

Magnitude and relevance of reperfusion injury

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Abstract

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI, the major cause of which is an acute thrombotic coronary arterial occlusion), the most effective therapeutic strategy for limiting myocardial infarct (MI) size, preserving left ventricular systolic function and improving clinical outcomes, is by timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI) to remove the obstruction. However, restoring blood flow in the infarct-related coronary artery comes at a price, as the process of myocardial reperfusion can in itself paradoxically inflict further injury to the myocardium—a phenomenon which has been termed “myocardial reperfusion injury.” Myocardial reperfusion injury results in myocardial stunning, reperfusion arrhythmias, microvascular obstruction and cardiomyocyte death, and its presence contributes up to 50% of the final MI size. Although the process of myocardial reperfusion by PPCI continues to be improved with recent advances in PCI technology, anti-platelet and anti-thrombotic therapy, there currently exist no effective therapy for preventing myocardial reperfusion injury. Therefore, novel therapeutic interventions, which are capable of reducing myocardial reperfusion injury, are needed to further reduce MI size, prevent the onset of heart failure and improve clinical outcomes in STEMI patients undergoing PPCI. In this article, a brief overview of myocardial reperfusion injury will be provided with special emphasis on its magnitude and relevance to clinical cardiology practice today.

Keywords: myocardial reperfusion injury; primary percutaneous coronary intervention (PPCI); ST-segment elevation myocardial infarction (STEMI)

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Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. The major manifestation of IHD is an acute ST-segment elevation myocardial infarction (STEMI), which is precipitated by the rupture of an unstable atherosclerotic plaque within the coronary artery and the formation of an acute thrombus resulting in complete occlusion and acute myocardial ischemia. For these patients, timely and effective myocardial reperfusion by primary percutaneous coronary intervention (PPCI) is the treatment of choice for limiting myocardial infarct (MI) size, preserving left ventricular (LV) systolic function and improving clinical outcomes. Paradoxically, the process of myocardial reperfusion is a “double-edge sword” [1] and comes at a price, as it can in itself paradoxically inflict further injury to the myocardium—a phenomenon

which has been termed “myocardial reperfusion injury” [1,2]. Although, the process of myocardial reperfusion continues to be optimized with recent advances in PCI technology, anti-platelet and anti-thrombotic therapy, there is currently no effective therapy for reducing myocardial reperfusion injury. Therefore, novel therapeutic interventions, which are capable of preventing myocardial reperfusion injury and which can be administered as adjunctive therapy to PPCI, are needed to improve clinical outcomes in STEMI patients undergoing IHD.

Myocardial reperfusion injury

Over 50 years ago, Jennings et al. [3] first documented in the canine heart, the histological changes which occurred on reperfusing ischemic myocardium. These comprised contracture of myofibrils, disruption of the sarcolemma, and the appearance of intramitochondrial calcium phosphate particles, features which appeared within minutes of myocardial reperfusion and which differed from those induced by myocardial ischemia alone, confirming myocardial reperfusion injury as a distinct pathological entity. However, the significance of these pathological findings only become apparent in the 1980s and 1990s when myocardial reperfusion by thrombolytic therapy and primary PCI was introduced as a therapy for STEMI patients. Clearly, myocardial reperfusion was shown to be essential for myocardial salvage but it soon emerged that the presence of myocardial reperfusion injury diminished the benefits of thrombolysis and PPCI in terms of MI size limitation. The effects of myocardial reperfusion injury include myocardial stunning (a term which describes the “mechanical dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow” and reperfusion arrhythmias, both of which are reversible and are easily managed in the clinical setting) [1,2]. This article will focus on the more serious and irreversible consequences of myocardial reperfusion injury, which are microvascular obstruction and lethal myocardial reperfusion injury.

Microvascular obstruction

Microvascular obstruction (MVO) was first described in 1966 by Krug et al. [4] in the feline heart as the “inability to reperfuse a previously ischemic region.” Its ultrastructural features were later characterized in the

reperfused canine heart by Kloner et al in 1974 [5]. Despite intensive research, the actual cause of the no-reflow phenomenon remains unclear although the major contributory factors are thought to include capillary damage with impaired vasodilatation, external capillary compression by endothelial cell and cardiomyocyte swelling, micro-embolization of friable material released from the atherosclerotic plaque, platelet micro-thrombi, and neutrophil plugging [5,6]. In reperfused STEMI patients it has been reported that the development of the coronary no-reflow phenomenon, the angiographic manifestation of MVO, is determined by several factors which include the extent of myocardial injury [7], the size of the myocardium at risk of infarction [7], the patency of the infarct-related artery [7], the presence of thrombus [8] or a large lipid pool [9] in the culprit lesion. The presence of coronary no-reflow at the time of PPCI is often treated with intracoronary adenosine or nitrates, although the efficacy of these therapeutic agents is unclear. Importantly, up to 60% of STEMI patients with normal coronary flow (TIMI 3) post-PPCI may still have evidence of MVO on cardiac MRI, the presence of which has been associated with a greater MI size, worse LV ejection fraction, adverse LV remodeling, and worse short-term and long-term clinical outcomes [10,11]. Therefore, a large proportion of STEMI patients undergoing may benefit from being administered at the time of PPCI, a therapeutic intervention capable of reducing the incidence and extent of MVO.

Lethal myocardial reperfusion injury

The existence of lethal myocardial reperfusion injury as a distinct entity, which is capable of independently inducing cardiomyocyte death following a sustained episode of myocardial ischemia, has been hotly debated over the years [1,2,12,13]. Part of the problem has been the inability to directly demonstrate that the actual process of reperfusion induces the death of cardiomyocytes, which were viable at the end of the ischemic episode. Indirect evidence for the existence of myocardial reperfusion injury has been provided by the large number of pre-clinical animal studies demonstrating 40–50% reductions in MI size with therapeutic interventions applied at the onset of myocardial reperfusion. This data would suggest that myocardial reperfusion injury may account for 40–50% of the final MI size [2]. The pathophysiology of lethal myocardial

reperfusion injury is closely related to the abrupt effects of myocardial reperfusion on mitochondrial function: the re-energization of the electron transport chain, the production of oxidative stress, mitochondrial calcium and phosphate overload, the rapid restoration of physiological pH, and the opening of the mitochondrial permeability transition pore (mPTP), a critical mediator of cardiomyocyte death in reperfused hearts [14-16].

Clinical relevance of myocardial reperfusion injury

Among many clinical cardiologists, the idea that myocardial reperfusion by thrombolysis or PPCI, which is essential for myocardial salvage in STEMI patients, may actually have detrimental effects on the heart appears implausible. After all, restoring coronary blood flow and maintaining the patency of the infarct-related artery are the major priorities of therapeutic myocardial reperfusion. The evidence that lethal myocardial reperfusion injury exists in man and may actually be relevant to the clinical setting has been recently provided in a small landmark proof-of-concept clinical study published in 2005 by Staat et al. [17]. These authors demonstrated that a therapeutic intervention applied to STEMI patients at the time of PPCI could reduce MI size by 38% (measured by 72 hour area under the curve total CK) [17]. The therapeutic intervention, ischemic postconditioning (IPost), which had been demonstrated in pre-clinical animal studies to reduce lethal myocardial reperfusion injury [18], comprised the interruption of coronary blood flow with four-1 min low-pressure angioplasty balloon inflations/deflations within the infarct-related artery [17]. Subsequent clinical studies have confirmed the beneficial effects of IPost using myocardial nuclear scanning, echocardiography, and cardiac MRI [19,20]. Taken together these clinical cardioprotection studies suggest that in STEMI patients undergoing PPCI, about 40–50% of the final MI is due to lethal myocardial reperfusion injury. Therefore, by applying a therapeutic intervention to prevent lethal myocardial reperfusion injury in STEMI patients at the time of PPCI may result in a further 40–50% reduction in MI size.

Myocardial reperfusion injury as a therapeutic target

Until the discovery of IPost, the translation of a large number of therapeutic interventions proven to be cardioprotective in the pre-clinical animal setting, have failed in the clinical setting. The reasons for this are

many and have been the topic of recent discussion and some of these problems may be overcome in the future with more rigorous testing of novel cardioprotective interventions in the pre-clinical setting and more careful design of the clinical studies [21-23]. However, there are a number of promising therapeutic interventions for reducing myocardial reperfusion injury in the clinical setting including cyclosporin A (an mPTP inhibitor) [24], exenatide (a glucagon-like protein 1 agonist) [25], and remote ischemic preconditioning (four-5 min cycles of upper limb ischemia/reperfusion induced by cuff inflation/deflation) [26], which have been demonstrated in proof-of-concept clinical studies to reduce MI size in STEMI patients when administered prior to PPCI. Large multicenter clinical trials are now required to determine whether preventing lethal myocardial reperfusion injury can improve clinical outcomes in STEMI patients treated with PPCI.

Conclusion

Myocardial reperfusion by PPCI is the treatment of choice for salvaging viable myocardium in patients presenting with a STEMI. However, the full benefits of myocardial reperfusion, in terms of myocardial salvage, are diminished due to the presence of myocardial reperfusion injury, which contributes up to 50% of the final MI size, and for which there currently exists no effective therapy. Therefore, the discovery of novel therapeutic interventions which are able to prevent myocardial reperfusion injury in STEMI patients undergoing PPCI, may allow us to realize the full benefits of myocardial reperfusion with further reductions in MI size, preserved LV systolic function and improved clinical outcomes. •

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