

Closing the Pore on Reperfusion Injury

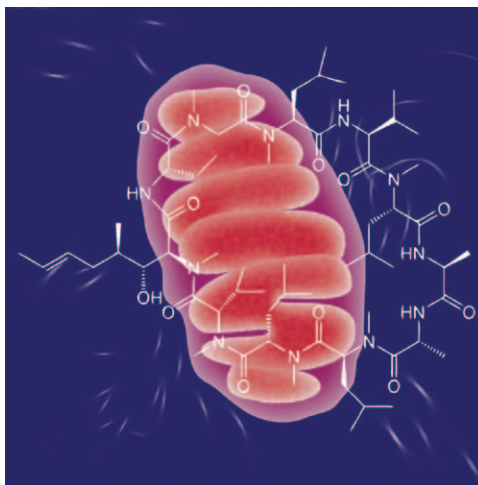
Myocardial Protection with Cyclosporine

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CARDIAC surgery with cardiopulmonary bypass and cardioplegic arrest leads to transient myocardial ischemia, characterized by hypoxia, energy depletion, and ion homeostasis alterations. Furthermore, reperfusion of ischemic myocardium leads to myocardial injury, resulting in the release of cardiac biomarkers. Ischemic postconditioning, in which the myocardium is exposed to brief episodes of intermittent ischemia during early reperfusion, is a promising strategy to attenuate reperfusion injury. Along these lines, but possibly easier to administer with a more controlled effect, is pharmacologic postconditioning, which is eloquently presented in this month's issue of *ANESTHESIOLOGY*.¹ Chiari *et al.* examined the administration of cyclosporine A

at the onset of reperfusion after aortic unclamping in patients undergoing aortic valve replacement with cardiopulmonary bypass and cardioplegic arrest. The study was randomized, placebo controlled, and patient blinded. The investigators focused on a distinct population of 61 patients undergoing aortic valve replacement without coronary artery disease and preserved ejection fraction. Their findings showed a significantly lower 72-h area-under-the-curve for troponin I release, their primary outcome, which remained significant after adjusting for relevant clinical and demographic covariates. There were no significant differences in those who received cyclosporine *versus* placebo in their secondary outcomes of short-term, in-hospital parameters or measurements of biological parameters or adverse events.

Mitochondria, which produce the majority of the cell's adenosine triphosphate, use oxygen as a substrate and are abundant in cardiomyocytes. During ischemia, mitochondria in cardiomyocytes are exposed to an imbalance of ion homeostasis. Upon reperfusion, amplification of ischemic injury and secondary damage occur, resulting in myocardial dysfunction, microvascular damage, and an inflammatory response.



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to be a potent inhibitor of mPTP opening. In prior pre-clinical studies, cyclosporine has been shown to preserve the function after reperfusion injury of severely impaired cardiac myocytes that are likely on the periphery of irreversibly injured cells. Upon unrestricted reperfusion, the intact myocytes whose mPTP opening has been inhibited by cyclosporine survive, but myocytes not treated with cyclosporine and whose mPTPs open die. The effect appears independent of the immunosuppressive properties of cyclosporine; nonimmunosuppressive derivatives of cyclosporine equally reduced infarct size in a rabbit model. Although long-term use of cyclosporine is associated with damaging side effects, such as increased susceptibility to cancer, infection, and renal and hepatic toxicity, the study by Chiari *et al.* and other studies have used a single bolus dose of 2.5 mg/kg without signs of acute toxicity or adverse events. The investigators in this issue's article have significant experience with cyclosporine. They were the first group to demonstrate that cyclosporine, administered shortly before reperfusion in the cardiac catheterization laboratory, reduced the extent of myocardial injury in patients with acute ST-elevation myocardial infarction.²

The majority of the damage occurs within the first minutes of reperfusion. Under physiologic conditions, a pore in the inner mitochondrial membrane, which is called the mitochondrial permeability transition pore (mPTP), is in a closed formation impermeable to metabolites and ions. The pore remains closed during ischemia; however, during the early minutes of reperfusion, calcium overload and excessive production of reactive oxygen species prompt opening of the mPTP, precipitating the collapse of its membrane potential followed by irreversible damage and cell death.

Cyclosporine, discovered more than 40 yr ago and in clinical use since 1982, was initially an immunosuppressant drug used to treat rejection after organ transplant. Meanwhile, it has also been found

Illustration: J. P. Rathmell; cyclosporin A molecule: Yikrazuul/Wikimedia Common.

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Cyclosporine is actively being investigated in the therapy of cardiac and neural injury. There are currently 249 active registered studies using cyclosporine in www.clinicaltrials.gov, of which only the minority are related to the prevention of myocardial injury, suggesting that this drug affects multiple different pathways. The effect of cyclosporine on the mPTP is not selective, as it also inhibits phosphatase calcineurin activity, which in turn may limit the degree of protection. Intralipid, in comparison, an agent that is similar to cyclosporine in that it prevents the opening of the mPTP and protects the heart from reperfusion injury, has recently been shown to be more effective than cyclosporine in an *in vivo* rat heart and isolated mouse heart experiment.³ How much this is applicable to humans and how much the effect of intralipid is actually related to the mPTP opening or to its other components is unclear.

These results corroborate, with very similar effect sizes, what has been found in ischemic preconditioning, an intervention that also reduces the extent of reperfusion injury by inhibition of mPTP opening. However, there are some aspects of this study that suggest consideration for further study. The small number of patients undergoing only one type of surgery limits the generalizability and does not allow for examination of long-term clinical benefits and/or adverse events. The investigators refrained from using inhaled anesthetics because of the known myocardial postconditioning effects associated with such agents, yet induced anesthesia using etomidate and maintained anesthesia with propofol, both supplied using intralipid as a vehicle, which also has postconditioning properties as previously discussed. Furthermore, the investigators used cold crystalloid cardioplegia, which is known to have higher creatine kinase MB fraction and troponin I release than blood cardioplegia.⁴ The latter might have resulted in a lower amount of cardiac troponin I release, and in turn resulted in nonsignificance between groups; at the very least, it might have required a greater sample size.

Before we incorporate giving a bolus of cyclosporine upon aortic unclamping into our daily clinical practice, we need to consider and perhaps address numerous issues. These include (1) the effect of cyclosporine on other pathways; (2) its effect on a more heterogeneous patient population; (3) the effect on longer-term outcomes; (4) confounders of genetics, sex, age, and/or comorbidities; (5) the time window of protection; and (6) the role of alternative and/or superior pharmacologic postconditioning agents.

According to the preclinical data and from the data presented, postconditioning with cyclosporine is promising. Although it is clear that ischemia is injurious and that reperfusion is a necessary evil to restore blood flow, it is unclear

at which point reversible injury becomes irreversible and for whom and when intervention should be considered. To date, in this small study of a relatively healthy patient population, we have not seen any adverse events associated with cyclosporine and we have seen a significant decrease in cardiac troponin I release. It is yet to be determined whether the protective effect of cyclosporine postconditioning is as good in patients who have a higher than average amount of cardiac biomarker release, such as patients who have undergone a surgical ablation procedure (MAZE) or mitral valve surgery with atriotomy. It is possible that the protective mechanisms are limited to those areas of myocardium on the periphery of irreversible injury and not those exposed to surgical manipulation. Larger studies in a more diverse patient population will tell us if we are ready for prime time with pharmacologic postconditioning with cyclosporine.

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Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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