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Commentary: Spinal cord protection using remote ischemic preconditioning in rodents: Will this concept “stand up” in humans?

Harold L. Lazar, MD

Spinal cord ischemia (SCI), which occurs during thoracic aortic procedures, can result in paraparesis and paraplegia, which contributes to increased morbidity, impaired quality of life, and ultimately decreased long-term survival. In this edition of the *Journal*, Mukai and colleagues¹ report the effects of remote ischemia preconditioning (RIPC) on SCI in a rodent model simulating the ischemia–reperfusion injury seen after aortic crossclamping performed during open descending aortic and thoracoabdominal aortic repairs.

In their model, RIPC was performed 80 minutes before 12 minutes of proximal descending aortic clamping and consisted of 4 cycles of ischemia in the right upper and lower extremities for 5 minutes followed by 5 minutes of reperfusion using tourniquets to interrupt blood flow. SCI increased extracellular glutamate levels, measured by direct spinal cord microdialysis, and N-methyl-D-aspartate (NMDA) membrane receptor 2B (NR2B) expression in the ventral horn of the spinal cord. Although glutamate plays an important role in increasing ATP levels during myocardial ischemia and has been shown to improve ventricular function and limit myocardial necrosis when added to blood cardioplegia and reperfusion solutions,^{2,3} the increased accumulation of extracellular glutamate contributes to neuronal injury termed “excitotoxicity.” Glutamate itself does not cause neuronal cell death but leads to overstimulation of NMDA receptors, which impairs Ca^{2+} homeostasis, resulting in increased activation of inflammatory cytokines, proteases, and free radicals, which ultimately lead to neuronal cell death. Mukai and colleagues

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CENTRAL MESSAGE

Spinal cord protection using remote ischemic preconditioning may be useful in minimizing spinal cord ischemic damage during thoracic aortic procedures.

demonstrate that RIPC prevented the increase in glutamate levels, improved post-SCI hindlimb motor function, prevented the increase in NMDA NR2B expression, and resulted in significantly more normal neurons on histologic sections of the spinal cord.

How then can we use these rodent data to minimize SCI during thoracic aortic surgery in humans undergoing open and thoracic endovascular repair (TEVAR) procedures? Although the mechanism for SCI may differ between open surgery and TEVAR, the end result is the same—decreased blood flow to the spinal cord. Unfortunately, the authors fail to tell us how these results can be adapted into clinical practice. In addition, there are limitations with their model. The aorta was clamped for only 12 minutes, much less than what is observed during open surgical procedures. The current practice during open aneurysm surgery and TEVAR is to employ cerebrospinal fluid (CSF) drainage to limit edema and ultimately neuronal death. The authors did not perform an additional set of experiments to determine whether CSF drainage alone would decrease glutamate levels and NR2B expression in the absence of RIPC. Instituting RIPC in humans may be cumbersome and difficult to perform, and the exact period of time to achieve RIPC in humans is currently unknown. Finally, the beneficial effects of RIPC in minimizing SCI in rodents may not be reproducible in humans undergoing

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longer periods of aortic clamping and diminished spinal cord blood flow.

Despite these limitations, Mukai and colleagues are to be congratulated in performing an elegant series of experiments to increase our knowledge of the pathophysiology of neuronal “excitotoxicity.” Their observations of the detrimental effects of excessive NMDA expression may lead to the development of NMDA antagonists that can be directly infused into the CSF during periods of aortic clamping followed by the current practice of CSF drainage for 24 to 48 hours postoperatively. This may lead to better spinal cord protection during both open and TEVAR procedures

and minimize the devastating effects of SCI during thoracic aortic surgery.

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Commentary: Building the bigger picture from patchwork-like research pieces

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Many seemingly small details determine outcomes after major aortic surgery. Spinal cord injury is a devastating complication after both open and endovascular aortic surgery.^{1,2} Decreased blood flow of the spinal cord increases the risk for spinal cord ischemia and may lead to excessive accumulation of glutamate and N-methyl-D-aspartate receptor activation, as reported earlier following cerebral ischemia.³ Would it be possible to intervene on a molecular pathway to secure spinal cord vitality?

In a well-performed experimental study, Mukai and colleagues⁴ investigated the effect of remote ischemic preconditioning after spinal cord ischemia–reperfusion injury in rats. The study included explanatory figures. Spinal cord ischemia was induced using an obstructing vessel clamp to prevent blood flow into the descending thoracic

Research results are like details in a patchwork.

CENTRAL MESSAGE

Detailed experimental research on glutamate builds a patchwork-like picture of spinal cord protection against ischemia–reperfusion injury.

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aorta for 12 minutes. Remote ischemic preconditioning was included using 4 cycles of ischemia–reperfusion maneuvers by filling an elastic tourniquet around the limb of the animal for ischemia and subsequently releasing it after 5 minutes for reperfusion. Microdialysis, motor-evoked potentials, and evaluation of motor function were investigated. Histopathology and immunofluorescence studies confirmed neuronal injury after ischemia–reperfusion injury that was associated with excessive extracellular glutamate and N-methyl-D-aspartate receptor activation. Remote ischemic preconditioning down-regulated these parameters, and it was concluded that remote ischemic