Pretreatment with diazoxide and erythropoietin: A novel strategy to prevent paraplegia after aortic surgery

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Spinal cord injury is the most feared complication of thoracic aortic procedures and may occur during surgery or in the early postoperative period. Intraoperative neuromonitoring using motor and somatosensory evoked potentials may alert the surgeon to alterations in spinal cord function. This allows for the initiation of modifications in hemodynamics and spinal cord perfusion, which can minimize spinal cord ischemia and prevent paraplegia.^{1,2} However, postoperative spinal cord ischemia can occur without warning after transient episodes of hypoxia or hypotension.

In this edition of the *Journal*, Yamanaka and co-workers³ have shown that pretreating mice subjected to 4 minutes of thoracic aortic occlusion with diazoxide (DZ) and erythropoietin (EPO) decreases spinal cord ischemia and preserves motor function. The authors have previously reported that EPO decreases spinal cord ischemia in a similar murine model of ischemia and reperfusion.⁴ The protective effect of EPO is due to the induction of the beta common receptor (BcR) subunit, which is distinct from the EPO receptor that mediates hematopoiesis. BcR subunit expression is upregulated in response to hypoxia and inflammation, which requires an ischemic response. To obtain the maximum protection from spinal cord ischemia, the BcR subunit should be activated before the ischemic injury. In this study,³ the authors sought to pharmacologically induce BcR subunit upregulation before spinal cord ischemia to optimize the neuroprotective effects of EPO by using DZ, an adenosine triphosphate–derived potassium channel opener.

In their murine model of 4 minutes of thoracic aortic clamping, BcR upregulation occurred 12 hours after the administration of DZ and achieved peak levels at 36 hours. The combination of pretreatment with DZ and EPO resulted in the best recovery of spinal cord motor function and the best preservation of motor neurons seen in histologic sections of the spinal cord. Mice treated with DZ and EPO had a significant increase in the activation of STAT 3. This pathway has significant antiapoptotic properties in the presence of inflammation.

Both EPO and DZ are currently approved for use in clinical medicine: DZ for managing symptomatic

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Central Message

Pretreatment with DZ and EPO decreases spinal injury after thoracic aortic ischemia.

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hypoglycemia and EPO for augmenting red blood cell production. This should facilitate their use in clinical trials for spinal cord protection in thoracic aortic surgery. Because the peak expression of BcR after DZ occurred at 36 hours, it seems that the combination of DZ and EPO would be best suited for elective aortic procedures. However, it could also be given to patients undergoing emergency surgery in an attempt to enhance spinal cord protection in the early postoperative period. Clinical trials will be necessary to determine whether the enhanced spinal cord protection achieved by DZ and EPO in the murine model can be duplicated in patients undergoing thoracic aortic procedures.

References

1. Liu LY, Callahan B, Peterss S, Dumfarth J, Tranquill M, Ziganshin BA, et al. Neuromonitoring using motor and somatosensory evoked potentials in aortic surgery. *J Card Surg.* 2016;31:383-9.
2. Murashita T, Pochettino A. Intraoperative electroencephalogram-guided deep hypothermia plus antegrade and/or retrograde cerebral perfusion during aortic arch surgery. *J Card Surg.* 2016;31:216-9.
3. Yamanaka K, Eldeiry M, Aftab M, Mares J, Ryan TJ, Meng X, et al. Optimized induction of beta common receptor enhances the neuroprotective function of erythropoietin in spinal cord ischemic injury. *J Thorac Cardiovasc Surg.* 2018;155:2505-16.
4. Mares JM, Foley LS, Bell MT, Bennett DJ, Freeman KA, Meng X, et al. Erythropoietin activates phosphorylated CAMP (adenosine 3'5' cyclic monophosphate) response element-binding protein pathway and attenuates delayed paraplegia after ischemia-reperfusion injury. *J Thorac Cardiovasc Surg.* 2015;149:920-4.