High-molecular-weight polyethylene glycol: A new strategy to limit ischemia–reperfusion injury

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Despite the most optimal myocardial protection using modern cardioplegic solutions, ischemic damage may still occur, especially in those hearts undergoing revascularization for acute coronary syndromes and in patients with depressed ejection fractions who require longer crossclamp periods. This damage first becomes evident when the cross-clamp is removed during the “reperfusion period.” Over the past 40 years, a tremendous amount of research has been undertaken to minimize the detrimental effects of this reperfusion injury after cardioplegic arrest. This included manipulating the initial perfusate by adjusting pH,¹ maintaining diastolic arrest,² increasing osmolarity to prevent edema,³ lowering the initial perfusate pressure,⁴ maintaining normothermia,⁵ enhancing substrate delivery with amino acids,^{6,7} and providing an oxygen environment using a blood solution.⁸

In this edition of the *Journal*, Xu and coworkers⁹ introduce a new agent to minimize reperfusion injury: polyethylene glycol (PEG). The authors previously showed that PEG inhibits apoptotic cell death in isolated rat cardiomyocytes after an ischemia–reperfusion injury.¹⁰ This protective effect seems to stem from PEG’s ability to decrease reactive oxygen species generation and lipid peroxidation, thereby stabilizing membranes, thus maintaining cell integrity and inhibiting apoptosis. These protective properties seem to be derived from PEG’s ability to upregulate myocardial prosurvival signaling pathways as measured by the phosphorylation of Akt ERK 1/2, glycogen synthase kinase-3 β , and endothelial nitric oxide synthase. The authors now sought to determine whether PEG administered intravenously before reperfusion would also result in improved myocardial protection in an in vivo model in adult rat hearts subjected to 60 minutes of left anterior descending artery occlusion followed by 48 hours or 4 weeks of reperfusion.

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In these studies, mortality within the first 24 hours was 40% in the non-PEG group compared with only 10% in PEG-treated rats. After 4 weeks of reperfusion, PEG-treated hearts had significantly better recovery of fractional shortening, near normal recovery of left ventricular (LV) ejection fraction, 50% less LV fibrosis, a 56% decrease in apoptosis as measured by terminal deoxynucleotidyl transferase dUTP nick end labeling–positive nuclei, and a significant up-regulation of myocardial prosurvival signaling as measured by increased activity of the signaling pathways. Other agents, such as steroids and glutathione, have been used for membrane stabilization in cardiac surgery with minimal impact. It is PEG’s ability to not only stabilize membranes but to up-regulate prosurvival pathways that make it a novel and potentially important intervention to limit ischemic injury.

The potential toxicity of PEG is unknown and was not studied in this model. However, PEG has been approved by the Food and Drug Administration for use in cosmetics, foods, and drugs. PEG has also been used to coat gene therapy vectors, such as viruses, to protect them from inactivation by the immune system in vivo.¹¹ In these studies, PEG was administered immediately before reperfusion. PEG also has been used as an additive to cardioplegic solutions during donor heart procurement and was found to be associated with a significant decrease in the incidence of acute rejection episodes during the first post-transplant year.¹² It has the potential to become an important adjuvant therapy during percutaneous coronary intervention or acute coronary syndromes and as an additive to cardioplegic solutions. Further experimental studies on large animals undergoing reperfusion on cardiopulmonary bypass after ischemic arrest and ultimately clinical trials will be necessary to determine the role of PEG in clinical practice.

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