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Commentary: Pharmacologic induction of spinal cord ischemic tolerance: Game changer in thoracoabdominal aneurysm repair?

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Spinal cord ischemia remains a dreaded and yet incompletely understood complication of thoracoabdominal aortic aneurysm repair. Protagonists are (1) loss of end-arterial perfusion via direct ligation of intercostals; (2) ischemia–reperfusion phenomenon during crossclamp of aortic segments and subsequent restoration of flow; and (3) creation of watershed territories with perfusion through intercostal patches and collaterals from above and below the resected segment. Aortic surgeons have multiple strategies aimed at reducing the risk of paraplegia. These focus on intraoperative monitoring of somatosensory- or motor-evoked potentials, facilitating early detection of spinal cord ischemia as well as perioperative measurement and potential drainage of cerebrospinal fluid, allowing cord perfusion by keeping arterial pressure and cerebrospinal fluid pressure at an equilibrium. Operative strategies include staged repair to minimize ischemic cord segments, restoring cord perfusion by reimplanting intercostals, or maintaining distal perfusion using left heart bypass. Despite this, paraplegia occurs at a rate of 2.9% to 16.0%, with the greatest risk unsurprisingly reported for extent II thoracoabdominal aneurysms.^{1,2} With rates of neurologic complications plateauing in recent years, exploration of new avenues for protection remains paramount.

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CENTRAL MESSAGE

Spinal cord ischemia remains a dreaded complication during repair of thoracoabdominal aneurysms. Exploration of pharmacologic induction of spinal cord ischemic tolerance remains largely uncharted.

In this issue of the *Journal*, Ikeno and colleagues³ explore a novel strategy of pharmacologic induction of spinal cord ischemic tolerance. The group has an impressive record in delineating the potential role of mitochondrial ATP-sensitive potassium channel (KATP) in improving cellular tolerance to ischemia.⁴⁻⁶ The authors use a murine model of spinal cord ischemia to evaluate neuroprotective effects of direct versus indirect activation of the KATP channel. In their elegant study design, they compared neuroprotective effects of nicorandil, a direct and indirect KATP activator via direct channel agonism as well as indirect stimulation via release of nitric oxide, and diazoxide, a direct KATP channel activator—both with and without the addition of cPTIO, a NO scavenger. Compared with controls, there was significant improvement in motor functional outcomes and neuron cell viability in the nicorandil group. Diazoxide alone as well as coadministration of nicorandil or diazoxide with cPTIO resulted in attenuation of ischemic protective effects. These results suggest that the trick might lie in combined direct and indirect channel activation.

As the authors note, there are limitations. A juvenile small animal model cannot reliably reproduce the complexity of chronic aortic and microvascular disease. The study does not account for the critical postoperative course, where even short bouts of hypotension and alterations of cerebrospinal pressure may lead to irreversible neuronal damage many hours after repair. Management of thoracoabdominal aneurysms is complex, and the spinal

cord remains at risk beyond the initial ischemia trigger. KATP channels are inward rectifiers, and opening thereof provides ischemic protection via hyperpolarization and suppression of neuronal activity in the classic preconditioning model. Both drug dose-dependent responses as well as time point of administration might further impact treatment efficiency. Additional mechanistic understanding of KATP downstream pathways is warranted to ultimately delineate its role.

Nevertheless, the aforementioned results are remarkable. Improving tolerance of the spinal cord to ischemic insults on a cellular level has the potential to be a game changer and may become an essential tool in the arsenal of the aortic surgeon. We look forward to hearing more from this group, and others, as they strive to carry work like this bench to bedside.

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Commentary: A little help from the bench to cut risk of paraplegia?

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Although open aortic repair is associated with substantial postoperative complications, spinal cord deficit (ie, paraplegia and paraparesis) may be the most devastating one. Regarding Crawford's lifetime experience with 1509 thoracoabdominal aortic aneurysm (TAAA) repairs, as presented

Illustration of the spinal cord.

CENTRAL MESSAGE

Preventing spinal cord deficit requires a multimodal approach.

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in the late 1990s by Svensson and colleagues,¹ the rate of postoperative spinal cord deficit was a staggering 31% after the most extensive form of such repair, the Crawford extent II TAAA repair. Since the Crawford era, the rates of spinal cord deficit have dramatically decreased; rates of temporary and permanent spinal cord deficit were 2.4% and 5.4%, respectively, across all extents of TAAA repair, and for extent II repair, the rate of permanent spinal cord deficit was 8.0%.² How were surgeons able to reduce the