Novel therapeutic concepts

Myocardial reperfusion injury: looking beyond primary PCI

Georg M. Fröhlich¹, Pascal Meier¹, Steven K. White¹,², Derek M. Yellon², and Derek J. Hausenloy¹,²*

¹The Heart Hospital, University College London Hospitals, 16-18 Westmoreland Street, W1G 8PH, London, UK; and ²The Hatter Cardiovascular Institute, 67 Chenes Mews, WC1E 6HX, London, UK

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Coronary heart disease (CHD) is the leading cause of death and disability in Europe. For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), timely myocardial reperfusion using either thrombolytic therapy or primary percutaneous coronary intervention (PPCI) is the most effective therapy for limiting myocardial infarct (MI) size, preserving left-ventricular systolic function and reducing the onset of heart failure. Despite this, the morbidity and mortality of STEMI patients remain significant, and novel therapeutic interventions are required to improve clinical outcomes in this patient group. Paradoxically, the process of myocardial reperfusion can itself induce cardiomyocyte death—a phenomenon which has been termed 'myocardial reperfusion injury' (RI), the irreversible consequences of which include microvascular obstruction and myocardial infarction. Unfortunately, there is currently no effective therapy for preventing myocardial RI in STEMI patients making it an important residual target for cardioprotection. Previous attempts to translate cardioprotective therapies (antioxidants, calcium-channel blockers, and anti-inflammatory agents) for reducing RI into the clinic, have been unsuccessful. An improved understanding of the pathophysiological mechanisms underlying RI has resulted in the identification of several promising mechanical (ischaemic post-conditioning, remote ischaemic pre-conditioning, therapeutic hypothermia, and hyperoxaemia), and pharmacological (atrial natriuretic peptide, cyclosporin-A, and exenatide) therapeutic strategies, for preventing myocardial RI, many of which have shown promise in initial proof-of-principle clinical studies. In this article, we review the pathophysiology underlying myocardial RI and highlight the potential therapeutic interventions which may be used in the future to prevent RI and improve clinical outcomes in patients with CHD.

Keywords
- Myocardial reperfusion injury
- ST-elevation myocardial infarction
- Primary percutaneous coronary intervention
- Cardioprotection

Introduction

Coronary heart disease (CHD) is the leading cause of death in Europe, accounting for 1.8 million deaths each year and costing the European Union economy €60 billion per year. Seminal experimental studies performed by Ginks et al.¹ in 1972 first established that myocardial reperfusion could reduce myocardial infarct (MI) size following an acute coronary artery occlusion. Nowadays, timely myocardial reperfusion using either thrombolytic therapy or primary percutaneous coronary intervention (PPCI) forms the cornerstone of therapy for acute ST-segment elevation myocardial infarction (STEMI) patients. However, mortality remains substantial in these patients with in-hospital mortality ranging between 6 and 14%.² As such, novel therapeutic interventions are required to reduce MI size, preserve left-ventricular (LV) systolic function, and improve survival in reperfused-STEMI patients.

Paradoxically, although myocardial reperfusion is essential for myocardial salvage, it comes at a price, as it can in itself induce myocardial injury and cardiomyocyte death—a phenomenon termed ‘myocardial reperfusion injury’ (RI) (Figure 1). There is currently no effective therapy for preventing myocardial reperfusion injury (RI) in reperfused-STEMI patients, making it an important residual target for cardioprotection. In this review article, we provide an overview of myocardial RI, and highlight potential therapeutic interventions for preventing it in reperfused-STEMI patients. We will not review those mechanical and pharmacological interventions which are used to optimize myocardial reperfusion during PPCI such as thrombus aspiration, distal protection...
devices, anti-platelet, and anti-coagulant therapy—these are dealt with in the recent ESC STEMI management guidelines.5

Types of myocardial reperfusion injury

Reperfusion arrhythmias
Experimental animal studies from the 1980s by Hearse’s group were among the first to describe ventricular arrhythmias specifically induced by reperfusion.6 In reperfused-STEMI patients, the most commonly encountered reperfusion arrhythmias are idioventricular rhythm, ventricular tachycardia, and fibrillation,7 all of which are easily dealt with.

Myocardial stunning
The reversible post-ischaemic contractile dysfunction which occurs on reperfusing acute ischaemic myocardium is referred to as ‘myocardial stunning’. This form of RI results from the detrimental effects of oxidative stress and intracellular calcium overload on the myocardial contractile apparatus.8

Microvascular obstruction and intramyocardial haemorrhage
Microvascular obstruction (MVO) is an irreversible form of myocardial RI which results in the death of both endothelial cells and cardiomyocytes. Microvascular obstruction was first described in a feline heart as the ‘inability to reperfuse a previously ischemic region’ by Krug et al.9 in 1966. The underlying aetiology of MVO is unclear but a number of factors have been implicated including10–12: (i) the embolization of particulate debris which can be captured by protection devices; (ii) the release of vasoconstrictor, thrombogenic, and inflammatory substances which can also be captured by protection devices or the effects of which can be attenuated by vasodilators; and (iii) structural collapse of the capillary bed. It may manifest at the time of PPCI as persistent ST-elevation, coronary ‘no-reflow’ (TIMI flow ≤2), and reduced myocardial blush grade. Even when post-PPCI coronary flow appears normal (TIMI flow 3), 30–40% of these patients actually have evidence of MVO when imaged by myocardial contrast echocardiography,13 myocardial perfusion nuclear scanning,14 or cardiac MRI (Figure 2).15 The presence of MVO in reperfused-STEMI patients is associated with a larger MI size, worse LV ejection fraction, adverse LV remodelling, and worse short-term and long-term clinical outcomes.13,15 In areas of severe MVO, extravasation of blood may occur causing intramyocardial haemorrhage within the myocardial infarct, a feature which can be detected by cardiac MRI (Figure 2) and portends to a worse prognosis.16 Importantly, there is currently no effective therapy for preventing MVO and improving clinical outcomes in reperfused-STEMI patients and so it remains a neglected therapeutic target for cardioprotection.

Lethal myocardial reperfusion injury
In the 1960s, Jennings et al.17 first described the histological features of myocardial reperfusion in the canine heart including explosive cardiomyocyte swelling, contraction bands, and intramitochondrial calcium phosphate granules. In the 1990s, controversy surrounded the existence of myocardial RI as an independent mediator of cardiomyocyte death.18 It has been difficult to demonstrate reperfusion-induced death of cardiomyocytes which were
viable or reversibly injured at the end of ischaemia. As such, the evidence for the existence of myocardial RI as a distinct entity has been indirect and relied upon the demonstration that a therapeutic intervention applied at the onset of myocardial reperfusion can reduce MI size.4 These experimental studies have reported reductions of 40–50% in final MI size, suggesting that myocardial RI may account for nearly half of the final infarct, making it an important target for cardioprotection (Figure 1).

Mediators of myocardial reperfusion injury

Mitochondrial permeability transition pore opening as a critical mediator of myocardial reperfusion injury

Pioneering work by Crompton and Costi19 and Griffiths and Halestrap20 in the 1990s first implicated the mitochondrial permeability transition pore (MPTP) as a critical mediator of lethal myocardial RI. The opening of the MPTP, a non-selective channel of the inner mitochondrial membrane, in the first few minutes of reperfusion in response to mitochondrial Ca\textsuperscript{2+} overload, oxidative stress, restoration of a physiological pH, and ATP depletion, induces cardiomyocyte death by uncoupling oxidative phosphorylation21,22 (Figure 3). Mitochondrial permeability transition pore opening at the time of reperfusion can be inhibited using either pharmacological (e.g., cyclosporin-A)23–25 or genetic inhibition26 of cyclophilin-D (a regulatory component of the MPTP), resulting in a 40–50% reduction in MI size. The role of the MPTP as a target for clinical cardioprotection has been investigated in reperfused-STEMI patients using CsA (discussed later). However, the discovery of the molecular identity of the MPTP, which is currently unknown, should allow more specific and potent MPTP inhibitors to be developed as novel therapeutic agents for preventing myocardial RI.

Calcium and myocardial reperfusion injury

In 1972, Shen and Jennings27 were the first to demonstrate that myocardial reperfusion resulted in cardiomyocyte calcium...
Intracellular calcium entry at the time of myocardial reperfusion is mediated by damage to the sarcolemmal membrane and oxidative stress-induced dysfunction of the sarcoplasmic reticulum, resulting in cardiomyocyte hypercontracture, mitochondrial calcium overload, and MPTP opening (Figure 3). Experimental animal studies have demonstrated that pharmacologically inhibiting intracellular and mitochondrial calcium overload at the onset of myocardial reperfusion can reduce MI size by 40–50%. However, clinical studies investigating this therapeutic approach have been negative. It may well be that specific inhibitors of the recently identified mitochondrial calcium uniporter may be more effective.

Oxidative stress, NO, and myocardial reperfusion injury

Experimental animal studies have established that reperfusing ischaemic myocardium generates oxidative stress which contributes to myocardial RI by inducing MPTP opening (Figure 3). Unfortunately, both animal and clinical studies examining the cardioprotective potential of antioxidant reperfusion therapy have been inconclusive. Oxidative stress also reduces the bioavailability of nitric oxide (NO) at reperfusion, and the administration of NO donors is cardioprotective. However, the NO donor, Nicorandil, did not limit MI size when administered to reperfused-STEMI patients. Other NO donors currently being investigated in this clinical setting are sodium nitrite therapy (NIAMI trial: NCT01388504 and NITRITE-AMI trial: NCT01584453) and inhaled NO (NOMI trial: NCT01398384).

Inflammation and myocardial reperfusion injury

The inflammatory response to myocardial RI is required for healing and scar formation in the MI. However, the release of chemoattractants (cytokines, complement, ROS) from injured endothelial cells and cardiomyocytes draw neutrophils into the infarct zone over the first 6 h of myocardial reperfusion. Over the next 24 h, they migrate into the myocardial tissue, a process which is facilitated by cell-adhesion molecules, where they cause vascular plugging and release degradative and proteolytic enzymes and reactive oxygen species (Figure 3). Whether this acute inflammatory response results in cardiomyocyte death or it is simply a response to the infarct is unclear. Experimental animal studies have reported reductions in MI size by up to 50% with several interventions administered at the time of myocardial reperfusion including leucocyte-depleted blood, antibodies against the cell-adhesion molecules, P-selectin, CD11/CD18, and ICAM-1. However, clinical studies targeting the inflammatory components of myocardial RI with anti-inflammatory agents, adenosine, or atorvastatin have failed to demonstrate any impact on clinical outcomes in reperfused-STEMI patients. It is important to appreciate that both adenosine and atorvastatin have been reported to cardioprotect via a number of different mechanisms unrelated to inflammation.

Intracellular pH changes and myocardial reperfusion injury

Myocardial reperfusion results in a rapid restoration of physiological pH from the acidic conditions induced by acute myocardial
ischaemia, resulting in cardiomyocyte death by releasing the inhibitory effect of the acidosis on MPTP opening and cardiomyocyte hypercontracture.\textsuperscript{49} (Figure 3). Reperfusing ischaemic hearts with acidic buffers and ischaemic post-conditioning can prevent lethal myocardial RI by inhibiting MPTP opening and cardiomyocyte hypercontracture.\textsuperscript{50–52}

**Cardiomyocyte hypercontracture**

Cardiomyocyte hypercontracture at the time of myocardial reperfusion is induced by the recovery of energy production in the presence of a high cytosolic calcium concentration.\textsuperscript{53} (Figure 3). Cytosolic calcium oscillations between the sarcoplasmic reticulum and mitochondria can induce both cardiomyocyte hypercontracture and MPTP opening.\textsuperscript{54} Contractile inhibition at the time of myocardial reperfusion can reduce MI size.\textsuperscript{55}

**Wavefront of myocardial reperfusion injury**

The current paradigm suggests that cardiomyocyte death induced by myocardial RI occurs in the first few minutes of reflow (early myocardial RI). However, a small number of therapeutic interventions have been reported to reduce acute MI size even when administered 30 min to 24 h into myocardial reperfusion, suggesting that there may be an extended window of cardioprotection. These therapeutic interventions, which include erythropoietin,\textsuperscript{56} PI3K-γ/δ inhibitors,\textsuperscript{57} and ischaemic post-conditioning,\textsuperscript{58} may target the inflammatory and apoptotic components of myocardial RI which generally manifest late into reperfusion (late myocardial RI).

Consistent with a possible ‘wavefront of reperfusion injury’, MI size has been reported to increase with reperfusion time,\textsuperscript{59} although not all studies have observed this finding.\textsuperscript{60} Whether this therapeutic window exists in reperfused-STEMI patients is not known, but it may allow one to target early myocardial RI with one agent and late myocardial RI with another agent.

**Evidence that lethal myocardial reperfusion injury exists in man**

Whether lethal myocardial reperfusion injury actually exists in man has been intensely debated over the years.\textsuperscript{15} However, in 2005, Staat et al.\textsuperscript{61} provided the first clinical evidence that lethal myocardial reperfusion injury actually exists in man. They demonstrated a 36% reduction in MI size in reperfused-STEMI patients randomized to receive ischaemic post-conditioning (IPost, four-30 s inflations/deflations of the angioplasty balloon following stent deployment). The fact that a therapeutic intervention, applied at the onset of myocardial reperfusion, could reduce MI size has provided convincing evidence that myocardial RI exists in man and is a viable target for cardioprotection.\textsuperscript{4} Whether preventing myocardial RI in reperfused-STEMI patients can actually reduce major adverse cardiac events (MACE) remains to be demonstrated.

**Therapeutic interventions for preventing myocardial reperfusion injury**

**Improving the translation of cardioprotection into clinic therapy**

Over the years, a number of therapeutic interventions have been tried in the clinical setting to prevent myocardial RI in reperfused-STEMI patients although the results have been largely disappointing. The difficulties in translating cardioprotection from the experimental animal studies into the clinical setting has been discussed in relation to three main topics.\textsuperscript{52–65}

The experimental animal model: The animal MI models which are used to test potential cardioprotective strategies in the pre-clinical setting do not adequately represent the typical MI patient, in terms of patient age, co-morbidities, concomitant medication, and MI pathophysiology, factors which are known to attenuate the cardioprotective efficacy of many therapeutic interventions.\textsuperscript{66} An important example of this are those patients with pre-infarct angina\textsuperscript{67} and concomitant medication the patient may be on (such as nitrates, statins, and so on),\textsuperscript{67,68} all of which may interfere with the cardioprotective effect. Therefore, the use of more clinically relevant animal MI models may result in more effective cardioprotective interventions being tested in the clinical setting.

The cardioprotective intervention: Many of the cardioprotective interventions which have failed in the clinical setting have relied on targeting an individual component of myocardial RI. Combination therapy aimed at multiple components of myocardial RI may be more effective. Furthermore, many of the cardioprotective interventions which have failed in the clinical setting had not been rigorously or systematically tested in the experimental animal setting. The NHLI-funded multicentre Consortium for preclinical asSEment of cArdioprotective therapies (CAESAR) has been set up to perform systematic preclinical testing of novel cardioprotective therapies using standardized protocols performed by blinded investigators.\textsuperscript{69} Hopefully, this will result in only the most robust cardioprotective interventions being tested in the clinical setting.

The design of the clinical trial: The STEMI patients which are most likely to benefit from a therapeutic intervention targeting myocardial RI are those with a complete occlusion (TIMI flow <1) in a large coronary artery (where the size of the AAR is >30%) and in whom there is little coronary collateralization to the area at risk (AAR). By including patients without these characteristics, there is a risk of diluting any cardioprotective effect. Furthermore, pre-existing coronary artery lesions in the infarct-related artery may affect cardioprotection as gentle reperfusion through a residual stenosis is protective, although coronary microembolization would be expected to add to the damage.\textsuperscript{70–72}

Because lethal myocardial RI occurs in the first few minutes of reflow, it is essential that the therapeutic intervention is applied prior to or at the onset of myocardial reperfusion and failure to do this may in part explain the negative findings of some clinical cardioprotection studies. Finally, it is crucial to select clinical endpoints which are relevant to cardioprotection such as MI size, the extent of myocardial salvage, LV size and function,
cardiac death, and hospitalization for heart failure, as opposed to coronary revascularization, re-infarction, and stroke.

Assessing the cardioprotective efficacy of novel therapies
Assessing the cardioprotective efficacy of novel therapeutic interventions for preventing myocardial RI requires an estimation of the size of AAR. This allows myocardial salvage (MI size subtract AAR size) to be calculated, which can then be normalized to the AAR, which varies greatly in man depending on the site of the coronary artery occlusion (Figure 4). T2-weighted cardiac MRI imaging can retrospectively delineate the AAR by detecting the extent of myocardial oedema in reperfused-STEMI patients, thereby allowing the estimation of myocardial salvage73,74 (Figure 4). However, its widespread use has been hampered by difficulties with T2 imaging sequences and concerns that the cardioprotective intervention may actually reduce the extent of myocardial oedema thereby leading to an underestimation of the AAR.75

Mechanical therapeutic interventions for preventing myocardial reperfusion injury
Ischaemic post-conditioning: modifying myocardial reperfusion
Ischaemic post-conditioning was first described in 2003 by Zhao et al.,76 who demonstrated in canine hearts that interrupting myocardial reperfusion with three-30 s cycles of LAD re-occlusion and reflow prevented myocardial RI and reduced MI size by 44%. This therapeutic approach was rapidly translated into the clinical setting of PPCI by Staat et al.61 in 2005 (Table 1). It is important to note that modifying the process of myocardial reperfusion had already been demonstrated to reduce myocardial RI in experimental studies.77,78 A number of clinical studies have confirmed the efficacy of IPost in reperfused-STEMI patients, although not all studies have been positive79 (Table 1). The DANAMI-3 trial (NCT01435408) is currently investigating whether IPost can reduce cardiac death, re-infarction, and heart failure at 3 years.

Therapeutic hypothermia and hyperoxaemia
Two other mechanical therapeutic interventions which have been reported in experimental animal studies to protect against myocardial RI are therapeutic hyperoxaemia80 and therapeutic hypothermia.81 Hyperbaric oxygen reduces MI size by decreasing tissue oedema, reducing formation of lipid peroxide radicals, altering nitric oxide synthase expression, as well as inhibition of leucocyte adherence and plugging in the microcirculation. Lowering myocardial temperature during ischaemia to 32–33°C can limit MI size in experimental studies by reducing metabolic demand, reducing the inflammatory response, decreasing platelet aggregation, and increasing myocardial efficiency. The results of proof-of-principal clinical studies in reperfused-STEMI patients using these invasive therapeutic interventions have shown some promise (Table 1). The ongoing CHILL-MI study (NCT01379261) is investigating whether this therapeutic approach can reduce acute MI size (expressed as a percentage of the AAR) on cardiac MRI performed at 4 days.

Remote ischaemic conditioning: give your right arm to protect your heart
The phenomenon of remote ischaemic conditioning (RIC) allows the therapeutic intervention to be applied to an organ or tissue away from the heart, thereby facilitating its clinical application.82 Remote ischaemic conditioning refers to the cardioprotective effect induced by non-invasively applying three-5 min cycles of brief non-lethal ischaemia and reperfusion using a blood pressure cuff applied to the upper arm.82 By applying this RIC protocol to STEMI patients in the ambulance en route to the PPCI centre, Botker et al.83 were able to demonstrate increased myocardial salvage (Table 1). The actual mechanisms underlying RIC cardioprotection remain unclear but have been attributed to a neuro-hormonal pathway conveying the cardioprotective signal from

Figure 4 This representative figure illustrates the use of cardiac MRI to assess myocardial salvage in a reperfused-STEMI patient. The area of late-gadolinium enhancement (dashed black outline on left panel) depicts the size of the myocardial infarct (MI) and the area at risk (AAR) is delineated by the T2-weighted imaging (dashed black outline on right panel). Myocardial salvage equals the AAR subtract MI size.
the limb to the heart. A large multicentre study is now planned in Europe to investigate whether RIC can actually reduce MACE in reperfused-STEMI patients.

**Pharmacological therapies for preventing myocardial reperfusion injury**

**Atrial natriuretic peptide**

Experimental studies have demonstrated that administering atrial natriuretic peptide (ANP) at reperfusion reduced MI size through the activation of pro-survival signalling pathways. In 2007, Kitakaze et al. demonstrated that an infusion of carperitide (an ANP analogue) reduced MI size and preserved LV ejection fraction in reperfused-STEMI patients (Table 2).

**Cyclosporin-A as an mitochondrial permeability transition pore inhibitor**

In 2008, Piot et al. were the first to translate MPTP inhibition at reperfusion using cyclosporin-A as a therapeutic intervention into the clinical setting (Table 2). The ongoing CIRCUS study (NCT01502774) is investigating whether this therapeutic approach can reduce death, hospitalization for heart failure, and a 15% increase in LV end-diastolic volume. Two newly described indirect MPTP inhibitors, TRO40303 (Mitocare study) and Bendavia (EMBRACE study: NCT01572909) are currently being investigated in this clinical setting.

**Exenatide as a novel anti-diabetic cardioprotective agent**

Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, is a new anti-diabetic drug, which has been shown in animal studies to reduce MI

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<tr>
<th>Table 1 Mechanical therapeutic interventions for preventing myocardial reperfusion injury which have been reported to have beneficial effects in reperfused-STEMI patients</th>
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<tr>
<td>Clinical study</td>
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<tr>
<td>Ischaemic post-conditioning</td>
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<td>Rentoukas et al.</td>
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AAR, area at risk; AUC, area under curve; CMR, cardiac MRI; LVESV, LV end-systolic volume.
size when administered at the time of reperfusion.88 Lonborg et al.89,90 have successfully translated this therapeutic approach into the clinical setting (Table 2).

**Metabolic modulation using glucose–insulin–potassium therapy**

Experimental animal studies have shown that promoting glucose metabolism using insulin during acute myocardial ischaemia is beneficial for the heart.91 A large number of clinical trials have investigated the effect of this therapeutic approach using glucose–insulin–potassium (GIK) therapy with mixed results. Although the large CREATE-ECLA trial92 was negative, it appears that GIK therapy may be more effective if administered in the ambulance en route to the PPCI centre (when the myocardium was still acutely ischaemic) as in the IMMEDIATE trial93 (Table 2).

**Other potential therapies for preventing myocardial reperfusion injury**

Several novel pharmacological agents for preventing myocardial RI in reperfused-STEMI patients are currently being tested in proof-of-principal clinical studies including intravenous metoprolol in the ambulance (METOCARD-CNIC trial),94 melatonin (MARIA trial; NCT00640094 and another trial; NCT01172171), RGN-352 (Thymosin Beta 4; NCT00378352), sevoflurane (a volatile anaesthetic agent; SIAMI trial; NCT00971607), and mecasermin (a recombinant human form of insulin-like growth factor-1) (RESUS-AMI trial; NCT01438086). Interestingly, preliminary experimental animal studies suggest that certain anti-platelet agents (such as clopidogrel and cangrelor but not aspirin) may actually prevent myocardial RI and reduce MI size when administered at the time of myocardial reperfusion,95,96 suggesting that anti-platelet therapy given to STEMI patients undergoing PPCI may be cardioprotective. A recent retrospective analysis has suggested that clopidogrel may reduce MI size in STEMI patients treated by PPCI.97

**Conclusions**

Although myocardial reperfusion is essential for myocardial salvage, it can itself induce myocardial injury (reperfusion arrhythmias and myocardial stunning) and cause cardiomyocyte death (MVO and myocardial necrosis), a phenomenon which is termed myocardial RI and which can contribute up to 50% of the final MI size. Crucially, there are currently no effective therapies for preventing myocardial RI in reperfused-STEMI patients, making it a neglected target for cardioprotection. An improved understanding of the pathophysiology of myocardial RI has resulted in the identification of novel therapeutic strategies (such as IPost, RIC, therapeutic hyperoxaemia and hypothermia, atrial natriuretic peptide, cyclosporin-A, and exenatide) for potentially preventing myocardial RI in reperfused-STEMI patients. Large multicentre randomized clinical trials are now required to determine whether preventing myocardial RI can actually reduce MACE in this patient group.

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**Table 2** Pharmacological agents for preventing myocardial reperfusion injury which have been reported to have beneficial effects in reperfused-STEMI patients

<table>
<thead>
<tr>
<th>Clinical study</th>
<th>Therapeutic intervention</th>
<th>n</th>
<th>Outcome</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Kitakaze et al.,38 J-WIND-ANP</td>
<td>Atrial natriuretic peptide</td>
<td>IV carperitide 72 h infusion started ‘after’ reperfusion</td>
<td>569</td>
<td>15% reduction in 72 h AUC total CK and 2.0% increase in LVEF</td>
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<tr>
<td>Piot et al.,86</td>
<td>Cyclosporin-A</td>
<td>IV cyclosporin A (2.5 mg/kg) 10 min ‘prior’ to PPCI</td>
<td>58</td>
<td>44% ↓ MI size (72 h AUC total CK) 20% ↓ MI size (CMR in subset of 27 patients) 28% ↓ MI size and smaller LVESV on CMR at 6 months97</td>
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<tr>
<td>Lonborg et al.,89</td>
<td>Exenatide</td>
<td>IV infusion of exenatide started 15 min ‘prior’ to PPCI and continued for 6 h</td>
<td>107</td>
<td>Increase in myocardial salvage index (from 0.62 to 0.71) at 90 days by CMR. Reduced MI size by 23% of AAR at 90 days by CMR Patients presenting with short ischaemic times (≤ 132 min) had greater myocardial salvage90</td>
</tr>
<tr>
<td>Mehta et al.,92 CREATE-ECLA</td>
<td>Glucose insulin potassium (GIK)</td>
<td>IV GIK infusion for 24 h started ‘after’ reperfusion in majority of cases</td>
<td>20,201</td>
<td>No difference in mortality at 30 days A significant proportion of patients had GIK therapy administered after the onset of myocardial reperfusion</td>
</tr>
<tr>
<td>Selker et al.,93 IMMEDIATE</td>
<td>IV GIK infusion for 12 h started by paramedics in ambulance ‘prior’ to reperfusion</td>
<td>357</td>
<td>Reduction in MI size and less in-hospital mortality and cardiac arrest</td>
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AAR, area at risk; AUC, area under curve; CMR, cardiac MRI; LVESV, LV end-systolic volume.
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