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Review Article

Reperfusion Injury after Acute Myocardial Infarction

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Summary

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality worldwide. Primary percutaneous coronary intervention (PPCI) is the gold standard treatment for patients presenting with ST-segment elevation myocardial infarction (STEMI). PPCI reperfusion therapy has the potential to reduce infarct size, preserve the left ventricle ejection fraction (LVEF), prevent lethal complications, and improve prognosis. A significant proportion of STEMI patients, however, develop post-infarct heart failure despite optimal PPCI. One of the reasons for post-infarct heart failure is that reperfusion injury increases the infarct area after PPCI. This article reviews the current understanding and up-to-date evidence basis for therapeutic intervention of reperfusion injury. Specifically, the combination of myocardial ischemia secondary to acute coronary occlusion and reperfusion injury leads to further myocardial injury and cell death. Multiple treatment modalities have been shown to be cardioprotective and reduce reperfusion injury in experimental animal models. Recent clinical trials have assessed multiple cardioprotective strategies, including ischemic pre- and post-conditioning, pharmacologic therapies, and mechanical devices. While several therapies have been shown to reduce infarct size in animal models or proof-of-concept studies, many large-scale trial results have proven inconsistent and disappointing. To decrease the incidence of severe heart failure in patients and extend healthy life expectancy in an aging society, further development of prevention strategies for reperfusion injury is needed, including novel maneuvers, drugs, devices, and combinations of the three.

Key Words: reperfusion injury, acute myocardial infarction

Background

The number of the patients with ST-segment elevation myocardial infarction (STEMI) has decreased over recent decades, mostly in developed countries as a result of the proactive management of coronary risk factors, including lifestyle modification and medications. In developing countries, however, the incidence of acute myocardial infarction (STEMI and non-STEMI) has increased[1]. The decreased STEMI mortality rate in developed countries, from 20% in the late 1980s to 5%-7% currently[2-4], has largely been attributed to primary per-

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cutaneous coronary intervention (PPCI).

The door-to-balloon time in patients with STEMI undergoing PPCI has consistently declined; however, the overall in-hospital mortality has not decreased[5], likely because the patient population has changed, such as aging and/or severe co-morbid diseases[6]. A recent patient-level meta-analysis demonstrated that the infarct size within 1 month after PPCI possibly predicts the rate of all-cause mortality and hospitalization for heart failure at 1 year[7]. Although optimal reperfusion by PPCI is the most effective strategy of limiting infarct size and subsequent ventricular remodeling[8], reperfusion injury associated with an irreversible injury to the myocardium and coronary circulation could increase infarct size after PPCI[9,10].

The prevention and treatment of reperfusion injury after PPCI is one of the most important remaining issues by which overall outcomes of patients with STEMI can be improved by reducing infarct size[11-16].

Pathophysiology of Myocardial Reperfusion Injury

1. History of reperfusion and reperfusion injury

STEMI infarct size is determined by the following three factors: size of the ischemic area at risk; duration of coronary occlusion and magnitude of residual collateral blood flow; and extent of coronary microvascular dysfunction.

The infarct develops in a typical wavefront manner, starting in the subendocardial layers in the center of the area at risk and progressing into the subepicardial layers and the border zones of area at risk with the ongoing duration of coronary occlusion[17-19]. Four to six hours from the onset of STEMI, 30%-50% of the area at risk remains viable, and therefore PPCI is very effective in salvaging the myocardium. Even after 12 h of coronary occlusion, viable myocardium is present and PPCI can reduce the infarct size[20].

In 1972 Ross et al.[21,22] reported that reperfusion after 3 h of coronary occlusion reduces infarct size in dogs; this observation marked the beginning of reperfusion strategies[23]. The GISSI[24] and ISIS-2 trials[25] used intravenous thrombolysis to demonstrate improved outcomes in STEMI patients; several other trials used intracoronary thrombolysis to confirm the feasibility of thrombolytic reperfusion[26,27]. PPCI, which is currently the first-line strategy for treating STEMI, has since gained wide acceptance in developing countries[28,29].

Although reperfusion is mandatory to salvage ischemic myocardium from incipient infarction and reperfusion strategies have improved STEMI patient outcomes, reperfusion *per se* inflicts additional injury on the heart, which manifests as increased infarct size and microvascular dysfunction. As a result of the reperfusion injury debate, the postconditioning phenomenon was reported to attenuate such injuries[30,31]. Staccato reperfusion as in ischemic postconditioning was shown to reduce infarct size in rabbit hearts.

2. Mechanism of reperfusion injury

Cardiomyocyte compartment

The mechanisms which contribute to myocardial reperfusion injury to the cardiomyocyte and coronary vascular compartment are shown in Fig. 1. Morphologically, the infarcted myocardium is characterized by myofibrillar contraction bands, swollen and/or ruptured mitochondria, sarcolemmal rupture, microvascular destruction, hemorrhage, and infiltrating leukocytes. Reperfusion likely leads to necrosis, which is reflected by the aforementioned histologic findings[17-19]. The contributors to necrotic cell death[16] include cellular calcium overload through reverse mode Na^+/Ca^{2+} exchange after sodium overload through the Na^+/H^+ exchanger[32,33], oscillatory release and re-uptake of Ca^{2+} into the sarcoplasmic reticulum with resulting uncoordinated and excessive myofibrillar contractions[34], digestion of the cytoskeleton and sarcolemma by calpains[35], and excess formation of reactive oxygen species (ROS)[36].

Necrosis may be an unregulated mode of cell death, and more regulated modes of cell death also occur in infarcted myocardium; however, the quantitative contribution to final infarct size has not been established[37,38]. Apoptosis is an energy-dependent mode of cell death with typical DNA fragmentation, but lacks an inflammatory response and is initiated extrinsically through sarcolemmal receptors and intrinsically by release of cytochrome C from damaged mitochondria[39,40]. Necrotic and apoptotic cardiomyocyte death is mainly attributed to opening of the mitochondrial permeability transition pore (MPTP)[41-44]. Autophagy is the process of lysosomal protein degradation, particularly of mito-

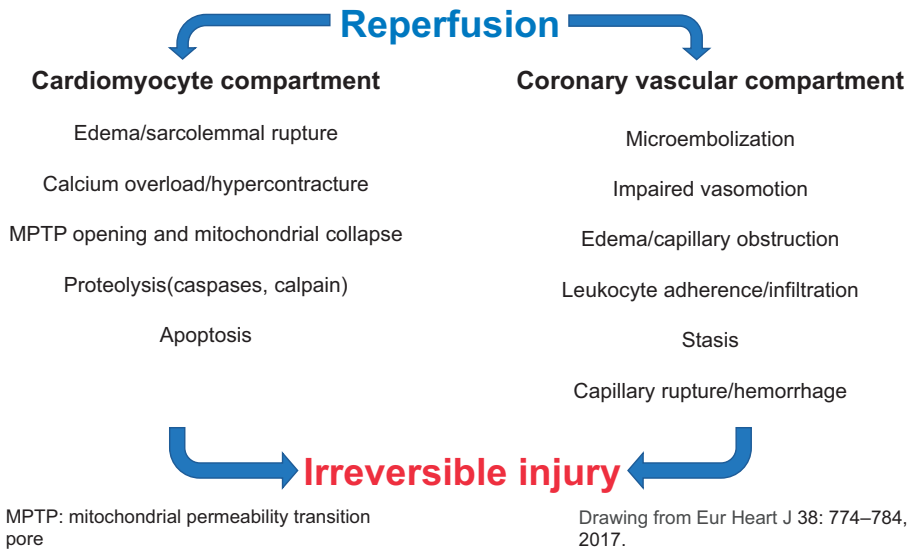


Figure 1 Mechanisms in the cardiomyocyte and coronary vascular compartment which interact and contribute to irreversible reperfusion injury.

chondrial proteins (mitophagy), and serves for recycling of proteins, but the role in human myocardial ischemia/reperfusion and cardioprotection has not been elucidated[45,46]. The quantitative contribution of different modes of cell death to infarction or cardioprotection is not clear; however, mitochondria plays an essential role in all of the modes of cell death. Indeed, the regulated modes of cell death may be specific targets for pharmacologic cardioprotection.

Coronary vascular compartment

Reperfusion injury in the coronary circulation leads to microvascular dysfunction via increased capillary permeability and edema[47,48], coronary microembolization of atherosclerotic particular debris, platelets, leukocytes, and erythrocyte aggregates[49-52], impaired vasomotion due to endothelial and vascular smooth muscle damage[53-55], and capillary destruction and hemorrhage[56,57].

Impaired myocardial blood flow, despite restoration of epicardial coronary patency, was first reported by Krug et al.[58] and Kloner et al.[59] as the no-reflow phenomenon, which is the most severe form of coronary microvascular reperfusion injury. No-reflow is observed in <35% of patients after STEMI[60].

It is possible that the delay to reperfusion increases the incidence of the no-reflow phenomenon[61] and no-reflow and/or intramyocardial hemorrhage are powerful predictors of a poor prognosis[62-64].

Reactive oxygen species (ROS) formation may be an important factor underlying the pathophysiologic mechanism in myocardial and coronary microvascular reperfusion injury[65]. Better coronary microvascular function, as reflected by better angiographic coronary artery flow, is associated with better left ventricular function and less remodeling after PPCI[66].

Strategy to Reduce Reperfusion Injury after PPCI

1. Preconditioning

A number of studies have demonstrated that pre-infarction angina is associated with reduced infarct size[67-70], reduced coronary microvascular injury[71,72], and better clinical outcomes[67,69,73]. A remote preconditioning maneuver (intermittent arm ischemia vis-a-vis 4 cycles of 5-min inflation and 5-min deflation of a blood pressure cuff) can simulate pre-infarction angina. Bøtker et al.[74] demonstrated that implementing the remote preconditioning maneuver in the ambulance before PPCI is an effective strategy to reduce reperfusion injury in patients with STEMI. More than 300 consecutive adult patients with a suspected first acute myocardial infarction were randomly assigned in a 1:1 ratio to receive PPCI with or without remote preconditioning. The remote preconditioning patient group received remote preconditioning during transport to the hospital and PPCI in the hospital. The infarct area in the patients

who received remote preconditioning was significantly reduced compared to the group of patients who did not receive remote preconditioning[74].

2. Pharmacologic strategies

Glucose-insulin-potassium administered in the ambulance has been shown to reduce infarct size in a small subgroup of patients in the IMMEDIATE trial[75]. Moreover, the in-hospital mortality/cardiac arrest rate was reduced[75]. Another glucose-lowering agent (glucagon-like peptide-1 [GLP-1] receptor agonist) has also been shown in a rat model[76] and small clinical trials to significantly reduce myocardial infarct size and increase the myocardial salvage index[77]. The mechanisms underlying the glucose-insulin-potassium and GLP-1 receptor agonist effects are unclear and the efficacy in an actual clinical setting has not been established because a multicenter randomized trial has not been conducted.

Two recent clinical studies using nitric oxide have failed to demonstrate a significant reduction in myocardial infarction size with intravenous or intracoronary routes in STEMI patients treated with PPCI[78,79]; however, major adverse cardiovascular events (MACE) at 1 year and the infarct size in patients with STEMI was reduced.

Intravenous metoprolol administered before reperfusion reduces infarct size and microcirculation in rabbits[80], and humans[81,82]. The mechanism underlying this effect is thought to depend on a reduction in ischemic injury by reducing energy demands[81]; however, it has been reported that metoprolol acts via β1 adrenergic receptors on neutrophils to decrease neutrophil-platelet co-aggregate formation during reperfusion[81], which could protect the microcirculation. The dual-target benefits of metoprolol appear to be specific to this drug and not a class effect.

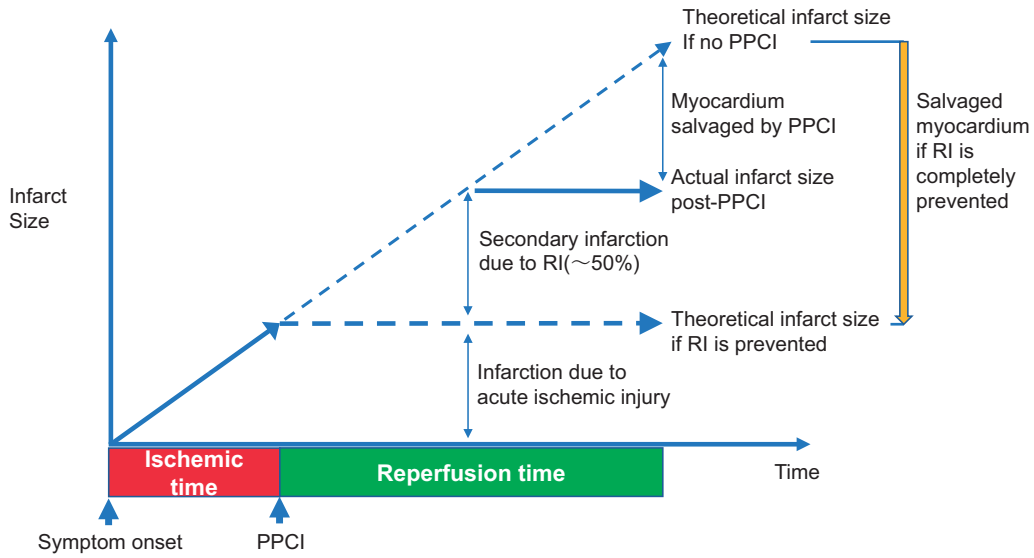
Adenosine infusion during reperfusion therapy improved patient survival and reduced the composite clinical endpoint of congestive heart failure or death at 6 months in a clinical trial involving STEMI patients[83]. Another randomized controlled clinical trial showed that the infarct area was reduced after a 70 μg/kg/min adenosine infusion[84].

Cyclosporin A, an inhibitor of MPTP, has been reported to have cardioprotective effects in several small clinical trials by reducing the creatinine kinase (CK) area under the curve (AUC) by 40% and infarct size between 20% and 28%[85,86]. The Cyclosporine and Prognosis in AMI Patients trial (CIRCUS), the largest multicenter, double-blind, randomized trial involving 970 patients with anterior STEMI to date did not result in better clinical outcomes than patients treated with placebo and did not prevent adverse left ventricular remodeling at 1 year[87].

MTP-131 is a peptide that may protect mitochondria by inhibiting cardiolipin and reducing production of ROS. In an experiment using rats, this drug reduced infarct size[88,89]. In the phase II EMBRACE STEMI trial, no significant reduction in infarct size occurred in 117 patients, even though the highly-selected population of patients had an anterior STEMI, TIMI 0, and similar reperfusion time[90].

Sodium thiosulfate (STS) is a metabolite of hydrogen sulfide (H_2S) and an endogenous gas transmitter that has been shown to mediate numerous physiologic activities in organs, such as the heart, brain, and kidneys, by its anti-oxidant effects in murine models, thus preserving mitochondrial activity and chelating calcium[91-93]. *In vitro* and murine studies have shown that STS protects against neuronal ischemia and IRI in isolated rat heart, thus significantly reducing infarct size[94,95]. These protective effects were shown to be associated with inhibition/reduced expression of caspase-3, a vital protein involved in cell apoptosis. Furthermore, in 2018 Ravindran et al.[96] showed that isolated rat hearts post-conditioned with STS had significantly reduced infarct size associated with RI by modulating cardiac mitochondria responsible for both contractile and metabolic function. Intravenous STS is currently being evaluated in a phase 2 trial (Sodium Thiosulfate to Preserve Cardiac Function in STEMI [GIPS-IV]).

Atrial natriuretic peptide and nicorandil are expected for the effect of nitric oxide (NO)-independent vasodilation and myocardial protection in patients with STEMI. Several studies have demonstrated that these agents improve the outcomes of STEMI patients undergoing PPCI[97-105]; however, a class II-B recommendation is given to these agents by the Japanese Circulation Society due to a lack of large randomized trials.



PPCI; primary percutaneous coronary intervention, RI; reperfusion injury

Figure 2 The individual components that make up final myocardial infarct size.

Table 1 Strategy to prevent reperfusion injury

Preconditioning	Remote preconditioning maneuver
Pharmacologic strategies	Glucose-insulin-potassium Nitric oxide Metoprolol Adenosine Cyclosporin A MTP-131 Sodium thiosulphate Atrial natriuretic peptide Nicorandil
Mechanical/maneuver strategies	Intra-aortic balloon counterpulsation Impella device Hypothermia Gradual reperfusion Lactate-enriched blood (PCLeB) injection

3. Mechanical/maneuver strategies

Intra-aortic balloon counter pulsation does not reduce infarct size in patients with an anterior STEMI[106]. In two small studies involving hypothermia using an endovascular cooling strategy, infarct size was reduced in the patients with acute myocardial infarction undergoing PPCI[107,108]. In the larger CHILL-MI trial involving 120 STEMI patients, the infarct size based on MRI, and creatine kinase-muscle brain and troponin levels were not reduced[109].

Use of an Impella device facilitates left ventricular unloading. Recent studies have demonstrated that left ventricular unloading by an Impella device reduces infarct size in porcine STEMI models[110-112]; a similar study involving humans has not been conducted.

Lactate-enriched blood (PCLeB) injection into coronary arteries during gradual reperfusion (staccato reperfusion) at the time of PPCI augments the postconditioning effect and leads to better outcomes in STEMI patients[113]. This method is simple, economical, and less invasive compared to a mechanical device without additional drugs. Further accumulation of clinical experiences is warranted to elucidate the true value of this approach.

Future Recommendation

Prompt reperfusion in patients presenting with STEMI and undergoing PPCI remains the gold standard treatment and improves outcomes; however, both experimental animal models and studies in patients with STEMI suggest that up to 50% of the final infarct size is a result of lethal reperfusion injury[10], thus making reperfusion injury an attractive therapeutic target (Fig. 2). For this purpose, the complex and multifactorial pathophysiology underlying reperfusion injury should be further elucidated. A comprehensive approach is warranted to elucidate the multiple pathways involved in reperfusion injury.

Many strategies have been tried in the past to prevent reperfusion injury (Table 1), including preconditioning, drugs, procedures, and mechanical support in each ischemic phase. There is currently no strategy recommended as class I according to any guidelines. Remote ischemic conditioning is a simple, effective, safe, and inexpensive intervention, and infarct size reduction has been evidenced by all trials in STEMI patients, whether undergoing primary PCI or thrombolysis for reperfusion. Therefore, establishment of a combination strategy, including effective methods in all ischemic phases, is needed in the future.

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