without having to worry about how to get GDNF across the blood–brain barrier.

Dr Ikonimidis. The astrocyte-conditioned media was delivered to your neurons after 1 hour in your oxygen glucose–deprived state. Clinically, that would equate to a patient developing paraplegia, and then we give the drug. Is that how you envision dexmedetomidine (Precedex) being used clinically? Could you comment on that?

Dr Freeman. I think what we envision for an actual clinical model would be patients admitted the day before, maybe receiving a lumbar drain, things like that, and maybe starting dexmedetomidine at that time. Patients generally tolerate dexmedetomidine (Precedex) very well. We don't know what the dosing would have to be to get the response we see in vitro, but of course that would be sorted out in the future, but giving dexmedetomidine (Precedex) as a pretreatment, I think instead of waiting to see if the patient is one who develops paralysis, that everybody potentially could get it, because the side effect profile is so low.

Dr Ikonimidis. My point being that you might want to consider an experimental design.

Dr Freeman. Absolutely.

Dr Ikonimidis. That includes pretreatment. You're talking about this hypoxia glucose deprivation model as a model of IR, and it probably isn't. Because the definition of ischemia is really a low-flow state, not a low-oxygen state. I think you could give consideration to how you frame your description of that. It might be more of a hypoxia reperfusion model than an IR model. It's semantic, but to basic scientists who do this sort of stuff with oxygen-deprived cultures, it's an issue. If you have a lot of volume, you won't develop toxic metabolite accumulation that could contribute to cell death. It's just something to consider.

Dr Freeman. Right. Sometimes we talk about things and it's just semantics, but word choice really is everything when you're describing a model. I think it's the best model we have right now, but there are always ways to improve on what we have.

EDITORIAL COMMENTARY

Do we have a novel, clinically applicable approach to spinal cord protection?

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See related article on pages 578-86.

Paraplegia remains the most devastating complication related to thoracoabdominal aortic surgery. The early and late presentations may have disparate mechanisms, but nevertheless the outcome is the same, with a profoundly life-changing impact on the patient.

Through the years, numerous strategies have been introduced with the hope of preventing paraplegia, including the use of profound hypothermic circulatory arrest, lumbar drains, intercostal artery reimplantation, and various pharmacologic adjuncts. Indeed, these efforts have shown

success, and in modern high-volume aortic surgical centers the incidence of paraplegia has dropped below 5%. This devastating complication still looms large, however, for patients undergoing thoracoabdominal aortic surgery.

Recently, various researchers have discovered the ability to “precondition” neurons against damage with pharmacologic agents, some of which seem quite idiosyncratic. The classic example of this is the use of erythropoietin.¹ Another fascinating and somewhat surprising neuroprotective strategy seems to involve α_2 adrenergic receptor stimulation. Previously, Bell and colleagues² showed that the α_2 adrenergic agonist dexmedetomidine, when given postoperatively, attenuates neuronal injury in a murine model of spinal cord ischemia and reperfusion causing delayed paraplegia. The mechanism of action is unclear but may involve increased phosphorylation of protein kinase B and subsequent phosphorylation of cyclic adenosine monophosphate response element–binding protein (CREB), a transcription factor found in previous studies to be critical for neuronal protection and survival. Cyclic adenosine monophosphate response element–binding protein has been shown to upregulate antiapoptotic factor B-cell lymphoma 2 and brain-derived factors such as glial cell line–derived neurotrophic factor (GDNF), produced by astrocytes. A criticism of the in vivo spinal cord injury

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models used for these studies, however, is that one can only study interventions on the entire spinal cord, making it difficult to separate the effects of various cells within the spinal cord, such as astrocytes and motor or sensory neurons.

In the current issue of the *Journal*, Freeman and colleagues³ have reported an eloquent series of experiments designed to increase the granularity of these findings. On the basis of the hypothesis that the astrocyte plays a critical role in neuroprotection through the release of GDNF, Freeman and colleagues³ tested the role of α_2 adrenergic receptor agonism with dexmedetomidine on development of GDNF in cultures of perinatal spinal cord astrocytes and neurons. Freeman and colleagues³ found that astrocytes treated with dexmedetomidine had significantly increased GDNF production relative to control levels. Neurons subjected to oxygen and glucose deprivation had significant preservation of viability with the use of dexmedetomidine-treated astrocyte media. Finally, GDNF-neutralizing antibody eliminated the protective effects of the dexmedetomidine-treated astrocyte media. Freeman and colleagues³ concluded that the α_2 adrenergic agonist efficacy of dexmedetomidine in providing neuroprotection is therefore related to stimulation of GDNF from astrocytes.

There are certain limitations associated with the study. First, adult neuron cell cultures are extremely difficult to obtain, and studies that use them are therefore very difficult to interpret. Only pediatric or perinatal neurons could be used for these experiments, limiting to some extent the ability to translate these results to adults. In addition, because it was not possible to separate sensory and motor neurons in culture, it cannot be known from this study whether the protective effect is skewed toward either cell type. Finally, the use of

the oxygen and glucose deprivation model is intended to simulate the conditions of ischemia–reperfusion; however, this model clearly may not be entirely translatable to the clinical realm.

The study of Freeman and colleagues³ also gives some insights into the potential applicability of α_2 adrenergic agonism in thoracoabdominal aortic surgery. The data from this laboratory suggest that the highest concentration of GDNF is seen 24 hours after treatment with dexmedetomidine. Clinically, it would therefore be necessary to treat patients 24 to 36 hours before surgery to maximize GDNF concentration in the spinal cord at the time of ischemia–reperfusion injury.

The studies of Freeman and colleagues³ are particularly intriguing because dexmedetomidine (Precedex) is already used in surgical settings as a highly effective short-acting sedative. There would therefore be few barriers to incorporating this agent into a neuroprotective protocol, potentially supplementing the largely but not entirely successful strategies that aortic surgeons use on a daily basis to prevent spinal cord injury in their patients undergoing complex thoracoabdominal aortic replacement.

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