Limiting Infarct Size in ST-Segment Myocardial Infarction
The Holy Grail of Reperfusion Therapy*

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Acute thrombotic occlusion of a coronary artery usually produces myocardial ischemia that can result in myocardial infarction if reperfusion is not restored. Reperfusion injury from reintroduction of blood and oxygen into the ischemic area at risk can result in additional myocyte cell death (1,2). Whereas early reperfusion therapy has been shown to reduce infarct size by decreasing ischemic injury time and results in lower morbidity and mortality rates (3), little progress has been made in decreasing the additional impact of reperfusion injury on infarct size despite 3 decades of effort (1,2,4). Although many interventions targeting reperfusion injury have seemed promising in experimental studies, they have failed to reduce infarct size consistently or improve clinical outcome in clinical trials and have not been endorsed by clinical practice guideline committees as effective therapeutic strategies (5). Nevertheless, reperfusion injury is a popular pre-clinical research area and the enthusiasts remain optimistic that a therapeutic breakthrough will eventually be achieved.

In this issue of JACC: Heart Failure, Kapur et al. (6) evaluated the therapeutic benefit of mechanical preconditioning on ischemic myocardium at risk for infarction in a swine model of acute coronary occlusion using a percutaneous circulatory support device to reduce left ventricular wall stress before establishing myocardial reperfusion. Ten Yorkshire swine underwent 90-min balloon occlusion of the mid left anterior descending artery: 5 were randomized to primary reperfusion for 120 min without mechanical support before humane killing and 5 were treated with a left ventricular axial flow catheter (Impella CP, Abiomed Inc., Danvers, Massachusetts) during an additional 60 min of ischemia time and during a similar 120-min reperfusion time before humane killing. This swine model of ischemia-reperfusion injury is well-established, but the experimental methodology to evaluate reperfusion injury was uniquely sophisticated. Changes in left ventricular pressure-volume curves were assessed using a conductance catheter system and left ventricular wall stress was evaluated by 3-dimensional echocardiography. Tissue protein levels were quantitated from sham-operated controls and infarct zones to measure cardioprotective signaling and apoptosis regulation. Apoptosis and myocardial infarct size as a percent of left ventricular area were also measured.

As expected, the axial flow catheter reduced left ventricular wall stress and myocardial oxygen demand. The authors demonstrated activation of a “myocardial protection program” in the myocardial infarct zone with upregulation of a cardioprotective signaling system that decreased apoptosis and resulted in a 43% reduction in myocardial infarct size. They concluded that mechanical preconditioning of the myocardium, despite an additional 1 hr of total ischemic time, may reduce infarct size and the subsequent development of heart failure after ST-segment elevation myocardial infarction (STEMI).

The authors are to be congratulated for conducting an elegant pre-clinical physiology study and further...
elucidating an interesting molecular and cellular regulatory system. However, the clinical translation of infarct size reduction with mechanical preconditioning seen in this study is less obvious, especially when one considers that the total ischemic time was relatively short by clinical standards and the reduction in infarct size was quite large despite a longer ischemic time. Animal models are limited by the fact that abrupt balloon occlusion of a normal artery is different than thrombotic occlusion of an inflamed atherosclerotic human artery with distal embolization. Also, human infarct size is additionally modulated by intermittent or persistent infarct artery occlusion, collateral circulation, oxygen demand, and microvascular reperfusion; and patients are heterogeneous, live in uncontrolled environments, have comorbidities, and are treated with medications that may affect ischemic injury (4). In short, there are many conflicting clinical factors that might impact cardioprotective signaling pathways and make it very difficult for a promising reperfusion injury therapy to show clinical benefit outside of a rigorously controlled laboratory experiment, especially given the success already achieved in decreasing the complications of myocardial ischemia with reperfusion therapy.

The theory behind the hypothesis of this study that further reductions in ischemic time will not improve clinical outcomes and that mechanical circulation can reduce infarct size are based on 2 major clinical assumptions that need to be challenged. First, Kapur et al. (6) claim that recent data have confirmed that “more rapid primary reperfusion does not improve clinical outcomes” in STEMI (6). The citation used to support the statement refers to a population-level analysis where recent decreases in annual door-to-balloon time at the population level were not associated with a parallel decrease in mortality (7). However, using the same dataset, Nallamothu et al. demonstrated that shorter patient-specific door-to-balloon times were associated consistently at the individual level with lesser in-hospital and 6-month mortality rates (8). The discordance in the 2 analyses is explained by an increasing mortality risk in the growing and changing primary percutaneous coronary intervention (PCI) population that has resulted in the recent absence of association between annual door-to-balloon time and changes in mortality at the population level, despite the consistent association between door-to-balloon time and mortality at the patient level. In fact, it has been demonstrated that STEMI can be aborted in 15% of patients if reperfusion is restored within 1 h of symptom onset and that the mortality rate is only 1 percent if reperfusion is successful within this golden hour (9,10).

Second, there are no compelling clinical data supporting the premise that left ventricular support devices improve prognosis in STEMI. In the fibrinolytic era of reperfusion, intra-aortic balloon pump (IABP) counterpulsation improved reperfusion rates and decreased reocclusion rates during fibrinolysis, presumably by augmenting diastolic coronary blood flow. However, primary PCI with stenting and dual antiplatelet therapy produces high reperfusion rates and low reocclusion rates, with no additional benefit gained with IABP counterpulsation in decreasing infarct size or mortality, even with cardiogenic shock (11,12). Nor is there any clinical evidence that higher systemic cardiac output, higher mean arterial pressure, or lower pulmonary capillary wedge pressure obtained with the use of a percutaneous left ventricular support device improves clinical outcomes compared with IABP counterpulsation (13). Support devices do increase bleeding complications, inflammation, and cost.

So, although I applaud the investigators for conducting an excellent pre-clinical study that demonstrates that left ventricular unloading activates cardioprotective signaling pathways in the infarct zone that decrease infarct size in a large animal model, I would predict that mechanical preconditioning with a percutaneous left ventricular assist device will not translate into a successful clinical strategy that reduces myocardial infarct size. Delaying reperfusion therapy for 1 h and routinely inserting an expensive percutaneous support device before primary PCI is not a clinically plausible strategy. Therefore, until the big breakthrough in reducing infarct size by decreasing reperfusion injury is attained, time to treatment will remain the most modifiable variable in decreasing infarct size in STEMI. Current efforts to decrease total ischemia time by earlier activation of emergency medical services, direct transport to a hospital with PCI capability, prehospital activation of the cardiac catheterization laboratory, and rapid performance of primary PCI remains the best strategy to decrease myocardial infarct size in STEMI (14).

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