benefit of CSFD on paraplegia probability, regardless of clamping time.

CSFD employment may be relevant also in the management of delayed onset paraplegia, especially if the pathophysiological mechanism underlying is a reduction in CPP secondary to spinal cord edema.[27]

Despite being one of the most relevant adjuncts for SCI prevention, CSFD is not 100% safe. The drainage itself is an invasive device and different complications have been reported, ranging from lumbar puncture headaches, to CSF leaks and intracranial hypotension, catheter occlusion, up to fatal intracranial hemorrhage.

A novel system was recently introduced by Moller Medical to allow automatic CSFD through a pressure and flow controlled machine, the Liquoguard.[28]

A spinal drain similar to the one used for classic passive CSFD is connected to a transducer and to the machine which, by means of a roller pump, can modulate draining flow according to recorded pressures and physicians' settings, together with total drained volume. All data can be recorded for subsequent analysis.

The CSF threshold usually set for start of drainage is usually 20mmHg. Although, if clinical symptoms arise (i.e. paraplegia/paraparesis) or if a stable systemic MAP >90mmHg can not be achieved, the active drainage pressure can be set to lower values to achieve higher spinal perfusion pressures.

This system allows an automated control of CSF pressure and drainage, removing pressure peaks and risk of human error in manual drainage, which carries significant and even lethal complications (i.e. intracranial hemorrhage).

Left heart bypass and distal perfusion

The hemodynamic and metabolic alterations caused by aortic clamping have been investigated both in animal and in human for many years.

The changes important for safe surgical and anesthetic management include variations in systemic and intracranial pressure, cardiac function, organ perfusion, and acid–base balance.

As already mentioned, the spinal cord blood supply relies on a vascular network fed mainly by intercostal arteries, vertebral arteries and hypogastric arteries. Any clamping of the aorta will stop perfusion through any of the vessels originating distally to the clamp. According to different aneurysm extents the proximal clamp can be positioned at different levels of the aorta. In the specific case of a type 2 TAAA the supply would be limited to vessels arising from the supraortic trunks since proximal clamping site is usually just distal to the origin of the left subclavian artery (LSA) or even in between the left carotid artery (LCA) and the LSA. This would intuitively result in extensive ischemia of the spinal cord.

While the so called “clamp and go” procedure relies on expeditious surgery to minimize the ischemic time, one technique which has been perfected along the years relies on the use of an extracorporeal pump to provide blood flow to territories downstream to the distal clamping site in order to allow longer clamping times without actual increase in ischemic times.

Various approaches have been tested for distal aortic perfusion, including passive shunts, roller pumps, centrifugal pumps, and total cardiopulmonary bypass. Passive shunts, such as the Gott shunt, cannot modulate their flow according to intra-operative flow and pressure requirements. Cardiopulmonary bypass requires significant systemic heparinization with the possibility of excessive bleeding and consumptive coagulopathy. Centrifugal pumps have the advantage of both reduced heparin dose and control on distal flow.

The most widespread use of these pumps is their employment in a left heart bypass (LHBP) configuration: by cannulation of a pulmonary vein or left atrium oxygenated blood is sucked by the pump and reinserted in the circulation through a different cannula inserted at any arterial site distal to the clamp, from the distal thoracic aorta to the femoral artery. With this device any territory supplied by arteries arising downstream to the clamp can be perfused, including the very delicate spinal cord.

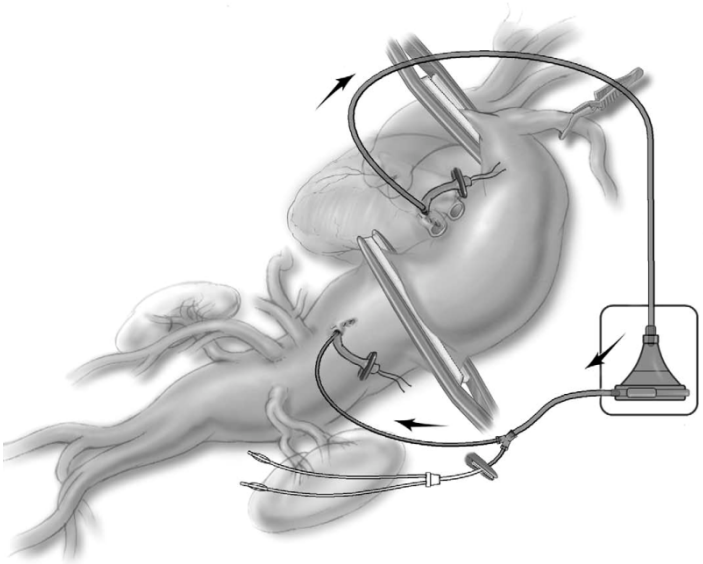

Figure 18: left heart bypass graft with cannulation of the inferior left pulmonary vein and distal thoracic aorta.

Usually studies on the effect of this adjunct on spinal cord injuries are difficult to interpret univocally because of concomitant use of other organ protection devices such as CSFD. Bavaria and Safi proved that these two devices used together considerably reduce incidence of paraplegia and paraparesis in type 1 and type 2 TAAA. And as paraplegia is correlated to long-term survival the decrease in SCI rates translated into an improvement in survival of patients on which LHBP and CSDF was employed (Figure 19).[29,30]

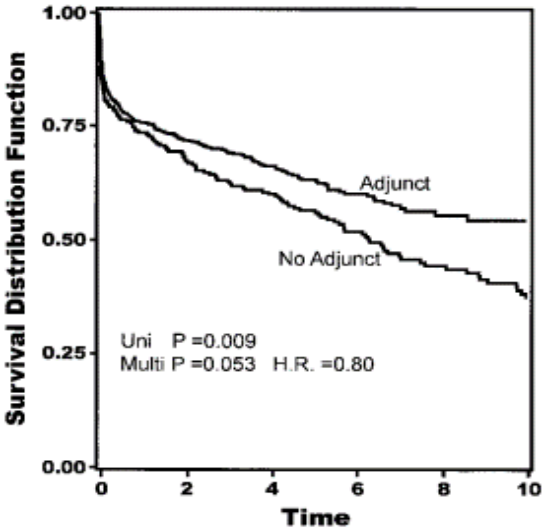

Figure 19: Impact on long-term survival of concomitant LHBP and CSFD use in type 1 and type 2 TAAA.

Coselli and colleagues eventually demonstrated that LHBP by itself already plays a role in decreasing significantly the rate of paraplegia and paraparesis (P/P) in type 2 TAAA (Figure 34). In the analyzed series clamping times were longer in the LHBP group. And, despite longer clamping time being a risk factor for SCI, there was no increase in the incidence of P/P in type 1 TAAA and there was a 43% reduction in its incidence in type 2 TAAA.[29]

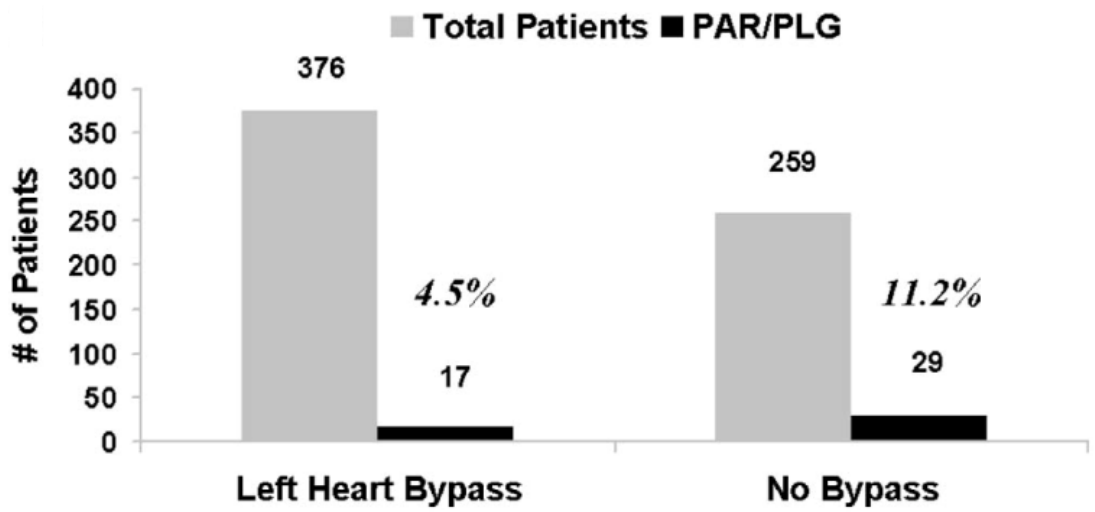

Figure 20: Effect of distal aortic perfusion through left heart bypass pump on paraplegia and paraparesis rates in type 1 and type 2 thoracoabdominal aortic aneurysms.

Regardless of the effect on SCI rates the use of LHBP grants the surgeon the possibility to complete an anastomosis with reduced time pressure. This advantage is especially relevant in patients with acute dissection or genetic syndromes, where an extremely fragile aortic wall requires additional care and time for a hemostatic anastomosis.

Sequential clamping

Throughout the ''clamp and sew'' era in Houston, when no assisted circulation was employed, aortic cross-clamp time was a direct predictor SCI together with aneurysm extent, patient age and baseline renal function. Correlation between aortic clamp time and P/P risk was almost linear (Figure 21).

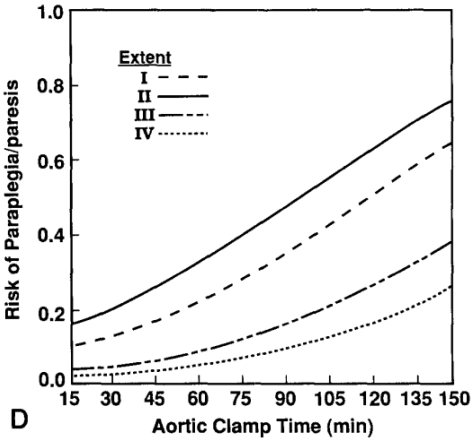

Figure 21: Correlation between aortic cross-clamp duration and risk of paraplegia and paraparesis divided per TAAA extent.

With the introduction of LHBP, at aortic clamping the only non-perfused segment is the one in between the two clamps since any territory proximal to the first clamp is perfused by cardiac action and any territory distal to the second clamp is perfused through the pump. Taking this in consideration sequential clamping has become regular practice because it allows minimization of the ischemic areas during clamping.

Step by step, considering distal blood supply from a femoral artery, it is indeed possible to perform the proximal anastomosis while most of the intercostal arteries are still supplying blood to the spinal cord. Then, moving the clamps downstream, it is possible to reattach these arteries while visceral vessels and lower limbs are being perfused. It is possible to re-vascularize visceral vessels while lower limbs and the thoracic aorta maintain blood supply. And finally the distal anastomosis can be performed while all the remaining vascular territories are receiving blood supply from the heart and LHBP (for the lower limbs).

If we go back to the collateral network concept, and the porcine studies supporting it, it is intuitive that shorter unperfused aortic segments correlate to fewer unperfused feeders into the collateral network at the same time, with consequent reduction in spinal cord ischemia.[5]

While no standardized trial is available to prove effectiveness of this commonly employed technique, Svensson et al. demonstrated in a swine model that perfusion of intercostal arteries, localized by polarographic identification, during aortic cross-clamping managed to reduce the risk of spinal cord dysfunction, monitored by intra-operative MEP (Figure 22).[31]

Despite the fact that perfusion to critical segments in this study was obtained through passive shunts rather than distal perfusion, we can postulate that similar results can be obtained by sequential clamping.[31,32]

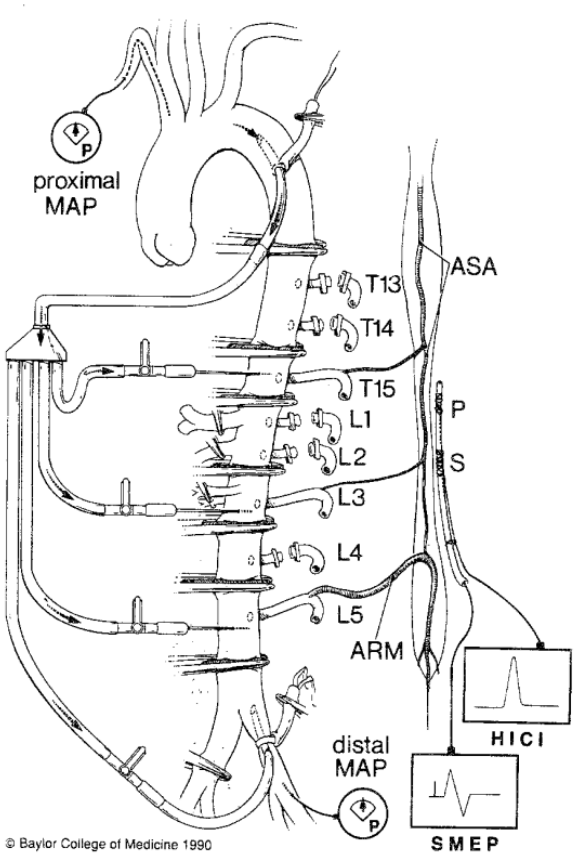

Figure 22: Svensson et al. investigation on intercostal arteries perfusion to maintain spinal cord function.

Peri-operative assessment: markers of injury, motor evoked potentials, and somatosensory evoked potentials

While clinical post-operative evaluation of spinal cord integrity is easy to achieve by straightforward neurologic examination, intra-operative monitoring of spinal cord function is more challenging and more relevant for prevention of irreversible ischemic injury. Any detected change in function could indeed drive immediate corrections in both anesthesiological (increase MAP) and surgical (speed, intercostal reattachment) management to avoid permanent neurological deficits.

If we consider hematological changes of tissue-specific markers such as S100, glial fibrillar acidic protein (GFAp), and neuron-specific enolase (NSE) we can detect elevated levels in patients with spinal cord injury. But all of these findings are too delayed to determine a change in intra-operative management and in patients' outcome.

A study by Zangrillo et al. suggested pre-operative intrathecal lactate level as a predictor of early-onset spinal cord injury after TAAA repair. Indeed, cerebrospinal fluid lactate level was found to be pre-operatively higher in patients who developed spinal cord injury immediately after the intervention when compared to those who didn't. The authors explained this was probably due to pre-operative ineffective spinal cord perfusion triggering anaerobic glycolysis and consequent production of lactates.

Intra-operative repeated evaluations instead did not show a statistically significant correlation between lactate levels and spinal cord injury.[33]

The only technique available up to date to monitor real-time variations in spinal cord function intra-operatively is the employment of motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP).

Motor evoked potentials are tested by transcranial stimulation of the motor cortex through electrodes placed on the scalp. Single transcranial MEP are evoked by applying paired stimuli to the scalp through various electrodes. Potentials are then recorded from the skin over different muscles. During cross-clamping MEP levels are measured every minute. A reduction of MEP amplitude to less than 25% of baseline is considered an indication of ischemic spinal cord dysfunction. Adequate anesthetic techniques are essential because complete neuromuscular blockade is not compatible with myogenic MEP monitoring.

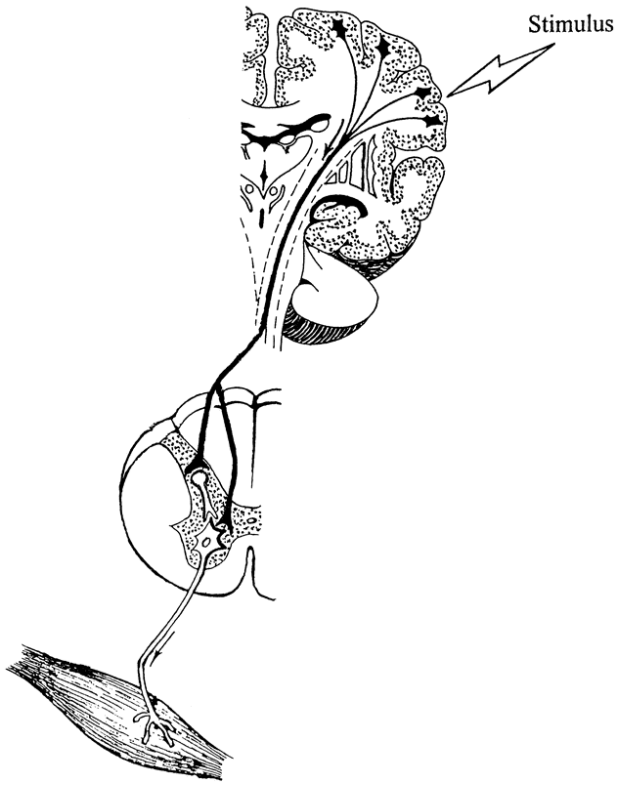

Figure 23: Motor evoked potentials mechanisms and pathways.

For SSEP instead, stimulatory electrodes are placed bilaterally at the malleolus. Recording electrodes are positioned at three different levels: the popliteal fossa, cervical spine, and vertex. A 10% increase in latency or 50% decrease in amplitude is considered to define SSEP

abnormalities. The use of these three channels allows discrimination of spinal cord injury from peripheral nerve ischemia or brain injury.[34,35]

Several studies have been conducted on the relevance of changes in MEP and SSEP, on the correlation of the different measurements with post-operative neurological impairment and on the effects of intra-operative strategies employed according to MEP and SSEP variations.

Jacobs et al. reported a series of 42 type 1 and 70 type 2 TAAA patients managed by open surgery with continuous MEP and SSEP monitoring, in which they described the intra-operative changes in management driven by variations in the recorded values at different surgery stages. If there was a fall in MEP at proximal clamping distal MAP was increased >60mmHg (starting target value) by means of LHBP until MEP increase.

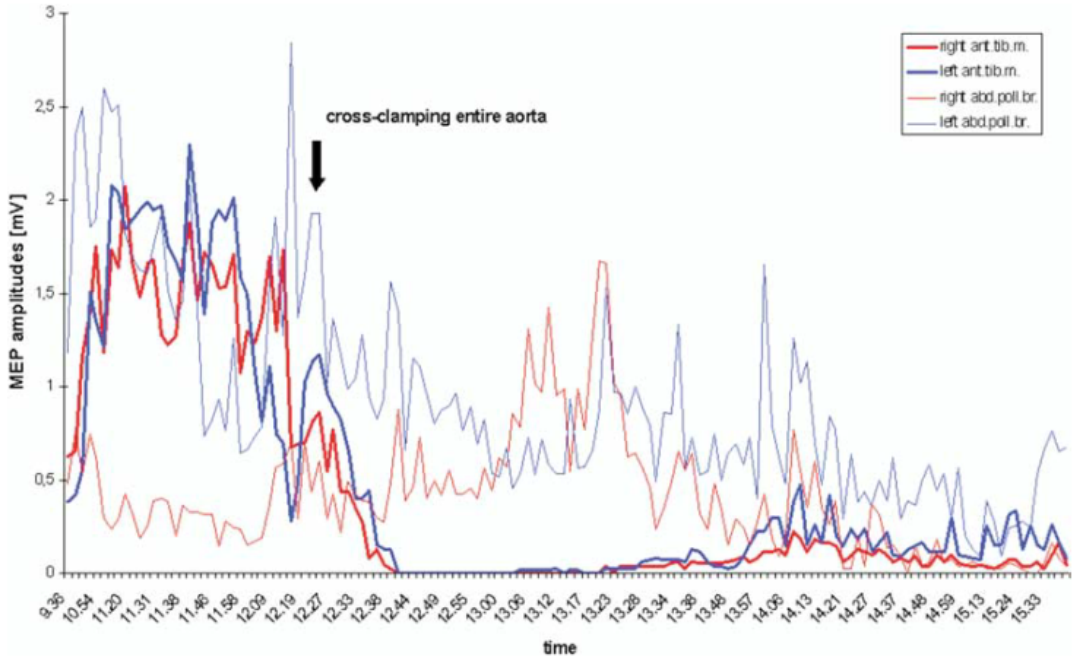

Figure 24: Fall in motor evoked potential amplitudes recorded at anterior tibial muscles at aortic cross-clamping. No changes are recorded at the level of the abductor pollicis brevis since upper spinal cord function is not usually compromised by descending thoracic aorta cross-clamping.

If at distal clamping there was rapid decrease of MEP probably critical intercostal arteries originated from the excluded portion of aorta thus clamps were removed and patient was cooled down to 32°C for neuroprotection before proceeding.[36] Eventually those intercostal arteries were reimplanted on the graft if possible. If MEP were lost later on during the procedure a more

aggressive approach to intercostal arteries reattachment could be employed, reducing the number of SAs ligated and maximizing reimplantation, with extreme focus on arteries arising from segments between T8 and L1.[37]

All patients with reliable MEP responses at the end of the procedure were neurologically intact upon anesthesia awakening, even if the amplitude was <10% compared to initial values. Absence of MEPs was invariably associated with irreversible paraplegia. These data suggest that moderate fall in MEP amplitude is not necessarily secondary to death of alpha-motoneurons.

Amplitude decline >50% or >75% are set as “intra-operative alarm sign” in different centers.

Jacobs et al. reported results of MEP monitoring, together with LHBP, on post-operative spinal cord complications in TAA/A patients, showing reduction in P/P to 2.3%.[37]

Despite its value in testing spinal cord function intra-operatively the main limit of MEP testing is that it can provide false positive results. Extreme care should be taken in anesthetic management as some agents depressing the CNS synaptic function may generate unreliable readings on neurological function of the spinal cord.

SSEP recording might also be useful in identifying spinal cord ischemia.

But SSEPs reflect functional status of the posterior column instead, which has a different blood supply from the anterolateral spinal cord and is usually free of post-operative deficits. However, Safi et al. compared MEP and SSEP readings in a large cohort of patients and demonstrated that these two methods for spinal cord function monitoring are well correlated when intra-operative changes are irreversible, and highlighted that each method has a strong negative predictive value.[34]

Dong et al. reported a 5.4% spinal cord dysfunction rate in open TAA/A repair utilizing MEP and SSEP monitoring to guide their reimplantation approach.

Intercostal arteries reimplantation

Regardless of the field, during any surgery, sparing of non-pathologic structures is key to an uncomplicated and expeditious recovery. Following this idea many authors advocate reimplantation of intercostal arteries, irrespective of collateral network status, as a key strategy for prevention of spinal cord ischemia. By restoring flow to more intercostal arteries the probability of critical ischemic injuries should be reduced.

Different techniques have been employed along the years to revascularize the spinal cord by anastomosing critical arteries on the graft. The most common procedure consists in the implantation of an aortic patch, from which the segmental arteries arise, onto the side of the graft. This allows revascularization of more than one artery through a single anastomosis. This technique has to be employed with care, especially in young patients affected by genetic syndromes, because it spares a portion of diseased aorta, keeping it under the stress of systemic blood pressure. In the long run this can lead to further dilatation of that part of aortic wall with associated risk of rupture. For this reason unnecessary reimplantations should be avoided.[38]

Another technique involves end-to-side reimplantation of selected intercostal arteries with interposition of synthetic or biological grafts. This technique is especially reserved to critical intercostal arteries arising from diseased aortic wall and that require aortic endarterectomy to be identified and reimplanted, and to SAs reimplantation in patients affected by collagenopathies. Long-term patency of segmental arteries reattached with this procedure is nonetheless inferior to the aortic-patch intercostal patency rate.[17]

Regardless of technique employed, different surgeons follow different criteria to choose which segmental arteries deserve to be spared.

It has been repeatedly demonstrated that intercostals arising from T8 to L2 have a greater weight on the incidence of post-operative paraplegia.[39]

Regardless some authors rely strictly on MEP readings during sequential clamping to plan their reattachment: an early fall of MEP would result in aggressive reimplantation strategies (Figure 39). More intercostal arteries could be reimplanted if MEP response is sub-optimal after first reimplantation.[34,37]

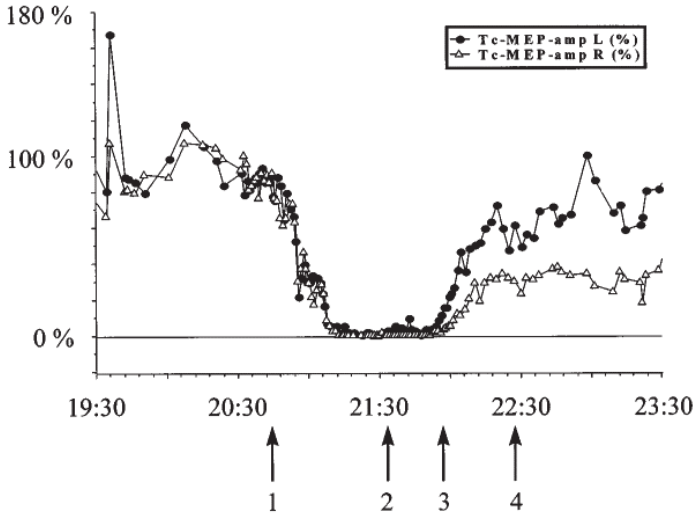

Figure 25: MEP changes following aortic cross-clamping (1) and intercostal arteries reimplantations (2,3).

Other surgeons rely mainly on anatomical location, irrespective of intra-operative appearance.[39] Some of them consider back-flow from intercostal arteries as a sign that they will feed the key collateral network and thus they reattach them to maintain at least one safe feeder to the network patent.

On the contrary some surgeons will ligate these arteries, thus relying on the other feeders to the network which are obviously providing enough supply to generate back-flow. They would instead focus on large-diameter, non-back-bleeding arteries which may indeed be critical for the spinal cord as no sufficient collateral is present to provide back-bleeding and consequent blood supply after artery ligation.

Safi et al. highlighted that patent SAs at T11/T12 level are associated to highly variable outcomes depending on whether they are reattached or ligated.[39]

An important caveat is that the additional time required for SAs reattachment prolongs spinal cord ischemic time during cross-clamping and, if the revascularized radicular branch is small or occluded, a great deal of time would be wasted in reperfusing only intercostal muscles.[40]

In human studies, polarographic studies accurately localized segmental arteries supplying the spinal cord, and when reimplanted, spinal cord perfusion through these segmental arteries was re-established with consequent paraplegia prevention.[24]

A completely different position is held by a few authors which nowadays still support the “clamp

and sew technique", a surgical strategy based on fast aortic cross-clamp with no reimplantation of intercostal arteries which, in a study by Biglioli et al. on descending thoracic aneurysm, proved to be more effective for SCI prevention than intercostal reimplantation.[41] The rationale behind this approach relies on the idea that the intra-operative "steal phenomenon" is the main cause of ischemia and, minimizing this, sufficient blood supply will be provided through the remaining collateral network.[10]

Steal prevention

Fundamentally, the community of aortic surgeons is divided by their opinion on the main intra-operative determinant of paraplegia. Those who believe that P/P are the result of tissue hypoperfusion after ligation of segmental arteries strive to reimplant many segmental arteries, trading prolonged acute cord ischemia for a theoretical superior post-operative blood supply. The other group believes that the blood supply is dependent on an extensive collateral system capable of providing sufficient spinal cord perfusion even after sacrifice of (almost all) SAs and thus aims at shortening acute spinal cord ischemia reducing cross-clamp time and relying on stable post-operative hemodynamics.

The latter argue that, without profound hypothermia of the cord, intercostal re-implantation jeopardizes spinal cord perfusion because it allows prolonged back bleeding from afferent collateral vessels. Back bleeding, besides increasing cardiac stress and need of transfusions, can potentially impair significantly spinal cord perfusion, thus inducing an ischemic injury per se.

Acher described a technique of TAAA repair with no intercostal artery revascularization, sewing off SAs ostia as soon as the aneurysm sac is opened.[42] This technique, combined with expedient surgery and hemodynamic stability has produced neurological outcomes far superior to those in reports exploiting all kinds of adjuncts. He believes that by suture ligation of these vessels the blood flow is directed to the spinal cord through the collateral network and the need for reimplantation is abolished.

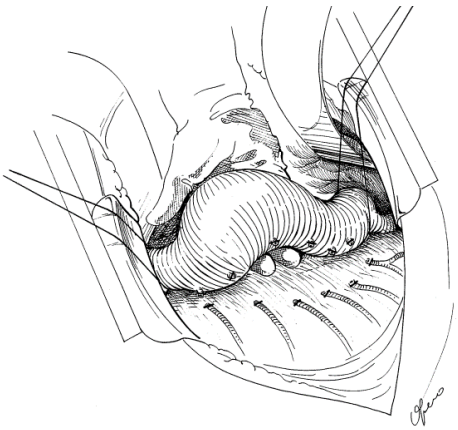

Figure 26: Biglioli's technique of segmental artery ligation before aneurysm sac opening.

Biglioli's similar approach implicates, instead, clipping of the intercostal arteries from the outside of the

aorta before cross-clamping, without SAs reimplantation, again with comparable results to that of Acher's group.[41] This technique not only prevents steal phenomena, but also decreases the probability of parietal thrombus embolization into segmental arteries during clamping and sac opening.

Etz et al. reported a series of 100 patients in which a similar technique was employed with astounding neurological outcomes. In his experience intercostal and lumbar arteries were ligated sequentially with concomitant MEP and SSEP monitoring. Changes in neurophysiological recordings only determined corrections in pressure managements. 99% of the patients had good MEP and SSEP reading at completion of procedure and were neurologically intact at awakening.

Furthermore, available data indicate that cord perfusion varies considerably even among patients with equivalent TAA extent. Variations in anterior spinal cord artery development and collateral circulation status are likely to determine this variability and they cannot be modified by any SAs reimplantation.

Furthermore, reimplantation removes a growth stimulus to the collateral network, leaving spinal cord perfusion to rely on the few reattached SAs. Without reimplantation, regardless of initial collateral network status, physiological compensatory mechanisms lead to expansion over time. Until then however, avoidance of hemodynamic instability and increased intrathecal pressure are of paramount importance in prevention of delayed neurological deficits.

Selective perfusion

A few authors reported a compound intra-operative management of intercostal arteries which prevents both ischemia and steal phenomenon, while preserving reimplantation chance, by means of selective SA cannulation and perfusion (Figure 27).

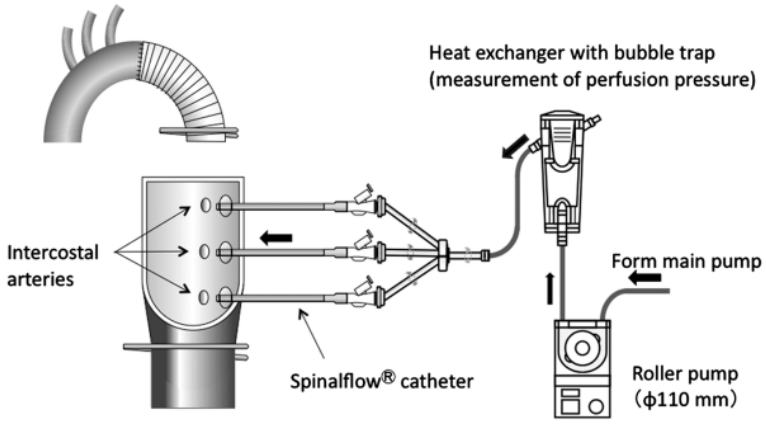

Figure 27: Selective segmental artery perfusion through catheters coming from a roller pump (i.e LHBP).

Kawaharada et al. reported 8 TAAA cases in which selective perfusion was

employed. The perfusion flow reached was 30-40 ml/min per SA. No post-operative paraplegia was reported.[9]

In another report recovery of MEP amplitude was achieved with selective perfusion to patent intercostal arteries (Figure 42).[43]

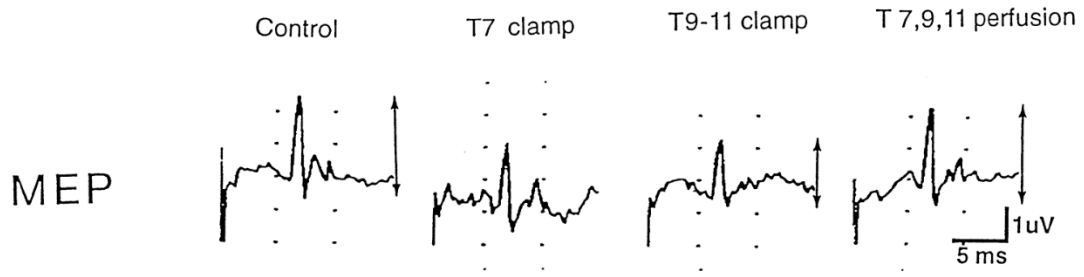

Figure 28: Recovery of motor evoked potentials amplitude after intercostal arteries selective perfusion.

Although this technique is complex and requires more experience, selective intercostal perfusion under MEP monitoring might be an effective method for spinal cord protection during TAAA surgery.

Systemic hypothermia

It is important to understand that while spinal cord injury cause is anatomic, prevention of neurological complications is mostly physiologic.

Nervous tissue is the most metabolically active and thus sensitive to lack of perfusion. We covered the bases of P/P etiopathogenesis and techniques for perfusion maintenance. Different procedures are proposed to reduce metabolic rate and demand of the spinal cord to further decrease the rate of paraplegia.

Hypothermia has been used throughout the evolution of cardiac and central aortic surgery for its neuroprotective effect.

Although it is widely believed that neuroprotection secondary to hypothermia is due only to decrease in metabolism, the actual mechanism could involve also membrane stabilization and reduced release of excitatory neurotransmitters. Indeed 30% of energy consumed by the CNS is for cellular homeostasis alone.

Hagerdal et al. proved in a murine model that cerebral blood flow decreases linearly with temperature in the temperature range 37°C to 22°C, and metabolic rate falls by about 5% per degree.[44]

Hypothermia also decreases production of cerebrospinal fluid, which translates in indirect increase in CPP.

Mild systemic hypothermia (32-34°C) should be achieved during TAAA repair by permissive body temperature decrease during surgery. Deep hypothermia (15-18°C) can be used to repair extensive TAAA, but its application is limited by coagulopathy and pulmonary and cerebral complications.

Kouchoukos et al. have used this approach specifically for spinal cord protection during TAA resections.[45]

Passive moderate hypothermia (32-34 °C) can be achieved by heat evaporation from the large surgical field, while active moderate systemic hypothermia requires use of a heat exchanger in the extracorporeal pump. The degree of hypothermia is limited by the potential cardiac arrhythmias arising due to conduction instability.

In another mouse model Vacanti et al. demonstrated that a temperature reduction of 3°C during aortic clamping caused a doubling of the duration of ischemia needed to induce irreversible SCI.[46]

The exact mechanism by which hypothermia exerts its protective effect still remains unknown.

It has been proposed that the release of excitatory amino acids in the extracellular space may play a role in irreversible neuronal damage causation.

In a porcine model by Rokkas et al seven amino acids believed to play a role in spinal cord injury were studied.[47] Glutamate, glycine and GABA extracellular concentration increased significantly during normothermic ischemia, while hypothermia uniformly prevented the release of amino acids in the extracellular space.

These results are consistent with the role of excitatory amino acids in the mediation of ischemic spinal cord injury and suggest that the mechanism of hypothermic protection may be related to decreased release of these amino acids within neuronal tissue.

Pharmacological antagonization of glutamate-induced SCI is an interesting concept, and in the future it may help mitigating the effects of spinal cord ischemia[47]

In the same study spinal cord function was also assessed intra-operatively with MEP and SSEP monitoring. Hypothermic animals had potentials with increased latency during cooling but these remained unchanged during aortic clamping. And both MEP and SSEP returned to baseline upon reperfusion and rewarming.

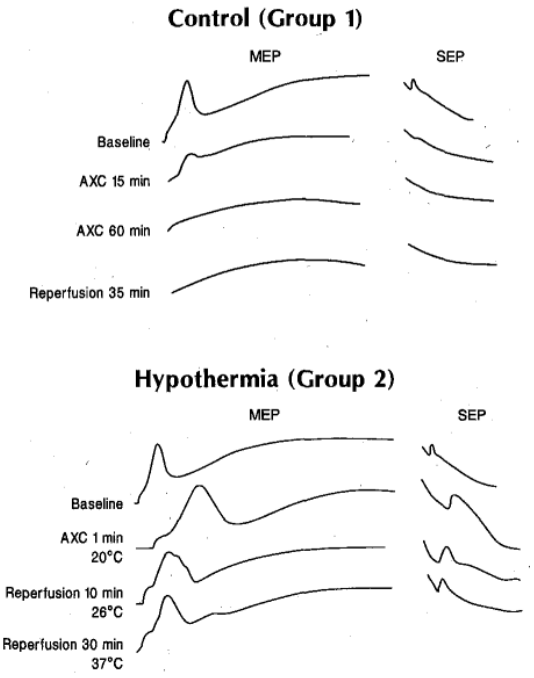

Figure 29: Neurophysiological recordings consistent with hypothermic protection of SCI

Hypothermia for cord protection in TAAA repair can be either systemic or regional.

Regional hypothermia

Several variations of regional hypothermia have been reported. These include the direct instillation of cold solutions into the epidural/intrathecal space or into isolated thoracic aortic segments supplying the spinal cord. A less invasive approach involves transvertebral cooling by means of an ice bag or similar.[48]

Coles et al. showed in canine models that, when perfusing isolated aortic segments with cold Ringer's lactate, cord temperature would rapidly fall to 20 °C and this was 100% effective in preventing paraplegia. Colon et al. achieved comparable results in a swine model. Isaka et al. demonstrated how transvertebral cooling further improved neurologic outcome.[48]

Both Marsala and Davidson achieved moderate cord hypothermia via 4°C saline injection through an epidural infusion system and it proved to be 100% effective against spinal cord ischemia induced by aortic clamping.

Cambria et al. have reported good results with regional hypothermia in a series of 334 TAAA repairs. Although cooling of the epidural space alone is hard to achieve quickly and may complicate the procedure unnecessarily it decreased the SCI incidence from 19.8% to 10.6%.[49]

The greatest advantage of regional hypothermia with respect to systemic hypothermia is prevention of systemic side-effects. Indeed, as recorded by Allen et al, spinal cord regional cooling to 22°C determined a fall in systemic temperature of only 2°C.[44]

Intrathecal pharmacological adjuncts

As different cooling techniques were employed also the effects of different intrathecal pharmacological adjuncts were tested.

One of the most investigated drug in this setting is papaverine, an antispasmodic drug commonly employed in vascular surgery to prevent reactive vasoconstriction. An interesting study by Svensson et al. showed that intrathecal papaverine (IP) and CSFD improved neurological outcome, especially if associated with hypothermia.[50]

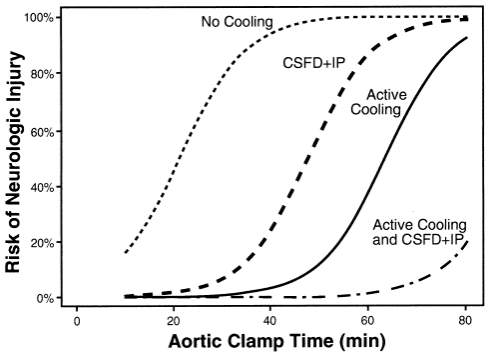

Figure 30: Cumulative protective effects of hypothermia, CSFD and intrathecal papaverine.

Similarly, in a murine model by Breckwoldt et al. intrathecal tetracaine significantly reduced neurological injury secondary to spinal cord ischemia induced by aortic occlusion.[51]

Intrathecal papaverine also prevented all cases of paraplegia in a baboon model by Svensson et al. by dilating the anterior spinal artery and possibly acting on other mechanisms.[52]

Perfluorocarbons have also been infused intrathecally and systemically in experimental canine models showing near complete prevention of neurological deficits.[53]

Spinoplegia

Besides cold perfusion of intercostal arteries other mechanisms to reduce metabolic consumption and to stabilize neuronal membrane have been tested.

In a small porcine model by Svensson et al. cold saline solution with lidocaine was infused into the aorta during cross-clamping. The decrease in spinal motor evoked potentials was significantly less ($p < 0.02$) in the treated group.

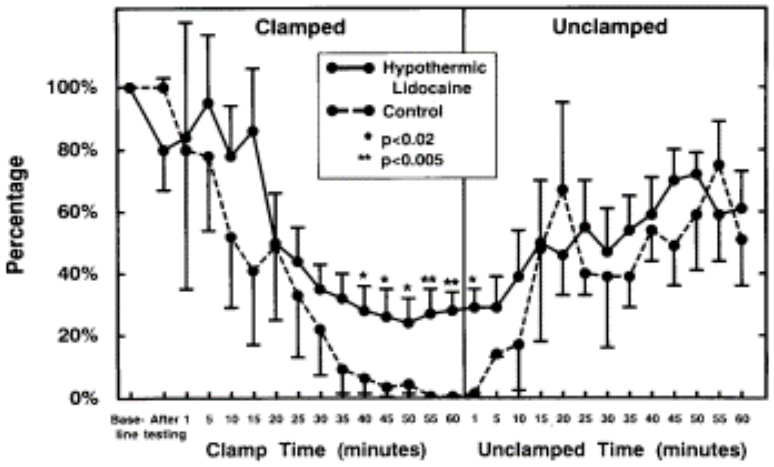

Figure 31: Lidocaine infusion exerts protective effects on MEP readings.

Manipulation of spinal cord energy production, metabolism, and protection of cellular membranes could potentially reduce the risk of paraplegia after major aortic operations.[7] Recent research has suggested that membrane stabilizers, including magnesium[46], lidocaine[24], lodoxamide tromethamine[54], 21-aminosteroids[36,55], and tetracaine[51], may be effective in reducing neurological injury.

According to Cho et al. induction of neurotoxicity by excitatory amino acids through the N-Methyl-D-aspartate (NMDA) receptor is the pathologic hallmark of ischemic and post-ischemic spinal cord injury. Systemic administration of NMDA antagonist has been reported to determine neuroprotective effect. Local administration, particularly of a noncompetitive NMDA antagonist (MK-801), could therefore be a potent intra-operative strategy.[56]

Baba et al. also tested the use of Rho kinase inhibitor Fasudil for selective segmental artery perfusion in order to obtain neuroprotection in a rabbit model. The results demonstrated that Fasudil improves collateral flow and microcirculation in the spinal cord under ischemic conditions, and reduces the inflammatory cells (neutrophil and monocyte) migration, thus determining a neuroprotective effect against spinal cord ischemic injury.[57]

Permissive hypertension

Raising arterial systemic blood pressure is another key point in preventing and managing spinal cord ischemia.[58]

This should result from teamwork of anesthesiologists, surgeons and perfusionists, to control hemorrhage and manage large blood losses while ensuring adequate organ perfusion. Hemodynamic stability, including satisfactory cardiac output and optimized oxygen delivery, is crucial.

Mean arterial pressure should be maintained at 80-90 mmHg, while maintaining a normal or reduced central venous pressure to avoid SCI from venous etiology. The actual target is a cerebral perfusion pressure (CPP) around 70 mmHg meaning that, if ICP raises over 10 mmHg and can't be corrected by CSFD, the MAP target should be increased accordingly.

Arterial pressure should be monitored when antihypertensive therapy is restarted after surgery, as unintentional post-operative hypotension may result in delayed spinal cord ischemia.[59]

Pharmacological management

Use of methylprednisolone, mannitol, lidocaine or thiopental, although widely practiced, has not been proved effective. Only naloxone had favorable results in a small clinical trial.[59]

Interpretation of the clinical literature is hampered by evolution in surgical and anesthetic techniques, and the use of other adjuncts including distal aortic perfusion, CSF drainage, and hypothermia. Several neuroprotective agents have shown promise in various settings and are worthy of review.

A 21-aminosteroid (U-74006F) devoid of glucocorticoid or mineralocorticoid side effects has been shown to have protective effects in models of spinal cord ischemia, presumably via inhibition of reperfusion-associated lipid peroxidation and hydrolysis.[55]

Naloxone, an opiate antagonist, has been shown to be neuroprotective in a variety of laboratory and clinical studies. While its mechanism of action is not completely understood, it also appears to affect lipid peroxidation and cell membrane stabilization via an attenuation of the inactivation of Na^{+}-K^{+}-Mg^{2+} ATPase. An integral part of the cascade is the eventual influx of calcium.

In experimental models of spinal cord ischemia calcium channel antagonists have been found to preserve function, and to reduce infarct size.

Barbiturates have been shown to be protective in spinal cord ischemia either by reducing metabolic demand or by acting as oxygen free radical scavengers.

Expeditious surgery

Large retrospective series have shown that the duration of aortic cross-clamping is intimately related to the risk of neurological complications. This was recognized early on in the history of thoracoabdominal aneurysm repair when Crawford developed the ‘‘clamp and sew’’ technique which consisted of three primary principles of aortic surgery: the use of a Dacron tube graft, a simple inlay technique to revascularize visceral and renal arteries and a short cross-clamp time. [32]

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 quick surgery and clamp times of shorter than half an hour. This value is lower than that achieved nowadays by most centers employing various adjuncts of spinal cord protection, to prove the fact that short clamping times are of paramount importance in decreasing morbidity rates.

For this reason, thoracoabdominal aortic pathology should be treated only in high volume, high-experience centers. Indeed, some experienced surgeons prefer discarding some of the aforementioned organ protection adjuncts in favor of a shorter, unprotected, clamping-time, hence reverting towards a modified and updated version of the old-school “clamp and sew” technique.

Chapter III: Intraoperative neurophysiological monitoring correlation with late onset spinal cord ischemia

Methods

This study is a physician-initiated, retrospective, single-, non-randomized study aimed to evaluate the correlation between intraoperative MEP/SSEPs monitoring with any postoperative neurological monitoring (TARLOV scale). [22] Patients data is collected in a prospectively compiled database – including demographics, anatomical, procedural, perioperative and postoperative details of patients undergoing between January 2016 and March 2020 a TAAA SR with intraoperative use of MEP/SSEPs monitoring. Sensitive patient information will not be available during data analysis. The clinical study will be carried out according to the ethical principles of the Declaration of Helsinki and following the active regulations on observational studies. Patients gave their consent for the anonymous collection of their data on the standard consent sheet provided by our Institution for the use of CE (Conformitè Européene) approved devices. Data collection was carried out in conformity with the Italian law on privacy (Art. 20–21, DL 196/2003) published in the Official Journal no. 190 of August 14, 2004 which explicitly exempts the need of ethical approval for the use of anonymous data.

Aim of the study

The aim of this study is to evaluate if spinal cord ischemia (SCI), especially its late presentation, and can be correlated to the results of intraoperative MEP/SSEPs monitoring.

Inclusion / Exclusion criteria

Inclusion criteria:

- patients who underwent TAAA SR with intraoperative use of MEP/SSEPs monitoring,
- patients treated in an elective setting.

Exclusion criteria:

- patients who underwent TAAA SR without intraoperative use of MEP/SSEPs monitoring,
- patients treated in an urgent/emergent setting.

Study endpoints

As primary endpoints, the following will be considered:

1. Development of late spinal cord ischemia complications at 30-day (modified TARLOV scale).[22]

As secondary endpoints, the following will be considered:

1. Thirty-day mortality.
2. Development of 30-day complications, including reintervention, cerebrovascular, pulmonary, renal insufficiency, bowel ischemia, spinal cord ischemia, coagulopathy and need for blood transfusion.

Reporting standards and statistical analysis

Reported results are in accordance with the SVS/AAVS current reporting standards.[33,34] Continuous variables are expressed as median, first quartile and third quartile (Q1-Q3) for non-normal distribution and as mean and standard deviation (SD) for normal distribution, and differences between groups are tested with the Mann-Whitney test or the two-sided t-test, respectively. Categorical variables are expressed as counts and percentage and the Chi-square

or Fischer exact test is used for comparison analysis. Primary analysis is not adjusted for covariates. Logistic regression model using stepwise selection will be used, if necessary, to identify predictors of the different endpoints. Data will be entered into the model if they present a univariate p-value of less than 0.05. In the multivariate analyses, clinical factors or potential confounding variables will be expressed as odds ratio with 95% confidence interval (CI).

Results

During the study period, 261 patients underwent TAAA SR with MEP/SSEPs monitoring [190 males, 73%; median age 65 (57-71)]. Thirty-seven patients suffered from SCI, for an overall rate of 14% (permanent 9%). The demographics of the entire cohort can be found in Table I.

Table 1: Demographics of the entire cohort.

	Total (n=261)	No SCI (n=224)	SCI (n=37)	p
Age (years)	65 (57-71)	64 (56-71)	67 (62-73)	.052
Males	190 (73)	163 (73)	27 (73)	.979
TAAA Extent				
I	51 (20)	46 (21)	5 (13)	.313
II	65 (25)	45 (20)	20 (54)	**<.001**
III	65 (25)	59 (27)	6 (16)	.183
IV	43 (17)	41 (19)	2 (5)	**.049**
V	13 (5)	11 (5)	2 (5)	.903
TAA	23 (9)	21 (10)	2 (5)	.426
Etiology				
Atherosclerotic	176 (67)	151 (67)	25 (68)	.888
Post-dissecting	85 (33)	73 (33)	12 (32)	.888
Max diameter (cm)	6 (5-7)	6 (5-7)	6 (6-7)	.403
BMI	26.2 (23.4-28.7)	26.0 (23.2-28.7)	27.2 (24.6-30.1)	**<.001**
Hypertension	228 (88)	195 (87)	34 (92)	.434
Diabetes	16 (6)	14 (6)	2 (6)	.872
Smoking history	152 (59)	124 (55)	28 (78)	**.011**
Dyslipidemia	103 (60)	87 (39)	16 (44)	.523
COPD	48 (19)	38 (17)	10 (28)	.121
CKD	47 (18)	38 (17)	9 (245	.245
CAD	55 (21)	47 (21)	8 (21)	.866
PTCA	29 (11)	22 (10)	7 (19)	.089
CAGB	15 (6)	13 (6)	2 (5)	.953
CTD	26 (10)	25 (11)	1 (3)	.120
Stroke	10 (4)	7 (3)	3 (8)	.131
Symptoms	34 (13)	29 (13)	5 (14)	.876
AF	21 (8)	17 (8)	4 (11)	.472
Beta Blockers	197 (76)	169 (75)	28 (78)	.762
ACE inhibitors	135 (52)	112 (50)	23 (64)	.122
Diuretics	57 (22)	42 (19)	15 (41)	**.002**
Previous surgeries				
Aortic valve repair	33 (13)	26 (12)	7 (19)	.190
Ascending repair	63 (24)	50 (22)	13 (34)	.073
Endo vasc repair	51 (20)	43 (19)	8 (22)	.671
Open vasc repair	70 (27)	60 (27)	10 (28)	.901

Preoperative blood levels				
Hb	12.8 (11.9-13.8)	12.9 (11.8-13.9)	12.6 (11.9-13.6)	.589
Ht	39 (36-42)	39 (37-42)	39 (36-41)	.426
PLT	204 (167-254)	204 (170-251)	187 (156-283)	.794
INR	1.06 (1.01-1.12)	1.06 (1.01-1.13)	1.06 (1.02-1.12)	.732
PTT	1.01 (.96-1.08)	1.01 (0.95-1.08)	1.01 (0.97-1.08)	.974
Creatinine	.96 (.80-1.19)	0.94 (0.80-1.17)	1.02 (0.80-1.39)	.67
Antiplatelet therapy				
ASA	183 (70)	159 (71)	24 (67)	.599
Other	20 (8)	17 (8)	3 (8)	.876
ASA + other	9 (3.5)	8 (4)	1 (3)	.809
Anticoagulation	31 (12)	26 (12)	5 (13)	.695

Patients who suffered from SCI were treated more frequently for an extent II TAAA (p<.001), had a smoking history (p=.011), had a higher body mass index (BMI) (p<.001). Intraoperative details can be found in Table II.

Table 2: Opertive details of the entire cohort

	Total (n=261)	No SCI (n=224)	SCI (n=37)	p
CSFD	246 (94)	209 (93)	37 (100)	.105
TEE	235 (91)	199 (90)	36 (97)	.137
LHBP	224 (86)	188 (86)	37 (97)	.034
Time (min)	54 (41-65)	52 (39-63)	55 (47-70)	.174
Aortic XC time (min)	52 (40-63)	52 (39-62)	52 (45-65)	.597
Custodiol time R (min)	31 (18-49)	30 (18-47)	47 (18-64)	**.007**
Custodiol time L (min)	47 (24-65)	46 (21-65)	62 (33-65)	.138
VV perfusion time (min)	32 (29-49)	31 (19-49)	37 (25-60)	.091
Proximal aortic cross-clamping				
Zone 2	82 (31)	70 (31)	12 (32)	.886
Zone 3	78 (30)	59 (26)	19 (51)	**.002**
Zone 4	22 (8)	20 (9)	2 (5)	.475
Zone 5	20 (8)	16 (7)	4 (1)	.437
Zone 6	39 (15)	39 (17)	0 (0)	**.006**
Zone 8	20 (8)	20 (9)	0 (0)	.066
VV Reconstruction				
No reconstruction	50 (21)	48 (21)	2 (5)	**.022**
Beveled	34 (13)	30 (13)	4 (11)	.666
Beveled + LRA	23 (9)	21 (9)	2 (5)	.430
Carrel Patch	17 (7)	16 (7)	1 (3)	.311
Carrell Patch + LRA	56 (22)	44 (20)	12 (32)	.079
Coselli	61 (24)	45 (20)	16 (42)	**.002**
Coselli + LRA	15 (6)	15 (7)	0 (0)	.105
Aortoplasty	5 (2)	5 (2)	0 (0)	.359

Intercostal arteries reconstruction				
No reimplantation	180 (69)	158 (71)	22 (60)	.177
Bypass	25 (10)	15 (7)	10 (27)	**<.001**
Patch	42 (16)	38 (17)	4 (11)	.345
Safi Loop	14 (5)	13 (6)	1 (3)	.438
Number of IC	0 (0-2)	0 (0-2)	0 (0-4)	.126
Need for inotropes				
Epinephrine	36 (14)	34 (15)	2 (6)	**.**121
Norepinephrine	142 (55)	113 (50)	29 (81)	**<.001**
Dopamine	13 (5)	10 (5)	3 (8)	.321
Dobutamine	5 (2)	4 (2)	1 (3)	.687
Intraop blood components				
RBC (units)	0 (0-2)	0 (0-2)	1 (0-2)	.567
PFC (ml)	0 (0-0)	0 (0-0)	0 (0-300)	.446
PLT (ml)	0 (0-0)	0 (0-0)	0 (0-1)	.617
Albumin (ml)	200 (0-200)	200 (0-200)	200 (50-300)	**.033**
EBL (ml)	4000 (3000-6500)	4000 (2750-6000)	4800 (3800-9000)	.**003**
Surgical time (hours)	5 (4-6)	5 (4-6)	6 (5-7)	**.003**

Patient with a longer operative times had an increased risk of SCI (p<.001). Eighty-two patients received an IA reconstruction [no SCI, 66 (30%) vs SCI, 16 (42%); p=.227] and the bypass reconstruction was more frequent in the SCI group [no SCI, 15 (7%) vs SCI, 9 (24%); p<.001]. Thirty-five patients (13%) required SA reimplantation due to IOM changes. Of those, a significant number of suffered from SCI (30% vs 11%, p=.002). In Table III, the postoperative details are summarized.

Table 3: Postoperative details of the entire cohort

	Total (n=261)	No SCI (n=224)	SCI (n=37)	p
Postop ICU blood levels				
Hb	11.7 (10.7-13)	11.8 (10.8-13.0)	11.2 (10.5-12.0)	.051
Ht	35 (32-38)	36 (32-38)	33 (32-36)	.149
PLT	110 (83-152)	111 (83-158)	104 (76-141)	.222
INR	1.44 (1.27-1.63)	1.42 (1.26-1.60)	1.61 (1.36-1.82)	**.007**
aPTT	32 (30-36)	30 (30-35)	35 (31-40)	**.005**
Creatinine	1.03 (.86-1.30)	1.02 (0.85-1.27)	1.17 (0.94-1.42)	**.042**

Mechanical ventilation (hours)	13.3 (8.5-18.0)	13 (7-16)	18 (12-45)	.067
ReIOT	18 (7)	12 (5)	6 (17)	**.013**
Tracheostomy	12 (5)	7 (3)	5 (14)	**.004**
Mini-Tracheo	10 (4)	4 (2)	6 (17)	**<.001**
Pleural effusion	47 (18)	31 (14)	16 (44)	**<.001**
Pneumothorax	12 (5)	10 (5)	2 (6)	.772
Pneumonia	26 (10)	21 (9)	5 (14)	.402
LOS	9 (7-14)	9 (7-12)	16 (12-20)	**<.001**
Sepsis	33 (13)	27 (12)	6 (17)	.440
AMI	8 (3)	6 (3)	2 (6)	.354
Pericardial effusion	6 (2)	5 (2)	1 (3)	.860
Reoperation	28 (11)	16 (7)	12 (32)	**<.001**
Bleeding	10 (4)	6 (3)	4 (11)	**.017**
Bowel ischemia	6 (2)	3 (1)	3 (8)	**.011**
Fogarty	7 (3)	4 (2)	3 (8)	**.027**
Other	14 (5)	4 (2)	10 (27)	**<.001**
In-hospital mortality	7 (3)	3 (1)	4 (11)	**.001**

Patients with higher INR levels (p=.005) and longer activated partial thromboplastin clotting time (p=.005) were more prone to develop SCI. The need for reintubation (p=.013) and the length of stay (p<.001) played a role as well. Reoperation was also identified as a risk factor for SCI (p<.001). Lastly, SCI was associated to a higher in hospital mortality (p=.001). When stratifying patients according to the SCI onset, 18 patients presented with an early SCI (11 of which permanent) and 19 with a late SCI (<24h) (11 of which permanent). (Table IV)

Table 4: Spinal cord ischemia details

	Total (n=37)	Immediate (n=18)	Late (n=19)	p
Severity	0 (0-3)	0 (0-3)	1 (0-3)	.742
Tarlov ≤2	27 (71)	12 (66)	15 (75)	.401
Associated events				
None	14 (38)	14 (78)	0 (0)	**<.001**
Hypotension	18 (49)	3 (17)	15 (80)	**<.001**
Hemorrhage	3 (8)	1 (6)	2 (10)	.580
Reintervention	2 (5)	0 (0)	2 (10)	.157
Permanent	22 (60)	11 (61)	11 (58)	.842
Tarlov ≤2	21 (96)	10 (91)	11 (100)	.306
Side				
Bilateral	30 (81)	15 (83)	15 (79)	.734
right	6 (16)	3 (17)	3 (16)	.942
left	1 (3)	0 (0)	1 (5)	.324

Of 261 patients undergoing TAAA SR with IOM, 15 were excluded due to changes in the upper extremity motor evoked potentials. For the remaining 246, the association between SCI and IOM was investigated: only irreversible IOM loss without peripheral changes in the reading have been found to be a risk factor for late onset SCI (p=.006). Furthermore, given that no statistical differences were found between the two groups when no IOM changes were recorded (p=.679), this situation cannot reliably rule out any SCI in our cohort. (Table V)

Table 5: Intropeative neurpphysiologic monitoring categories.

MEP/SSEPs	Overall (n=246)	Any SCI (n=33)	p	Early SCI (n=16)	p	Late SCI (n=17)	p
No changes	142 (58)	15 (46)	.125	6 (38)	.090	9 (53)	.679
With peripheral changes	29 (12)	4 (12)	.949	2 (13)	.927	2 (12)	.997
Without peripheral changes	113 (46)	11 (33)	.118	4 (25)	.082	7 (41)	.683
Reversable changes	84 (34)	7 (21)	.092	2 (13)	.059	5 (29)	.670
With peripheral changes	39 (16)	1 (3)	**.030**	0 (0)	.073	1 (6)	.243
Without peripheral changes	45 (18)	6 (18)	.986	2 (13)	.535	4 (24)	.563
Irreversible changes	19 (8)	11 (33)	**<.001**	8 (50)	**<.001**	3 (18)	.112
With peripheral changes	8 (3)	3 (19)	**.042**	3 (19)	**<.001**	0 (0)	.433
Without peripheral changes	11 (5)	8 (24)	**<.001**	5 (31)	**<.001**	3 (18)	**.006**

Independent risk factors for late spinal cord ischemia onset found at multivariate analysis were smoking history (p=.008), BMI>28 (p=.048) and TAAA extent II (p=.009). The irreversible MEP change without peripheral showed a trend of significance (p=.052). (Table VI)

Table 6: Late spinal cord ischemia onset univariate and multivariate analysis.

	Univariate			Multivariate		
Variables	**OR**	**CI 95%**	**p**	**OR**	**CI 95%**	**p**
BMI ≥30	3.	1.4 – 10.5	**.011**	3.3	1.1 – 9.8	**.034**
TAAA Extent II	2.7	1.5 – 9.7	**.006**	3.4	1.1 – 10.6	**.037**
Surgical time >6h	2.7	2.0 – 6.9	**.046**	1.4	0.4 – 4.4	.589
Reoperation	3.4	1.1 – 10.3	**.030**	1.7	0.4 – 6.7	.440
Irreversible MEP change without peripheral	5.9	1.4 – 24.8	**.015**	5.8	1.0 – 33.5	.052

Discussion

In the authors' current practice, the use of IOM has become a standard part of intraoperative patient monitoring,[60] although it can still be considered a controversial adjunct monitoring during TAAA SR due to its low predictive value.

While different studies have shown the reliability of MEP monitoring in predicting postoperative SCI,[37,61,62] only few tried to establish a connection between the use of intraoperative MEPs monitoring and late spinal cord ischemia events.[63] In their publication, Tanaka et al found no correlation between delayed SCI and signal loss during surgery, including patients negative for intraoperative evoked potential loss, and explained this with the fact that late onset SCI is multifactorial. They stipulate that in addition to the first hit during distal aortic repairs, a postoperative "second event" to the spinal cord, such as fluctuation in blood pressure due to acute blood loss, hypotension from renal replacement therapy, and malfunctioning CSF drainage, leads to the onset of delayed SCI. Although this could be an accurate account, not all "fist event" can be classified the same, and different MEP monitoring situations can be used as predictive measurements for late SCI. In the present study cohort, irreversible MEP loss without peripheral changes was predictive of late SCI. It is important to measure both peripheral and central SSEPs to differentiate peripheral nerve ischemia versus SCI. If a loss of evoked potential is seen in the cervical and cortical channels, but the peripheral signals are preserved, the findings are indicative of SCI. When a loss of evoked potential signals in the lower extremities is seen in all channels, it is a peripheral nerve injury.

Intraoperative patient optimization is of the upmost importance during TAAA SR to achieve optimal outcomes and this is a combination of maneuvers performed from both the surgeon and the anesthesiologist/perfusionist. Surgical measures include performing distal aortic anastomosis first or as soon as possible to reestablish early pulsatile flow to the pelvis and reattachment of critical SA.

Anesthesiologic/perfusionist maneuvers include increasing proximal and distal blood pressure (80 mmHg) with the help of the left heart bypass operated by the perfusionist, optimizing hematocrit,[64] and draining cerebrospinal fluid (CSFD) to maintain less than 10 mmHg of intracranial pressure.[65]

Comparing the present study outcomes after TAAA SR with those without IOM, such as Coselli

and colleagues,[66] Wongkornrat and colleagues[67] and Tanaka and colleagues,[63] who also use intraoperative adjunct to prevent SCI comparable to the ones used in the present study cohort (mild hypothermia, left heart bypass for distal aortic perfusion, and CSFD), no differences in the incidence of overall SCIs (9% vs 5%-9%) were found. This may be due to an aggressive SA reattachment strategy, guided by SA suitability to reimplantation (backflow, diameter, and aortic wall quality) rather than evoked potential loss at cross-clamping. Furthermore, postoperative management improvements of the patients who had IOM loss to avoid the "second event" (eg, abrupt blood pressure changes, high intracranial pressure, low hemoglobin, thrombosis) to prevent patients from developing delayed SCI is needed, as all late SCI case in the present series are correlated with hypotensive events, hemorrhages or need for reintervention. (Table IV)

The first case of late SCI after TAAA SR was reported in 1988, when deficit correction was thought to be beyond the surgeon's control.[68] Since then, different studies provided a clearer picture on the need for CSFD during and after TAAA SR.[26] The protocol used in the current series is CSFD by gravity intraoperatively and for three days postoperatively in all patients, generally draining 10 to 15 mL of CSF hourly to maintain CSF pressure less than 10 mm Hg.[65] In case of SCI, the CSFD is maintained in placed on a case by case basis. This protocol, associated to controlled hypertension in the postoperative period has allowed us to revert 7 cases of early (39%) and 8 cases of late SCI (42%).

Lastly, it should be noted that IOM is operator dependent with a somewhat steep learning curve, therefore a dedicated team of neurophysiologists and technicians should be a part of the multidisciplinary aortic team. Furthermore, clear communication during SR is of the upmost importance for a correct interpretation: anesthesiologists, neurophysiologists, and surgeons should all be working as one to decrease as much as possible SCI complications, each one with their expertise.

Study limitations

This study should be viewed with limitations. First, this is a retrospective, nonrandomized, single-center study. This may restrict the generalizability of the present findings, and center-specific biases were independently present. Second, MEP and SSEP measurements are operator

dependent and require an experienced neurophysiologist to obtain and interpret the results. Peripheral changes are especially technically difficult to be correctly interpreted. Third, residual confounding may always be present in observational studies, and, due to moderate to small event rates, statistical power for multivariable adjustment may be low. Last, the article's focus is on the role of evoked potential in predicting late SCI onset and not a comparison with other SCI prevention techniques.

Conclusions

Evoked potential intraoperative monitoring is an important adjunct during thoracoabdominal aortic open repair to predict and possibly prevent spinal cord ischemia. Irreversible MEP loss without peripheral changes was predictive of late SCI, therefore more attention should be paid to the postoperative management of this subgroup of patients to avoid any hypotensive or associated event which could lead to a late SCI onset.

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