Clinical perspectives on reperfusion injury in acute myocardial infarction

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Prompt reperfusion therapy in acute myocardial infarction enhances clinical outcome. However, reperfusion itself may contribute to myocardial cell death. The current review outlines the multifocal mechanisms of reperfusion injury and focuses on understanding the potential role of each element and its contribution to the injury pattern inflicted upon the myocardium. We evaluate the spectrum of contemporary therapies that have been tested in an attempt to reduce myocardial injury. Finally, we explore promising innovative strategies targeting novel reperfusion injury pathways to protect ischemic myocardium during reperfusion. (Am Heart J 2014;0:1-9.)

Although prompt reperfusion therapy has been shown to reduce mortality, infarct size, and improve left ventricular function in ST-elevation myocardial infarction (STEMI), residual morbidity and mortality still exist. Despite the progress achieved through reperfusion therapy, it is also recognized that restoration of blood flow is associated with adverse events. This phenomenon, termed *reperfusion injury*, leads to lethal cell death and has been estimated to account for up to half of the ultimate infarct size.[1] Our aim is to provide insight into the concept of reperfusion injury and outline the various mechanisms contributing to the injury pattern inflicted upon the myocardium. We also review contemporary therapies and novel future strategies aimed to protect ischemic myocardium during reperfusion.

Historical perspective

In 1960, Jennings et al [2] induced myocardial necrosis and reperfusion in the canine model and showed histologic features of "explosive" cell swelling along with contracture of myofibrils. Significant disruption of the sarcolemma was noted with an abundant appearance of intramitochondrial calcium phosphate particles. Similar findings were reported in 1977 when Bulkely and Hutchins [3] reported a "paradox of myocardial necrosis" in humans after successful revascularization with coro-

nary artery bypass grafting surgery and speculated that this was related to calcium overloading and subsequent myocardial cellular edema distal to the patent bypass grafts. In 1985, Braunwald and Kloner [4] characterized reperfusion as a "double-edged sword" recognizing the multifactorial mechanisms involved with reperfusion in myocardial infarction (MI).

No-reflow phenomenon

Described by Kloner et al,[5] no reflow occurs when the release of vascular occlusion does not translate toward restoration of coronary blood flow. It refers to the impedance of microvascular blood flow encountered despite patency of the epicardial infarct-related artery. The clinical significance of suboptimal coronary blood flow is of particular importance given its association with poor inhospital major adverse cardiac events (MACE) and 1-year mortality.[6] The presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 (normal epicardial flow) after reperfusion is a strong predictor of survival.[7] However, even with epicardial TIMI flow grade 3, suboptimal perfusion of the myocardium may occur (angiographic myocardial perfusion grade ≤2) resulting in reduced 30-day survival.[8] Complete ST-segment resolution after reperfusion appears well aligned with overall myocardial perfusion and provides robust prognostic information regarding clinical outcomes.[9] As seen in Figure 1, the optimal clinical outcome and standard of care in STEMI is to achieve both epicardial patency (assessed by angiography) and myocardial perfusion (assessed for example by electrocardiogram).[10]

Reperfusion injury

During reperfusion, the inflammatory cascade facilitates white blood cells to release inflammatory mediators such as interleukins and activating complement leading

Figure 1
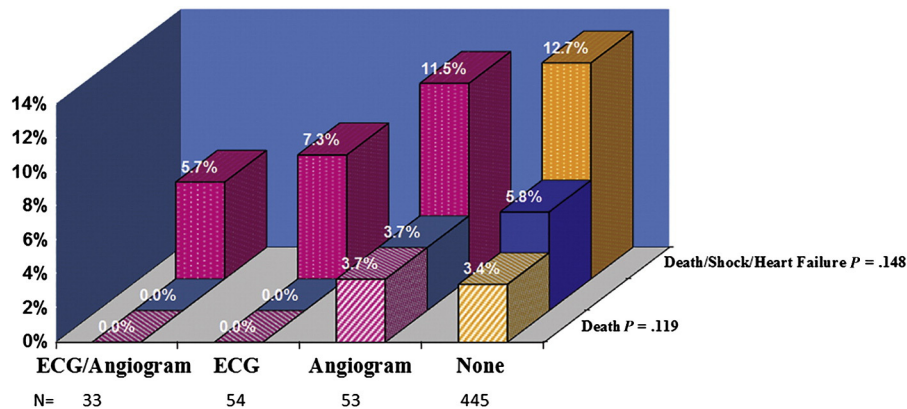
Thirty-day clinical outcomes according to metrics of epicardial patency in STEMI patients undergoing primary percutaneous coronary intervention (n = 585). Modified from Bainey et al[10] with permission from the journal.

to myocardial injury.[11] Reperfusion is a prothrombotic environment in which platelets become activated resulting in "platelet plugging" of the microvasculature.[12] This distal occlusive phenomenon is further exacerbated by atheromatous debris disrupted during the course of mechanical intervention. Reintroduction of oxygen potentiates formation of reactive oxygen species and accumulation of intracellular calcium, which damages cellular proteins, organelles, and plasma membranes.[13] Activation of proapoptotic signaling cascades potentiates further myocyte injury.[14] Because of inner cell membrane instability, ventricular fibrillation can occur resulting in sudden death after reperfusion of the infarct-related artery. As seen in Figure 2, the molecular mechanisms of reperfusion injury appear to be multifactorial with various consequences to cellular function.

Modulators of reperfusion injury

The mediators of lethal reperfusion injury have continued to elude clinicians despite ongoing research efforts to attenuate cardiac myocyte injury. Figure 3 outlines the various pharmacologic therapies tested in clinical trials of which the details are summarized below.

Glycoprotein IIb/IIIa inhibitors

Upon reperfusion, distal embolization of platelet-rich thrombus occurs, which obstructs the microvasculature resulting in impaired myocardial perfusion and altered clinical outcomes. Glycoprotein (GP) IIb/IIIa inhibitors prevent the aggregation of platelets and formation of occlusive thrombus. Reduced emboli in the microvasculature inhibit the release of proinflammatory/vasoactive particles. When administered at presentation in STEMI patients undergoing percutaneous coronary intervention

(PCI), GP IIb/IIIa inhibitors enhance clinical outcome[15]; however, their particular role in the treatment of reperfusion injury remains less defined.

Free radical antagonists

Molecular enzymes become supercharged with reintroduction of oxygen during reperfusion generating potent free radicals from ischemic myocardium, which are known to compromise cell membrane structure leading to myocardial necrosis.

A multicenter, randomized, placebo-controlled, randomized trial evaluating the efficacy of superoxide dismutase (a scavenger of oxygen-free radicals) in patients undergoing angioplasty for acute MI enrolled 120 patients and found no improvement in global left ventricular function when superoxide dismutase was given as an intravenous bolus followed by a 60-minute infusion before angioplasty (50.9% + 14.0% versus 50.1% ± 16.7%, P = not significant).[16]

Allopurinol, a potent inhibitor of xanthine oxidase, was tested in a 38-patient, single-center, randomized, placebo-controlled trial with oral allopurinol (400 mg) versus placebo given before primary percutaneous transluminal coronary angioplasty in acute MI. Improvement in free radical inhibition and recovery of left ventricular function at 6 months was found with allopurinol (urinary 8-epi-prostaglandin F2 as a surrogate for free radical production 15% ± 8% versus 111% ± 15%, P < .01; left ventricular ejection fraction (LVEF) 57% ± 2% versus 49% ± 2%, P = .04).[17] This small single-centered trial requires confirmation in a larger more definitive study.

Edaravone, another free radical scavenger, was evaluated in a single-center, randomized, placebo-controlled study involving 104 patients with an acute MI and undergoing primary PCI. Infarct size and reperfusion