From Door-to-Balloon to Door-to-Unload Time

An emerging view on the management of STEMI complicated by cardiogenic shock.

BY NAVIN K. KAPUR, MD

A 50-year-old man presents to your emergency department with a 120-minute history of acute-onset substernal chest pain. His initial electrocardiogram shows an anterior ST-segment elevation myocardial infarction (STEMI). The patient's blood pressure is 80/50 mm Hg, his heart rate is 100 bpm, his oxygenation is normal, and a physical examination shows an elevated jugular venous pressure, an S4 heart sound, and cold, clammy extremities. While the catheterization laboratory is being activated, an echocardiogram shows an estimated left ventricular ejection fraction of 25%, with anteroapical hypokinesis without valvular disease, septal rupture, or pericardial effusion. What's the next best step? Immediate primary percutaneous coronary intervention (PCI), hemodynamic interrogation with a pulmonary artery catheter, vasopressors, or acute circulatory support to stabilize the patient's hemodynamic status before primary PCI? What would you do?

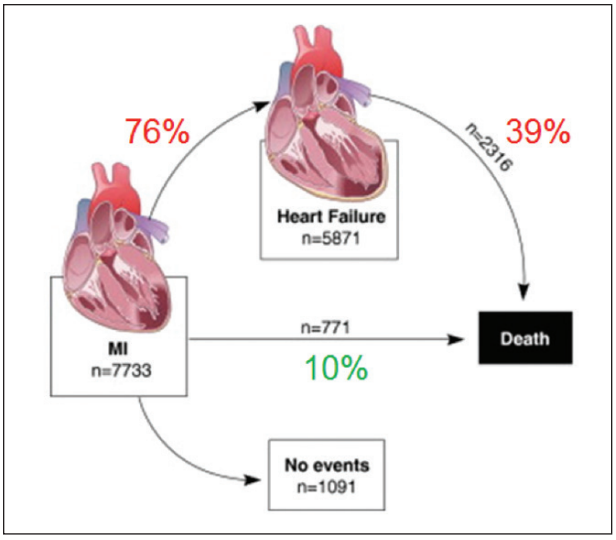

Figure 1. Despite timely reperfusion, nearly 10% of patients with acute MI die during their index hospitalization, and the majority of survivors progress to develop chronic heart failure. Reprinted with permission from Ezekowitz JA, Kaul P, Bakal JA, et al. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol. 2009;53:13–20.[6]

THE DOUBLE-EDGED SWORD OF REPERFUSION IN STEMI

Beginning with the "open artery theory" in the 1970s, the field of STEMI management has been ruled by the fundamental principle that "time is muscle," indicating that prolonged coronary occlusion leads to myocardial injury.[1,2] For this reason, the well-established paradigm of contemporary management for STEMI focuses on rapid coronary reperfusion via balloon angioplasty and stenting to limit myocardial injury. The metric for success in STEMI therapy is a door-to-balloon time (DTB) that is < 90 minutes, which is defined as the interval from the first electrocardiogram showing STEMI in the emergency department to mechanical reperfusion of the occluded coronary artery. The DTB time is a standard part of American College of Cardiology/American Heart Association guidelines and a core quality measure of hospital and operator performance.[3] However, recent data have suggested that there is no incremental benefit to a DTB time < 90 minutes in the setting of an anterior STEMI or cardiogenic shock.[4] Furthermore, despite timely reperfusion, nearly 10% of patients with acute myocardial infarction (MI) die during their index hospitalization, and 25% of survivors progress to develop chronic heart failure.[5]

A recent analysis of nearly 8,000 patients older than 65 years presenting with an acute MI undergoing early revas-

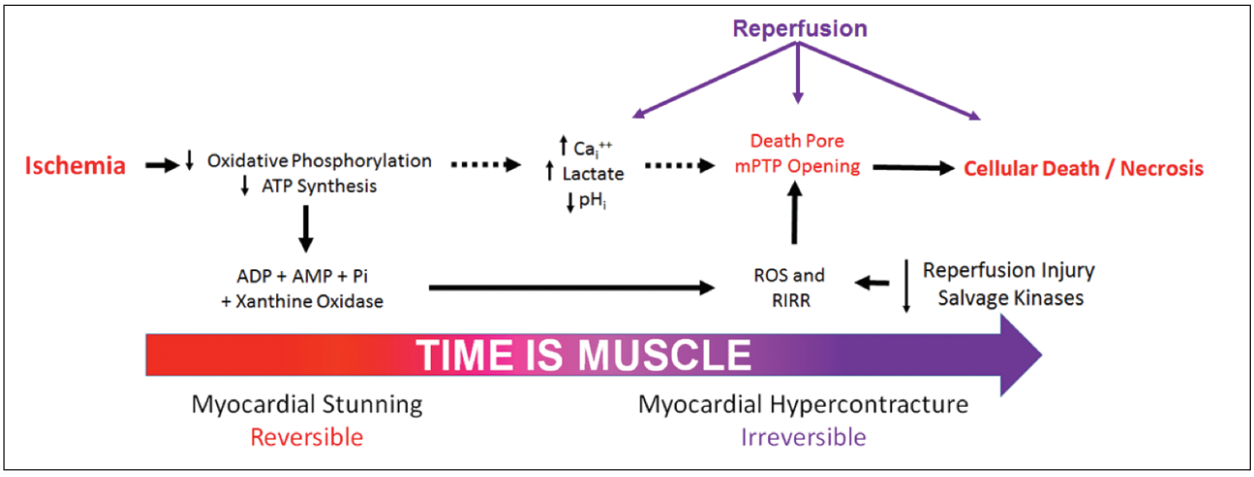

Figure 2. The mechanism of ischemia-reperfusion injury in acute MI. Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; Pi, inorganic phosphate; ROS, reactive oxygen species; RIRR, ROS-induced ROS-release.

cularization confirmed a low in-hospital mortality rate, but identified that nearly 76% of survivors go on to develop heart failure within the next 5 years (Figure 1).[6] Of the survivors who developed heart failure, 39% died within 5 years. These findings suggest that a re-examination of therapeutic priorities in the setting of a STEMI and cardiogenic shock may be necessary. Although coronary reperfusion to restore myocardial oxygen supply is ultimately necessary, perhaps contemporary interventionists should be focused on reducing myocardial oxygen demand and supporting systemic hemodynamics before moving to coronary reperfusion.

Described best by Braunwald and Kloner in 1985, myocardial reperfusion is a "double-edged sword" due to the fact that reperfusion of ischemic myocardium promotes cardiomyocyte death and microvascular damage through a process referred to as "myocardial ischemia-reperfusion injury."[7] Once a coronary artery is occluded, the myocardial injury clock begins immediately ticking. With every passing minute, oxidative phosphorylation becomes uncoupled, and adenosine triphosphate (ATP) synthesis is reduced within the mitochondrial engines that drive cardiomyocyte function.

This loss of ATP generation has two effects. First, intracellular calcium and lactate levels increase while intracellular pH decreases. Second, reduced ATP synthesis provides the substrate for generation of reactive oxygen species (ROS) that activate a feed-forward process known as *ROS-induced ROS-release*. The net effect of increased ROS levels is the opening of a hole in the mitochondrial membrane known as the *mitochondrial permeability transition pore* (mPTP). Further loss of protective signaling through the reperfusion injury salvage kinase pathway compounds injury by enhancing the mPTP opening. Depending on the length of time spent in this ischemic stage (artery occluded), the myocardium may be simply stunned or may transition to irreversible damage. Reperfusion will effectively restore blood flow to the myocardium; however, reperfusion also promotes opening of the mPTP pore and drives further cellular necrosis and infarct size (Figure 2).[8]

For an estimate of the extent of residual damage after successful, timely reperfusion therapy in an anterior STEMI, one should examine the results of the CRISP-AMI trial, which showed that nearly 40% of the myocardium was infarcted as measured by magnetic resonance imaging within 1 week of successful reperfusion therapy.[9] The percentage of these patients who go on to develop systolic heart failure remains unknown.

CONTEMPORARY AND EMERGING APPROACHES TO HALT THE MYOCARDIAL INJURY CLOCK

Contemporary approaches to stop the myocardial injury clock without sacrificing the absolute benefit of reperfusion therapy in STEMI are limited.[10] One of the best-studied approaches to cardioprotection in acute MI is ischemic conditioning whereby brief, intermittent periods of intentional coronary occlusion are created either before (preconditioning) or after (postconditioning) the onset of total coronary occlusion. Other approaches include pharmacologic therapies that target specific proteins involved in myocardial ischemia-reperfusion injury, such as cyclosporine or Bendavia (Stealth BioTherapeutics Inc.). Finally, global approaches, such as systemic hypothermia, have also been tested without clear evidence of benefit.

Although promising, critical barriers to current cardioprotective strategies are (1) the multifactorial nature of reperfusion injury, thereby limiting the impact of a single-target pharmacologic strategy; (2) the potential for coronary

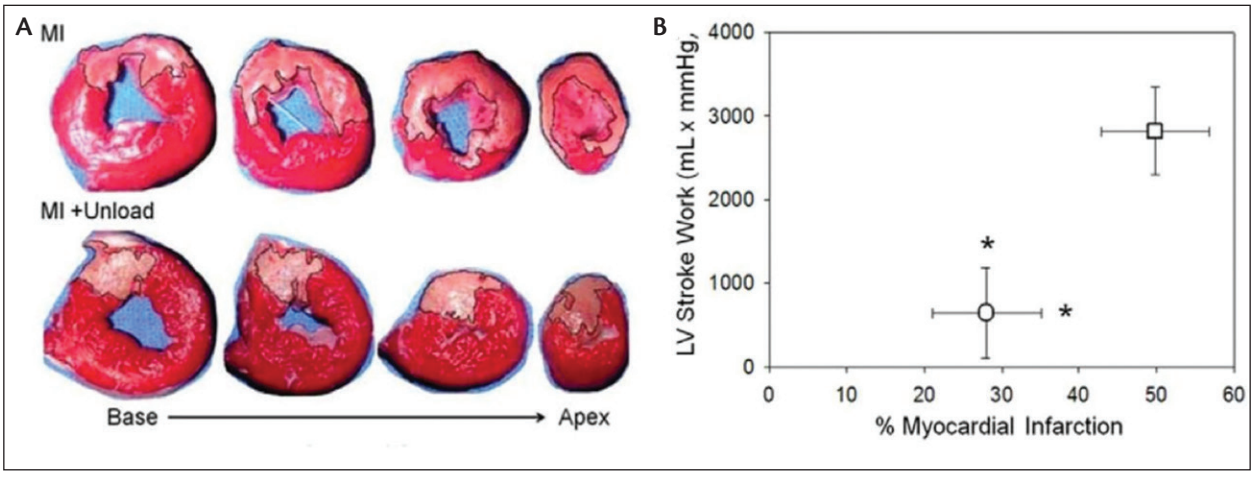

Figure 3. Reduced infarct with a door-to-unload strategy. Reduced infarct size (outlined white/pink region) with mechanical unloading before reperfusion (MI + unload) compared to reperfusion alone (MI) (A). Reduced myocardial infarct size correlates with reduced left ventricular stroke work (B). Reprinted with permission from Kapur NK , Paruchuri V, Urbano-Morales JA, et al. Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size. Circulation. 2013;128:328–336.[11] Abbreviations: LV, left ventricle; MI, myocardial infarction.

vascular injury (dissection or perforation) with ischemic conditioning; and (3) the mandate for rapid coronary reperfusion and therefore insufficient time for any cardioprotective therapy to affect myocardial injury zones. There exists a need for improved strategies to limit reperfusion injury that broadly affect the multiple levels of reperfusion injury without causing further myocardial damage while also providing time for drug penetration and efficacy.

More recently, our interventional research laboratory has been challenging the paradigm of DTB therapy by testing the idea that first reducing myocardial oxygen demand by reducing left ventricular wall stress and intentionally delaying coronary reperfusion, which every card-carrying interventionist does not want to do during a STEMI, will reduce infarct size. We first tested this idea using the TandemHeart left atrial-to-femoral artery bypass pump (CardiacAssist, Inc.). In the control group, 120 minutes of left anterior descending artery (LAD) occlusion was followed by 120 minutes of reperfusion. In the treatment group, 120 minutes of LAD occlusion was followed by activation of the TandemHeart pump, an additional 30 minutes of LAD occlusion (150 minutes of total ischemic time), and finally 120 minutes of reperfusion.[11] In this study, we observed a 43% reduction in infarct size, which correlated with a reduction in left ventricular stroke work (Figure 3).

In contrast to multiple reports over the past 2 decades suggesting the potential benefit of mechanical unloading of the heart in acute MI,[12,13] the novel aspects of this report included (1) the concept that reducing left ventricular wall stress and delaying reperfusion led to small infarct sizes despite a higher ischemic burden, and (2) the use of left atrial-to-femoral artery bypass as a method to reduce left ventricular wall stress. The clinical utility of primarily left ventricular unloading as opposed to primary reperfusion in STEMI with a left atrial-to-femoral artery bypass pump will be tested in the TRIS trial.

We have now completed a second series of experiments to address several questions, including the mechanism of benefit with primary left ventricular unloading, the reproducibility of this finding, the optimal timing for the delayed reperfusion, and whether the Impella CP axial flow catheter (Abiomed, Inc.) would achieve similar results. In this analysis, we observed a 43% reduction in infarct size and identified a previously unrecognized link between mechanical unloading and a myocardial protection program involving a cardioprotective chemokine known as *stromal-cell derived factor 1-alpha*.[14]

DOOR TO UNLOAD: EMERGING REALITY OR PUMP FICTION?

With respect to real-world practice, the concept of first unloading the heart with a circulatory support device and then providing reperfusion when it is safe to do so should not be so foreign to us. First, we know that myocardial perfusion is driven by a balance of several factors, including coronary perfusion pressure versus ventricular filling pressure and myocardial oxygen supply versus demand. The net effect of acute circulatory support may affect these factors in favor of optimal myocardial perfusion. Second, we can learn from our surgical colleagues, who often approach STEMI and shock management by first initiating cardiopulmonary bypass

to unload both the right and left ventricles, followed by a period of time to harvest bypass conduits (during which time the culprit artery remains occluded), and ultimately reperfusion. Third, we know from a recent analysis of the USPELLA registry that implantation of an Impella device before PCI in STEMI and shock may improve survival.[15] Finally, we are now developing preclinical data suggesting that "mechanically conditioning" the myocardium with a primary unloading strategy may activate a myocardial protection signaling program that reduces infarct size.

Over the next few years, increasing use of mechanical circulatory support devices will translate into a rapid growth in our understanding of ventricular hemodynamics, coronary physiology, and optimal management of cardiogenic shock in the setting of STEMI. Whether we will ultimately treat patients with a door-to-unload strategy instead of a DTB strategy remains to be determined, and much work needs to be done to answer several questions before this concept becomes a clinical reality. ■

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