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EDITORIAL COMMENT

Cardioprotective Therapy and Sodium-Hydrogen Exchange Inhibition: Current Concepts and Future Goals*

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Following acute myocardial infarction (MI), limitation of infarct size is central to long-term outcome (1). Successful reperfusion results in smaller infarct size and a marked reduction in mortality (1,2). However, following fibrinolytic therapy, ischemic myocardial injury continues during the process of clot lysis. Although reperfusion arrests the acute ischemic injury, it may cause further injury (3) and lead to cell death (4). In addition, successful epicardial reperfusion may still be associated with a "no reflow" phenomenon at the myocardial level (5). Hence the need for effective cardioprotective strategies against ischemic-reperfusion injury. Such strategies may be employed during three key time intervals—prior to onset of ischemia, following onset of ischemic injury but prior to reperfusion, and following reperfusion.

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The feasibility of cardioprotection prior to onset of ischemia has been well demonstrated by the studies of ischemic preconditioning—that is, where short periods of ischemia may precondition the myocardium to withstand a longer period of ischemia, may slow ischemic injury, and may limit infarct size (6,7). Two phases of ischemic preconditioning are recognized—an early phase of protection and a delayed phase of protection lasting up to three days (7,8). In early preconditioning, endogenous substances are released including adenosine, bradykinin, and opioid peptides, which bind to myocytes via specific receptors and are thought to exert their cardioprotective effects by initiating a complex kinase signaling cascade, leading to opening of the K_{ATP} channel on the mitochondrial inner membrane (7). Thus, possibilities exist for pharmacological preconditioning.

Intermittent administration of an adenosine A1 receptor agonist has been shown to prolong the delayed phase of myocardial protection (8). Administration of exogenous bradykinin is limited by hemodynamic side effects. However, endogenous bradykinin may theoretically be potentiated by angiotensin-converting enzyme (ACE) inhibitors or neutral endopeptidase (NEP) inhibitors (7). Opioid preconditioning appears to act via the delta-receptor subtype. Morphine activates the μ, κ and δ opioid receptors and has been shown to have cardioprotective properties (9). The antianginal agent nicorandil, a relatively selective mitochondrial K_{ATP} channel opener, is currently being evaluated in the Impact Of Nicorandil in Angina (IONA) study—a randomized, double-blind, placebo-controlled trial testing the hypothesis that nicorandil will reduce the incidence of cardiovascular events in patients with effort angina and additional risk factors (10).

For patients who present following onset of ischemic injury but prior to reperfusion, the efficacy of cardioprotective agents before reperfusion probably depends on drug access to the ischemic region via some residual culprit artery flow or via a collateral circulation. Adenosine has been studied in this setting as an adjunct to fibrinolytic therapy in the AMISTAD trial (11). Use of adenosine did result in smaller anterior infarct size, although there was no reduction in morbidity/mortality (11).

Cardioprotective strategies following reperfusion aim to limit reperfusion injury, which may contribute as much as 25% to 50% of final infarct size (7). Whereas cell death during reperfusion may be a continuation of the necrotic process initiated during the preceding ischemia, apoptosis (programmed cell death) is now recognized as an additional mechanism of cell death during ischemia-reperfusion and may be particularly activated during reperfusion. Inhibitors of apoptosis by growth factors such as insulin and transforming growth factor-beta$_1$ (TGF-β_1), or by inhibiting the caspase cascade (which leads to apoptosis), are currently being investigated (7). Such a mechanism may partly explain the apparent benefit of adjunct glucose-insulin-potassium in patients with MI (12).

A key advance in cardioprotection was elucidation of the role played by the sodium-hydrogen exchange (NHE) mechanism in ischemia-reperfusion (13,14). The NHEs consist of a family of membrane proteins involved in the transport of protons in exchange for sodium. Six NHE isoforms have been recognized, with myocyte sarcolemma composed predominantly of the NHE-1 isoform. The NHE mechanism is normally a useful protection against acidosis; however, during ischemia it may be paradoxically harmful as intracellular accumulation of protons leads to NHE activation and sodium overload. As the ATP (adenosine triphosphate)-dependent Na^+/K^+ transport system becomes inoperative during ischemia, the sodium overload leads to reduced calcium efflux and/or increased calcium influx via the sodium-calcium exchanger mechanism, resulting in intracellular calcium overload. Elevated intracellular

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calcium concentrations cause cell death by several methods including protease activation, cell contracture, membrane rupture, and gap junction dysjunction. Successful reperfusion washes out the extracellular metabolites to accelerate the ionic exchanges, leading to further calcium influx.

In experimental studies NHE-1 inhibitors have been shown to reduce infarct size when administered before the onset of ischemia (15) or early after the onset of ischemia (16). It has also been suggested that NHE inhibition can minimize microvascular plugging/no-reflow (13,17) and reduce apoptosis in hearts submitted to an ischemic insult (18). Several NHE inhibitors have been developed. Most are amiloride derivatives, including cariporide and eniporide. Three recent clinical trials have assessed these agents in the setting of ischemia-reperfusion.

Rupprecht et al. (19) studied 100 patients with acute anterior MI treated with primary percutaneous transluminal coronary angioplasty (PTCA) who were randomized to receive placebo (n = 51) or 40 mg IV bolus of cariporide (n = 49) before the intervention. At 21-day follow-up, those receiving cariporide compared with placebo had a higher ejection fraction by paired left ventriculogram analysis (50% vs. 40%; $p < 0.05$), lower end-systolic volume (69.0 vs. 97.0 ml; $p < 0.05$), and improved regional wall motion indices, including the percentage of chords with hypokinesis less than −2 SD ($p = 0.045$). In addition, creatine kinase (CK), creatine kinase-MB fraction (CK-MB), or lactate dehydrogenase (LDH) release was significantly reduced in the cariporide patients.

The GUARd During Ischemia Against Necrosis (GUARDIAN) trial (20) enrolled a heterogeneous population of 11,590 patients with unstable angina or non–ST-elevation MI or patients undergoing high-risk percutaneous or surgical revascularization. Patients receiving placebo were compared with those receiving cariporide (20 mg, 80 mg or 120 mg every 8 h). There was no overall difference in the primary end point—incidence of death or MI at 36 days. However, subgroup analysis showed that in those patients receiving the highest dose (120 mg) a significant reduction occurred in death or MI in those undergoing bypass surgery (risk reduction 25%, 95% CI [confidence interval] 3.1% to 41.5%, $p = 0.03$). In addition, Q-wave MI was reduced by 32% (2.6% vs. 1.8%, $p = 0.03$), and non–Q-wave MI was reduced in those undergoing surgery (7.1% vs. 3.8%, $p = 0.005$).

In this issue of the *Journal*, Zeymer et al. (21) present the results of the Evaluation of the Safety and Cardioprotective effects of eniporide in Acute Myocardial Infarction (ESCAMI) trial. In a dose-ranging phase, 430 patients were randomized to placebo or eniporide (50, 100, 150 or 200 mg) administered as a 10-min infusion, before the onset of a reperfusion regimen (fibrinolytic therapy or primary angioplasty). The primary end point was infarct size estimated by area under the release curve of α-hydroxybutyrate dehydrogenase from 0 to 72 h. Significant reductions in enzyme release were noted in patients receiving 100 mg or 150 mg eniporide compared with placebo, particularly in the primary angioplasty subgroup. These doses were thus evaluated in a larger dose-confirmation phase (959 patients). Unfortunately, there was no difference in enzymatic infarct size among the three groups (placebo, eniporide 100 mg, eniporide 150 mg) nor any difference in secondary end points including major adverse clinical events and ST-segment resolution. Subgroup analysis showed that patients receiving 150 mg eniporide who reperfused late (>4 h after onset of pain) appeared to derive a small benefit from adjunct eniporide with respect to enzymatic infarct size and incidence of heart failure (Killip class ≥2) at one week. However, given the modest number of patients in this subgroup, such benefit should be interpreted with caution.

Thus, despite promising preclinical findings, the clinical trials did not support the hypothesis that NHE-1 inhibition with cariporide or eniporide prevented the progression from ischemic injury to necrosis. What reasons might account for the disparity between preclinical and clinical findings?

First, although in preclinical evaluation there was clear evidence of benefit when administration occurred before the onset of ischemia, the evidence for benefit following the onset of ischemia or following reperfusion was less clear (7,15). It has been shown that, in the initial minutes following the onset of ischemia, voltage-gated sodium channels constitute a major port of sodium entry (22). With falling intracellular pH, the NHE mechanism is activated and forms the dominant influx pathway over the next 30 min of ischemia. However, in the later course of ischemia, the NHE mechanism is partially inactivated (22). Thus, NHE inhibition would appear to be best administered prior to or *early* after the onset of ischemia. In the GUARDIAN trial, benefit was achieved when cariporide was given before coronary artery bypass graft surgery (CABG)—such patients undergo a scheduled ischemic arrest of limited and predictable duration.

Second, the optimum dose for NHE inhibition in humans is not yet clear, although the GUARDIAN trial would suggest that, given the favorable safety profile, near complete NHE inhibition is desirable. Larger doses may be required if administered after coronary occlusion but before reperfusion, as drug delivery to the subtended myocardium is likely to be unreliable. In contrast, in the ESCAMI trial, there was a nonsignificant trend toward excess deaths, particularly in the 200 mg eniporide group. This is most likely to have been a chance finding given the small numbers. However, it does suggest the need for a little caution with high doses in future eniporide dose-ranging trials. Zoniporide, a novel NHE-1 inhibitor, 2.5 to 20 times more potent than cariporide or eniporide, is currently undergoing preclinical evaluation (23).

Third, the optimal duration of administration also requires evaluation. The availability of an oral NHE-1 inhibitor (13) raises the possibility of an extended treatment window for patients presenting with unstable angina and at increased risk of subsequent infarction.

In summary, optimization of cardioprotection strategies continues to represent a challenge. The NHE-1 inhibitors have a clear potential when administered before or early after onset of ischemia, although their role in treatment of established ischemia or for prevention of reperfusion injury is less certain. Other potential cardioprotective strategies include antioxidants and free radical scavengers, anti-integrins, antiselectins, anticytokines, and anti-C5 complement. Ultimately it is likely that a combination of cardioprotective agents will be required to address individual components of the ischemia-reperfusion sequence adequately.

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