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Optimizing Myocardial Recovery Post-ST-Elevation Myocardial Infarction – An Unfulfilled Promise

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In patients presenting with ST-elevation myocardial infarction (STEMI), early reperfusion with primary percutaneous coronary intervention (PPCI) and the use of evidence-based pharmacological therapy have led to a dramatic reduction in morbidity and mortality [1,2]. Despite advances in device technology and pharmacotherapy, 30-day mortality in patients presenting with MI remains as high as 7.8-11.4% [3]; up to 18% of men and 23% of women age ≥45 years will die within 1 year of their first MI, and these rates rise to 36% and 47%, respectively, at 5 years [3].

Although restoration of blood flow in the infarct-related artery is critical to myocardial salvage, injury to cardiac myocytes also occurs upon reperfusion of the myocardium so that overall infarct size is determined by both the original ischemic insult and further cellular necrosis following reperfusion. Limiting both the original ischemic insult and the subsequent reperfusion injury has emerged as an important strategy in optimizing myocardial salvage following MI.

The concept of myocyte injury following reperfusion was first proposed in the 1960s and is broadly divided into four types: reperfusion-induced arrhythmias, myocardial stunning, microvascular obstruction, and myocardial reperfusion injury [4–6]. Myocardial reperfusion injury, the focus of much of the research community, is mediated by a complex series of signaling cascades involving free radicals, intracellular calcium accumulation, acidosis, inflammation, activation of mitochondrial permeability transition pores (mPTP) and, ultimately, apoptosis. Therapeutic modalities that have attempted to minimize myocardial reperfusion injury in animal and/or human studies may be broadly divided into nine strategies: (1) anti-inflammatory agents such as pexelizumab, colchicine, and IL-1 inhibitors, (2) intracellular ion channel mediators such as cyclosporine and cariporide, (3) modulators of the reperfusion injury salvage kinase pathway such as nicorandil and magnesium, (4) modulators of the nitric oxide signaling pathway such as intravenous sodium nitrite and inhaled nitric oxide, (5) modulators of mitochondrial function such as trimetazidine and delcasertib, (6) antiapoptotic agents such as SB239063 and insulin, (7) ischemic pre- and post-conditioning techniques, (8) stem cell therapy, and (9) gene therapy.

Based upon animal studies, a number of clinical trials have been undertaken to examine the efficacy of agents that reduce reperfusion injury, with disappointing results. For example, the APEX-AMI investigators evaluated the efficacy of pexelizumab, a humanized monoclonal antibody that binds the C5 component of complement, as an adjunct to PCI to improve 30-day mortality in 5745 patients presenting with STEMI and undergoing PPCI [7]. There were no differences in 30-day mortality or the composite endpoint of death, shock, or heart failure [7]. Similarly, the Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction Patients (CIRCUS) trial of 970 patients with acute STEMI undergoing PPCI within 12 hours of symptom onset and receiving a single intravenous dose of cyclosporine administered immediately before PCI failed to demonstrate any benefits with regard to clinical outcomes or adverse left ventricular (LV) remodeling [8]. In one of the largest studies of stem cell therapy, the Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction (REPAIR-AMI) trial randomized 204 patients with acute MI to receive an intracoronary infusion of progenitor cells derived from the bone marrow (BMC) or placebo into the infarct artery 3-7 days after successful reperfusion therapy [9]. At 4 months, the absolute improvement in left ventricular ejection fraction (LVEF) was greater in the BMC group (5.5% vs. 3.0%; p=0.01). Subgroup analysis indicated that the benefit was greatest in patients with the worst LVEF at baseline.

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The enthusiasm generated by this study was subsequently dampened by the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial, in which improvements at 6 months in LVEF after infusion of BMC were no longer significant at 18 months [10].

Ischemic conditioning studies have also yielded conflicting results in reducing reperfusion injury, perhaps in part because the magnitude of benefit conferred in human studies has been modest, although statistically significant, confined to biomarker and scintigraphic estimates of infarct size, and without evidence of clinical outcomes. The impact of ischemic post-conditioning (IPO) upon the myocardium and LV function has been assessed using cardiac magnetic resonance imaging (CMR) in 118 STEMI patients in whom an IPO protocol of four cycles of 30-second balloon occlusion in the culprit vessel was associated with reduction in infarct size at 3-month follow-up [11]. By contrast, the Effects of Postconditioning on Myocardial Reperfusion in Patients with ST-Segment Elevation Myocardial Infarction (POST) trial of 700 patients, adopting a protocol of four cycles of 1-minute occlusion and 1-minute reperfusion did not show any benefit upon ST-segment resolution, myocardial blush grade or rate of major adverse cardiac events [12]. Studies examining the impact of remote ischemic conditioning have also produced encouraging, yet inconclusive, results, with higher mean myocardial salvage as assessed by myocardial perfusion imaging, a trend toward improvements in LVEF, improvements in ST-segment resolution, and reduced peak troponin [13,14].

In this issue of *Cardiovascular Revascularization Medicine*, Parviz et al. provide a comprehensive review of both animal and human studies of pharmacological and gene-based therapies that have been utilized in the treatment of reperfusion injury [15]. For many of the "negative" human studies, a thoughtful perspective as to potential reasons why the study may have failed to show a positive outcome has been provided. The review is a timely addition to the growing literature in reperfusion injury and emphasizes the complex and often interchanging molecular pathways that underpin this phenomenon. The review also highlights the pitfalls in translating *in-vitro* and animal observations into human clinical trials and emphasizes the need for further improvements in trial conduct, targeting multiple pathways that have been implicated in the pathophysiology of reperfusion injury, and selection of appropriate patients to tackle this clinically relevant pathology.

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