Editorial

Myocardial Cell Protection
A Challenging Time for Action and a Challenging Time for Clinical Research

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Left ventricular dysfunction, most often the consequence of coronary artery disease and acute myocardial infarction (MI) in our society, is the primary determinant of prognosis in coronary artery disease and the major cause of cardiac disability. The principles for cell protection have long been established: on one hand, metabolic preservation; on the other, restoration of flow. Reperfusion therapy led most progress in the past 2 decades, leaving in the shadow other means of cell protection. The success of reperfusion therapy is measured in clinical trials in terms of lives saved. The more subtle benefits of direct cell intervention are difficult to assess in humans, given the large interindividual variability in infarct size, the small to moderate benefit expected from interventions, and the lack of a sensitive method to quantify exactly the area of necrosis versus the area at risk. Meanwhile, mechanisms involved in the progression of ischemia to necrosis have become better defined, opening new therapeutic perspectives. Some of the new or renewed concepts are ischemic insult, reperfusion damage, no-reflow, stunning, hibernation, and ischemic preconditioning.

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Cell necrosis involves multiple mechanisms, including metabolic changes, ionic shifts, complement activation and generation of cytotoxic substances, inflammation, tissue edema, apoptosis, and matrix degradation. The respective roles of these mechanisms differ at various stages of ischemia and reperfusion and are cumulative. Unless interrupted, the process leads to irreversible damage. Early interventions will profit more and late interventions less; multiple interventions acting at different levels will probably be more successful.

The time constraints of 15 minutes to 3 hours for saving the jeopardized myocardium, learned from experimental models, apply only to a limited extent in humans. Reperfusion therapy saves life for up to 12 hours after onset of symptoms. Less profound ischemia associated with hibernation extends the period of time for salvage, whereas stunning delays recovery of function. Paradoxically, extensive necrosis can occur prematurely, despite early restoration of blood flow, as a result of no-reflow at the tissue level.

Clinical research on cell protection may target ischemia, reperfusion, prevention in high-risk situations, or reversible dysfunction. Rupprecht et al. in their study published in this issue of Circulation, set optimal conditions for detecting benefit of an intervention during an evolving infarct. Patients with anterior ST-segment-elevation MI and no flow through the culprit lesion who were undergoing primary angioplasty within 6 hours of onset of symptoms were enrolled. Success was measured as change in function on paired contrast ventriculograms obtained before and 3 weeks after the intervention. They studied cariporide, an inhibitor of the sodium-potassium exchanger (NHE) that is highly effective for reducing infarct size in experimental models of ischemia-reperfusion. Although the laboratory studies have shown maximal benefit when the drug was applied before or early during ischemia, higher doses administered before reperfusion are still effective. Rupprecht et al administered relatively low doses of the drug just before reperfusion. Yet, the drug improved global ejection fraction, end-systolic and end-diastolic volumes, and indices of regional function, such as percentage of left ventricular contour with akinesis, dyskinesis, or hypokinesis. The improvement was not statistically significant or was of borderline significance in the presence of an imbalance between groups at baseline, treated patients showing less severe wall motion abnormalities and better left ventricular function than placebo patients. In addition, 45% of enrolled patients had no control angiographic study, and the clinical characteristics of these patients are not provided. Nevertheless, all results, including enzyme release, converge to suggest a true benefit of cariporide.

The NHEs compose a family of membrane proteins involved in the transport of H+ in exchange for Na+, the driving force being the transmembrane Na+ gradient. It is regulated by the intracellular pH through interaction of H+ with a sensor site on the exchanger protein. Six NHE isoforms have been recognized. NHE-1 and NHE-6 are ubiquitously distributed in tissue, whereas NHE-2 through NHE-5 have limited expression. Myocyte sarclemna is composed predominantly of the NHE-1 isoform. The system protects against acidosis; paradoxically, it can be deleterious. As the ATP-dependent Na+/K+ transport system becomes inoperative during ischemia, Na+ is exchanged for Ca2+. Elevated intracellular Ca2+ concentrations directly mediate cell death by activating various proteases and causing cell contracture, membrane rupture, and gap junction disjunction. Reperfusion washes out the extracellular metabolites to accelerate the ironic exchanges; Ca2+ then enters the cell massively to cause the

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reperfusion injury. A burst of free radicals is also generated on reperfusion, contributing to cell necrosis. NHE inhibition has consistently prevented cell contracture and necrosis, stunning, reperfusion arrhythmias, and mortality in various models of ischemia/reperfusion.8

The sensitivity of the exchanger to intracellular H+ is influenced by numerous extracellular signals, such as those induced by catecholamines, angiotensin II, thrombin, endothelin-1, and free radical species. Thus, NHE inhibition has the potential of counteracting many morbidity processes associated with ischemia, some manifested acutely and some long-term as remodeling.9,10 NHE inhibition interferes with leukotriene B4 production, and agonists induced platelet activation and reduced platelet and leukocyte activation to minimize microvascular plugging and the no-reflow damage.11 The inhibition can also prevent apoptosis in hearts submitted to an ischemic insult.12 It does not interfere with the mechanisms of ischemic preconditioning and can possibly enhance them.13

Cariporide was recently investigated in the GUARD During Ischemia Against Necrosis (GUARDIAN) trial, which enrolled close to 12,000 patients.14 The phase 2/3 trial was designed to assess drug safety and efficacy in preventing necrosis in various clinical situations at risk of MI. These were unstable angina or non–Q-wave MI and high-risk coronary angioplasty and coronary artery bypass surgery. Three doses of cariporide were evaluated against placebo. The trial showed a very favorable safety profile but did not support the hypothesis that cariporide would prevent progression of ischemia to necrosis through a large spectrum of physiological effects, including preservation of energy phosphate stores, inhibition of neutrophil activity and of free radical formation. Inhibition of the cleavage of C5 prevents the generation of the complement byproducts C5a and C5b-9, which promote inflammation, induce procoagulant activity, and cause direct myocardial tissue damage.

Other Targets for Treatment
Other targets for treatment are free radical toxicity, neutrophil infiltration causing cellular edema, plugging of small arteries and no-reflow, the inflammation process, and matrix degradation. Antioxidants and free radical scavengers, antibody against cytokines, the complement system, and selectins and integrins and perfluorochemicals are all potentially useful interventions, as well as modulation of the activity of the matrix degradation molecules. GP IIb/IIIa antagonists interfere with the binding of neutrophils and platelets and, possibly, the interactions between inflammation and thrombosis.17

Ongoing Clinical Research
On the basis of strong and consistent effects in experimental studies, large clinical trials on cell protection are actually ongoing in coronary artery bypass surgery and in ST-segment-elevation MI with various NHE antagonists, with anti-integrins and anti-selectins and anti-C5 component of the complement system, with agonists to the adenosine receptors A1 and A2, and with ATP-sensitive potassium channel openers, which mediate preconditioning. Adenosine has a broad spectrum of physiological effects, including preservation of energy phosphate stores, inhibition of neutrophil activity and of free radical formation. Inhibition of the cleavage of C5 prevents the generation of the complement byproducts C5a and C5b-9, which promote inflammation, induce procoagulant activity, and cause direct myocardial tissue damage.

Clinical Application
Cell protection is more than a promise for the future; it is already a leitmotiv in current practice. Left ventricular dysfunction in a patient with an acute coronary syndrome dictates investigation of its reversibility. Acute ischemia, stunning, and hibernation are reversible causes of dysfunction. Current anti-ischemic therapy protects by reducing myocardial oxygen needs. Restoration of blood flow, however, is still required in most instances, urgently when hemodynamic compromise is present. Stunning usually recovers rapidly unless new ischemia supervenes. Hibernation, which may represent repeated episodes of stunning, needs revascularization. Ischemic preconditioning is probably un-
derused during reperfusion procedures, and the potential of pharmacological reconditioning has been little explored. 18

Cell protection is the new challenge for patient management in coronary care units, the catheterization laboratory, and the operating room, broadening our management strategies for acute coronary syndromes. Cell protection may be the next breakthrough in clinical cardiology. Yet, now is a time for clinical application.

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