

Strategies to prevent and detect intraoperative spinal cord ischemia during complex aortic surgery: from drainages and biomarkers

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Spinal cord ischemia (SCI), a frequent complication following open and endovascular thoracoabdominal aortic aneurysm (TAAA) repair, is a feared complication with relevant impact on a patient's quality of life. In the early days of open TAAA repair, more than one third of the patients suffered from SCI. Nowadays, due to improved preventive measures and the option of staged endovascular TAAA repair, 10 % of all patients are affected by spinal cord problems after TAAA repair (Rocha et al., 2020). A recently published meta-analysis could not confirm a significant lower rate of SCI after endovascular TAAA repair if compared with open repair. The particular risk factors such as an extended length of covered aortic segments above 20 cm, the placement of endografts between T9–12, the occlusion of the left subclavian or hypogastric arteries, perioperative hypotension and anemia as well as a long total procedure time remain as relevant factors affecting the risk of post-procedural SCI (Tenorio et al., 2019). Recently, preemptive interventional occlusion of intercostal arteries in the area of stent deployment has been described as a possibility to amplify the collateral network of the spinal cord before the covering of relevant arteries (Simon et al., 2020).

Among others, cerebrospinal fluid drainage (CSFD), spinal cord cooling, re-implantation of segmental arteries during open TAAA repair as well as permissive hypertension and avoidance of anemia have been described to be preventive regarding SCI (Figure 1; Xue et al., 2018). Although all these measures follow a comprehensive physiological theory, current literature reveals only limited clinical success and the current guidelines of the European Society of Vascular Surgery give no clear recommendation for the majority of these strategies (Riambau et al., 2017). In this respect, some options to prevent spinal cord ischemia during open and endovascular TAAA repair will be discussed.

CSFD: Cerebrospinal fluid (CSF) pressure increases during aortic cross clamping and occlusion of intercostal arteries after stent deployment during endovascular surgery and will eventually exceed venous pressure, leading to compromised venous outflow and spinal cord ischemia. Randomized control trials revealed a prophylactic effect of CSFD with a risk reduction of 75%. Yet at present,

there is little consensus regarding the role of CSFD in TAAA repair. Some authors promote routine use of prophylactic CSFD in all patients undergoing open and endovascular TAAA repair, whereas others recommend selective or emergency CSFD as required. In accordance with recent metaanalysis, CSFD placement may be related to a relevant rate of complications, including spinal canal hematomas, neurologic injury, and postdrainage headache. In the context of prophylactic CSFD usage, the benefits should be weighed up against the potential risks of drainage placement. The application of CSFD, which has been an inherent part of open and endovascular TAAA repair, has been questioned lately because of this potentially underestimated complication rate and a questionable benefit regarding the ability to prevent SCI (Karkkainen et al., 2020). Focusing on clinical practice, the benefits of a prophylactic CSFD placement outweigh potential complications, which are mainly formed by postdrainage headache.

Somatosensory evoked potentials (SSEP): SSEP monitoring is able to record stimulation of the posterior tibial nerve by use of electrodes placed on the scalp. According to clinical studies, SSEP can be used for identification of dominant intercostal arteries and to determine if these vessels should be re-implanted intraoperatively (Galla et al., 1999). However, SSEP is not able to record motor function as perfusion of the anterior corticospinal tract is not assessable. Therefore, SSEP can be associated with delayed detection of ischemia, which means a relevant reduction of its specificity.

Motoric evoked potentials (MEP): Transcranial stimulation and the technique of MEP recording has been described regarding its potentially beneficial application during TAAA repair due to its ability to monitor the spinal cord integrity. Especially the correlation of MEP-amplitudes decrease intraoperatively and postoperative SCI has been assessed and leads to a broad usage of MEP-measurements as part of the neuromonitoring during open and endovascular TAAA repair (Jacobs et al., 2002).

A series of 5 stimuli with an interstimulus interval of 2 ms and a stimulus intensity of 500 V is applied to the scalp through four

electroencephalographic disc electrodes placed in the vertex position with three inactive electrodes over the forehead. The MEPs are recorded with skin electrodes over the right and left anterior tibialis and rectus femoris muscles as well as over the abductor pollicis brevis muscles on both sides which serves as control for confounders that might influence the MEP-amplitudes other than SCI. Without the use of intraoperative neuromonitoring by means of MEP-measurement, no online information about spinal cord function is available during surgery. Based on clinical experience, a decline of at least 50% to 75% is evaluated as expression of critical spinal cord ischemia. This may correlate with postprocedural paraplegia. If MEPs remain normal, intercostal arteries are reattached if the aortic wall allows a safe anastomosis. If MEPs decrease to critical levels, patent intercostal or lumbar arteries should become revascularized. In any case, attempts to revascularize the spinal cord are carried out until the MEPs are restored. The influence of anesthetic agents on MEPs potential amplitude and the resistance of axonal conduction to ischemia leading to a slow assessment are major disadvantages of MEP measurement. Furthermore, the application and the evaluation of the findings is sophisticated and institutional experience is relevant regarding the practicability of the technique.

Near infrared spectroscopy (NIRS): NIRS has been described as a non-invasive, promising option to monitor spinal cord perfusion during and after TAAA repair. Bilaterally placed NIRS optodes at the thoracic (T5–7) and lumbar (L1–3) levels are used to measure the oxygenation level of local perfusion in several cubic centimeters of tissue underneath the NIRS optode. This information can be used for the determination of spinal cord oxygenation. Reliable data, which would support the application of this technique is pending as multicentric trials are ongoing (Vanpeteghem et al., 2020).

Biomarkers: The application of biomarkers, which can be measured in patients' blood and CSF, would enable the detection spinal cord ischemia intra- and postoperatively. Additionally, these biomarkers could be a viable option to assess the spinal cord function pre-, intra-, and postoperatively.

So far, several biomarkers have been evaluated regarding their potential association with acute spinal cord trauma and ischemia. Elevated levels of lactate in the CSF as well as elevated levels of glial fibrillary acidic protein, S100B and neuron-specific enolase in CSF and serum have been described as useful biomarkers to monitor acute spinal cord damage (Lases et al., 2005). Yet, ambiguous results can

be found in literature: neurone-specific enolase, a dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues, is a 78 kDa gamma-homodimer with a biological half-life of 24 hours. Lasas et al. (2005) found a poor correlation between levels of neurone-specific enolase in CSF and postoperative paraplegia.

Glial fibrillary acidic protein, first described in 1971, is an intermediate filament protein expressed by many cell types within the central nervous system. Anderson et al. (2003) were able to show a rather weak correlation between glial fibrillary acidic protein and SCI as clinically relevant endpoint. According to the authors' appraisal, no study is available leading to clear results, which would support a recommendation for the routine application of biomarkers of SCI during open and endovascular TAAA repair so far.

Pharmacological agents: A multitude of pharmacological agents has been suggested being effective in protection of the spinal cord during the period of intraoperative hypoperfusion (Reece et al., 2003). These positive effects on the spinal cord perfusion have been mainly observed in animal models. Among others, naloxon, phenobarbital, memantine and riluzole showed significant neuroprotective effects in dogs and rabbits. Dexmedetomidine, a selective α -2 adrenoceptor agonist, is known as an adjuvant to general anesthesia. Its potential organoprotective effects have become evident within the last years, as it shows *in vitro* and *in vivo* protective effects in kidney, lung, brain, heart, and liver tissues by ameliorating ischemia/reperfusion injury and inhibition of pro-inflammatory signaling pathways. In an animal study with rabbits, perioperative treatment with dexmedetomidine was associated with a significant preservation of neurological function following induced spinal cord ischemia/reperfusion injury with improved neuronal survival in the spinal cord. Yet, so far, no clinical application has been described.

Superoxide dismutase, which catalyzes the dismutation of superoxide radicals, was not related to neuroprotective effect because of its short half-life. In combination with polyethylene glycol its durability and its ability to get through membranes could be increased, leading to promising results in an animal model with rabbits regarding a prolonged spinal cord ischemia tolerance. In a primate model, these effects could not be observed. In case of intrathecal papaverine, a randomized clinical trial is available. In this study, intrathecal papaverine in combination with CSF and active cooling of the patient showed neuroprotective effects. Logistic regression analysis revealed that the combination of all three measures

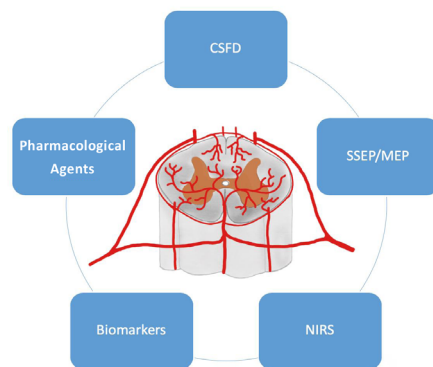


Figure 1 | Techniques and methods of spinal cord surveillance and protection.

CSFD: Cerebrospinal fluid drainage; MEP: motoric evoked potentials; NIRS: near infrared spectroscopy; SSEP: somatosensory evoked potentials.

significantly reduced the risk of spinal cord injury.

Conclusion: A multitude of techniques and methods of spinal cord surveillance and protection was developed within the last decades of open and endovascular TAAA surgery. CSF drain placement, which is well established so far as part of the standard protocol of open and endovascular TAAA repair so far, has been scrutinized recently regarding a potentially underestimated risk of complications and a doubted SCI-prophylactic effect in fields of endovascular TAAA repair. Yet, new techniques, such as NIRS and spinal-cord specific biomarkers were not able to proof their impact as less invasive possibilities of spinal cord function monitoring. As a perspective, pre-operative interventional occlusion of intercostal arteries leading to an improved spinal cord network as well as scoring systems for SCI risk assessment during TAAA repair may lead to a decreased necessity of invasive spinal cord protection measurements.

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