Attenuation of postischemic myocardial injury by cariporide

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Recent evidence supports the sodium-hydrogen antiport system as an important player in the pathophysiology of myocardial ischemia-reperfusion injury.¹⁻³ Accumulation of hydrogen ions in the myocyte cytosol during ischemia creates a proton gradient that promotes the efflux of hydrogen ions in exchange for the influx of sodium ions. This hydrogen ion-driven process may be self-limiting during ischemia because the hydrogen ion gradient is blunted by the accumulation of H⁺ in the interstitial (extracellular) compartment, and extracellular acidosis and accumulation of acid products attenuates activity of the exchanger.³ However, reactivation of the antiport mechanism during early reperfusion leads to a reactivation of the exchange system. The buildup of intracellular sodium secondarily activates the Na⁺-Ca²⁺ exchange mechanism to operate in the reverse mode, resulting in a net calcium accumulation. The intracellular Ca²⁺ accumulation is thought to be the event that leads to dysfunction and cell death. Therefore, realkalinization of intracellular pH by the sodium-hydrogen exchange system and subsequent reversal of the sodium-calcium exchange system favoring net calcium accumulation work in concert to cause cell injury during ischemia and/or reperfusion.

Inhibition of the sodium-hydrogen exchange mechanism during ischemia (ie, before treatment) has been reported to reduce infarct size, degree of contracture, and arrhythmias in experimental coronary artery occlusion studies, reduce edema in postischemic myocardium, and restore systolic function in isolated perfused heart models.¹ Inhibition of the antiporter may be more effective than ischemic preconditioning.⁴ Furthermore, studies in which inhibitors of the sodium-hydrogen antiporter were used as adjuncts to cardioplegia showed greater myocardial protection than unsupplemented cardioplegic solutions.^{5,6} Inhibition of the sodium-hydrogen exchanger during ischemia, and to some (inconsistent) extent during reperfusion, was a cardioprotective strategy that showed promise. The GUARDIAN trial confirmed the cardioprotective potential of the sodium-hydrogen exchange inhibitor cariporide in patients undergoing coronary artery bypass graft surgery, in which there was a 23% risk reduction with the higher dose of cariporide (120 mg tid). The benefits of cariporide in cardiac surgery is the subject of another multicenter clinical trial, the EXPEDITION trial.

In this issue of the *Journal*, Muraki and associates⁷ evaluated the cardioprotection of cariporide (HOE 642) as an adjunct to blood cardioplegia in an experimental model that simulates surgical revascularization of evolving infarction. The authors chose a 10-fold higher concentration of cariporide than used in other studies, a concentration that did not inhibit neutrophil oxidant generation and degranulation. The authors found that this concentration of cariporide used as an adjunct to blood cardioplegia reduced infarct size (ie, decreased morphologic injury to severely injured myocardium), preserved postcardioplegic function of coronary artery endothelium from the area at risk, and attenuated neutrophil accumulation in the reperfused myocardium.

The protocol in the study by Muraki and associates differs from that used in the GUARDIAN clinical trial. In this clinical trial, cariporide was given intravenously preoperatively and postoperatively over a range of 2 to 7 days. The results of Muraki's group suggest that a shorter period of delivery of cariporide is beneficial,

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albeit at a higher concentration. However, further studies are required to determine whether these results represent optimal protection using the strategy of inhibiting the sodium-hydrogen antiporter. For example, pretreatment before cardiopulmonary bypass may be tested to determine whether greater degree of protection could be obtained than that observed with cariporide as an adjunct solely to cardioplegia. Additionally, the additional benefits of intravenous administration of cariporide concomitant with cardioplegia and subsequent reperfusion would be consistent with the data from some studies that inhibition of the antiporter during reperfusion is also an effective strategy in preventing ischemia-reperfusion injury. Last, although the sodium-hydrogen antiporter is active at hypothermic temperatures, the efficacy of inhibitors should be examined in other modalities of cardioplegia, such as warm induction, tepid and warm cardioplegia temperatures.

The concentration of cariporide used (10 $\mu\text{mol/L}$) by Muraki and associates did not alter neutrophil oxidant activity and degranulation. However, treatment with cariporide-enhanced blood cardioplegia attenuated the accumulation of neutrophils in the reperfused area at risk myocardium, ostensibly by inhibiting the local neutrophil-mediated inflammatory response to ischemia-reperfusion, rather than by a direct effect. The data for a significant contribution of neutrophils and other inflammatory cells and cytokines to postischemic injury is convincing.

This makes a compelling case for a multi-strategy approach to myocardial protection, and underscores the philosophy that there is no single magic bullet that will adequately address the complex, multi-pathway pathophysiology of ischemia-reperfusion injury. Increasing the concentration of cariporide or other sodium-hydrogen exchange inhibitors to directly inhibit neutrophils may express the toxic effects of these inhibitors. On the other hand, inhibitors of the sodium-hydrogen antiporter can be combined with other specific strategies that deplete leukocytes and inhibit neutrophil function, such as neutrophil filters,⁶ nitric oxide or adenosine.⁸

The concept of cardioprotection using inhibitors of the sodium-hydrogen antiporter can be expanded to include a number of other scenarios: (1) attenuation of multi-organ injury, particularly cerebral injury during circulatory arrest; (2) protection of the spinal cord during abdominal aortic repair; (3) protection during off-pump coronary artery bypass surgery. Although there is a paucity of compelling data

that the myocardium subtended by the target coronary artery is injured by transient and brief “elective” occlusions, this area of investigation is fertile ground. (4) Finally, and less related to cardiac surgery per se, the use of sodium-hydrogen exchange inhibitors during percutaneous coronary interventions can be further investigated. The clinical study by Rupprecht and colleagues⁹ has provided a proof of concept that systemic administration of a sodium-hydrogen exchange inhibitor reduces clinical end points of cardiac injury. A localized intracoronary approach to the delivery of therapy may potentially provide cardioprotection by allowing higher concentrations necessary to target neutrophil function to be delivered, without the threat of systemic accumulation and toxicity. The present report by Muraki and associates is an excellent reference for the investigators working in this area of research.

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