Salt before your heart?

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Central Message

Hypertonic saline solution administered to the cardiac transplant recipient before reperfusion of the allograft may reduce graft dysfunction and improve clinical outcomes.

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For the last several decades, hypertonic saline solution (HTS) fluid resuscitation has existed as a treatment looking for a disease. Despite research investigating HTS resuscitation for cardiac arrest survival,¹ prehospital treatment of hemorrhagic shock,^{2,3} reducing positive fluid balance in cardiac⁴ or major general⁵ surgery, or improving outcomes in burn patients,⁶ HTS therapy has not gained widespread use beyond that of an osmotic agent for elevated intracranial pressure.⁷ In this edition of the *Journal*, Ribeiro and colleagues⁸ propose a novel frontier for HTS resuscitation: perhaps graft dysfunction of a newly transplanted heart is the “right disease” for HTS treatment.

Primary graft dysfunction (PGD) and cardiac allograft vasculopathy (CAV) are the predominant causes of early (PGD) and late (CAV) morbidity and mortality after cardiac transplantation. Etiologic factors of PGD and CAV likely involve donor-recipient immunomodulation and ischemia-reperfusion injury. Previous investigations have focused on novel preservation methods for donor hearts, hoping to decrease incidence of PGD and CAV. A group of seasoned investigators have previously shown in a porcine model that administration of HTS to the donor before organ procurement improves cardiac functional recovery after transplant.⁹ HTS possesses immunomodulatory effects and can attenuate ischemia-reperfusion injury; however, treating the donor animal does not affect the recipient’s immune system. In this issue’s study by this same group of investigators, Ribeiro and colleagues⁸ administered HTS to the porcine model *recipient* before cardiac transplant and again demonstrated potentially clinically important benefits.

In the study of Ribeiro and colleagues,⁸ 16 pigs received heart transplants, with donor hearts stored in routine fashion (hypothermia, crystalloid cardioplegia) for 6 hours before transplant. One hour before recipient crossclamping, animals received either 7.5% sodium chloride solution (8 pigs) or 0.9% sodium chloride solution (8 pigs) given intravenously (4.5 mL/kg total) at 25 mL/min. Hearts were then implanted, and weaning from cardiopulmonary bypass

(CPB) was attempted. After CPB, numerous parameters were assessed, including hemodynamics, ventricular function, endothelial function, and myocardial metabolism. Myocardial and lung biopsy specimens were obtained to assess oxidative stress and inflammatory mediators.

The results were remarkable. Pigs receiving HTS exhibited less lactate production, an attenuated inflammatory response, limited cardiac and pulmonary oxidative injury, less endothelial-dependent and -independent vasomotor dysfunction, reduced vasospasm, improved hemodynamics, improved cardiac functional recovery, and reduced need for inotropic support. Most impressively, all 8 pigs receiving HTS were successfully weaned from CPB, whereas only 2 of 8 control pigs were successfully weaned. Although this study certainly has limitations (preclinical animal study, lack of randomization and blinding, CPB weaning not precisely defined, small sample size), the results seem to indicate that a simple intervention in a cardiac transplant recipient may have clinical benefits.

Ribeiro and colleagues⁸ suggest that this simple intervention may reduce allograft failure and propose several possible mechanisms for this clinical benefit. Hypernatremia modulates postischemic cardiac dysfunction by preventing the reperfusion-induced increase in intracellular calcium that otherwise occurs.¹⁰ Hypertonicity also triggers signaling pathways for enhanced cellular immune function by way of T-cells¹¹ and decreases neutrophil cytotoxicity.¹² Whether these effects will translate into any meaningful long-term benefits for the cardiac allograft remains to be seen. Considering the simplicity and accessibility of this

therapy, however, further investigations to determine the potential for human benefit, as well as how and when to implement this therapy, seem warranted.

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