The winding road to cardioprotection

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Abstract

Over the past two decades, the mortality from acute myocardial infarction (AMI) has been reduced dramatically. Timely reperfusion is the most powerful intervention for limiting infarct size, alongside antiplatelet, antithrombotic and anti-ischemic therapies. Paradoxically, reperfusion itself can also exacerbate myocardial injury, so called ''reperfusion injury'', which can cause additional cardiomyocyte death or microvascular obstruction. This may partially explain why the rate of death after an AMI still approaches 10%, despite optimal reperfusion. ''Postconditioning'' describes the exciting phenomenon whereby a pharmacological agent or a repeated brief ischemic stimulus can provide cardioprotection, despite administration after the lethal ischemic event. Furthermore, cardioprotection has also been demonstrated when ischemic stimuli are applied in a distant organ, so called ''remote'' postconditioning. Basic laboratory and animal studies have demonstrated significant reductions in infarct size with both pharmacological and ischemic postconditioning. Despite further promising results from proof of concept clinical studies, subsequent larger randomised controlled trials (RCTs) have failed to confirm beneficial effects with pharmacological agents. However, ongoing clinical trials using novel pharmacological agents, alongside RCTs investigating ischemic postconditioning and additional trials investigating ''remote'' postconditioning, all hold promise.
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Introduction

After an acute myocardial infarction (AMI), reperfusion is paramount, and is the most powerful intervention for limiting infarct size. Minimizing infarct size is essential to preserve left ventricular systolic function, which is the critical determinant of clinical outcome. With the widespread use of reperfusion strategies alongside ancillary anti-ischemic, antithrombotic, and antiplatelet therapies, the overall 1-month mortality from AMI has been reduced from 18% in the mid-1980 s [1] to 6–7% [2] currently. However, despite such advances from these established therapies, the morbidity and mortality from AMI remains significant, with 5–6% of patients having a subsequent cardiovascular event by 30 days [3]. It is therefore necessary to develop novel cardioprotective strategies that can further reduce infarct size, preserve left ventricular function, and improve clinical outcome.

Over the past two decades, the focus on primary percutaneous coronary intervention (PCI) as the gold-standard reperfusion therapy in acute ST-segment elevation myocardial infarction (STEMI) provides a

unique opportunity for adjunctive pharmacological agents, given just before or simultaneously with reperfusion, to attenuate reperfusion injury. This concept defines the pathophysiological process via which myocardium that is viable at the onset of reperfusion subsequently dies – not as an indirect result of predetermined events that occurred during ischemia, but as a direct result of the reperfusion process itself. Such pharmacological manipulation also has great potential for improving clinical outcome in other forms of ischemia-reperfusion injury outside acute STEMI; for example, during coronary artery bypass graft surgery, or in PCI for unstable angina or non ST-segment elevation myocardial infarction (NSTEMI). It seems appropriate, therefore, to dedicate this Special Anniversary Issue of *Heart and Metabolism* to summarizing established therapies in the treatment of AMI, and to focus on novel treatments that specifically target reperfusion injury.

Established therapies

Reperfusion therapies

The landmark studies Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-1 [4] and International Study of Infarct Survival (ISIS)-2 [5] demonstrated a 23% reduction in 30-day mortality with fibrinolytic treatment compared with placebo after STEMI. Nine subsequent phase III trials confirmed a similar benefit, and reinforced the time-dependent loss of benefit. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-1 [6] trial subsequently demonstrated a further 15% mortality reduction with ''accelerated'' alteplase compared with streptokinase, albeit associated with a greater risk of intracranial hemorrhage. The role of primary PCI as compared with thrombolysis in STEMI was debated for a considerable period; however, 22 randomized trials (involving 7437 patients) undertaken between 1990 and 2003 demonstrated a 19% mortality benefit with PCI when compared with accelerated alteplase, alongside a reduced incidence of myocardial re-infarction, stroke, and intracranial hemorrhage [7].

Antiplatelet and antithrombotic therapies

The role of antiplatelet therapy in AMI is also very well established: four clinical trials encompassing 3096 patients with NSTEMI were the first to demonstrate a 53% reduction in relative risk with aspirin against the incidence of death or myocardial infarction, albeit with dosing varying between 324 and 1300 mg [8–11]. The Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial [12] highlighted a further 20% reduction in cardiovascular death, myocardial infarction, or stroke with the use of clopidogrel, a prodrug causing irreversible inhibition of the ADP receptor $P2Y_{12}$, in dual antiplatelet therapy. Prasugrel and ticagrelor are more novel ADP inhibitors, ticagrelor having the advantage of reversible inhibition without any need for metabolic activation [13]. With regard to efficacy, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial [14], involving 13 608 high-risk patients with acute coronary syndrome undergoing PCI, demonstrated a 19% reduction in relative risk of cardiovascular death with prasugrel compared with clopidogrel, but with an adverse significant increase in major and life-threatening bleeds. Wallentin et al [15] have recently published impressive data from the Platelet Inhibition and Patient Outcomes (PLATO) trial (involving 18 624 patients with AMI), demonstrating a 17% reduction in relative risk of composite vascular deaths achieved with ticagrelor as compared with clopidogrel, and without an increase in the rate of overall major bleeding.

Glycoprotein IIb/IIIa inhibitors are potent antiplatelet agents, blocking the final common pathway in platelet aggregation. A meta-analysis [16] of the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) [17], Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment (CAPTURE) [18], and Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS) [19] trials demonstrated a 41% reduction in relative risk in periprocedural complications with glycoprotein IIb/IIIa inhibitors in patients with NSTEMI undergoing early PCI. However, prolonged treatment after PCI actually showed a significant adverse effect on mortality [20].

With regard to antithrombotic therapy, six randomized trials involving 1353 patients with NSTEMI demonstrated a 34% reduction in relative risk in the composite endpoint of death and myocardial infarction with unfractionated heparin [10,11,21–24]. Subsequently, the low-molecular-weight heparin enoxaparin was show to afford a marginally significant advantage over unfractionated heparin in the same composite endpoint [25]. More recent research has been targeted towards the use of direct thrombin inhibitors, which may be administered orally, although they are not currently licensed for use in AMI.

Anti-ischemic therapies

Anti-ischemic treatments in AMI include β-blockers, nitrates, and calcium-channel antagonists. However

despite symptomatic benefit observed with all three agents, β-blockers have been the only treatment to demonstrate a reduction in mortality: the ISIS-1 trial, albeit before the use of fibrinolysis, revealed a 20% reduction in relative risk of overall mortality at 1 year [26]. The reflex tachycardia associated with some calcium-channel antagonists led to a non significant adverse effect in STEMI [27] and limited their use to third-line agents for symptomatic relief in NSTEMI. After an AMI, evidenced-based therapies include early treatment with angiotensin-converting enzyme (ACE) inhibitors (following the large GISSI-3 [28] and ISIS-4 [29] trials), alongside statins, antiplatelet, and anti-ischemic therapies.

Pathogenesis of reperfusion injury

In order to discuss targets for pharmacological manipulation of reperfusion injury, it is first necessary to understand the proposed mechanisms via which such injury occurs. The term ''reperfusion injury'' encompasses stunning, the no-reflow phenomenon, and reperfusion arrhythmias (which all occur in the absence of irreversible damage), and irreversible or lethal reperfusion injury. This distinction is very important, as the latter implies reperfusion as an independent mediator of cell death, as opposed to an exacerbator of cellular stress initiated during ischemia. Some controversy remains as to whether reperfusion injury provokes such independent pathology, although consistent basic laboratory data demonstrating reduction in infarct size with pharmacological agents added to the reperfusate have provided striking evidence, which has been taken very seriously.

During ischemia of cardiomyocytes, mitochondrial production of ATP is compromised as a result of inadequate supply of substrates and oxygen. This results in derangement of the mitochondrial electron transport chain, causing further incapacitation of aerobic glycolysis and adverse generation of reactive oxygen species (ROS). Reduced ATP results in the failure of the sarcolemmal Na^+/K^+-ATPase and the sarcoplasmic reticulum Ca^{2+}-ATPase pumps. Anaerobic glycolysis compensates in an attempt to meet energy demands, and results in increased accumulation of H^+ ions, leading in turn to intracellular acidosis. Overactivity of the Na^+–H^+ exchanger occurs to attempt to correct this acidosis. However this, in combination with ATPase pump failure, results in intracellular Na^+ overload, which can reverse the Na^+–Ca^{2+} exchanger, leading to intracellular Ca^{2+} overload. The degree of Ca^{2+} overload is also influenced by the extent of generation of ROS, and both are dependent upon the duration of ischemia (*Figure 1*).

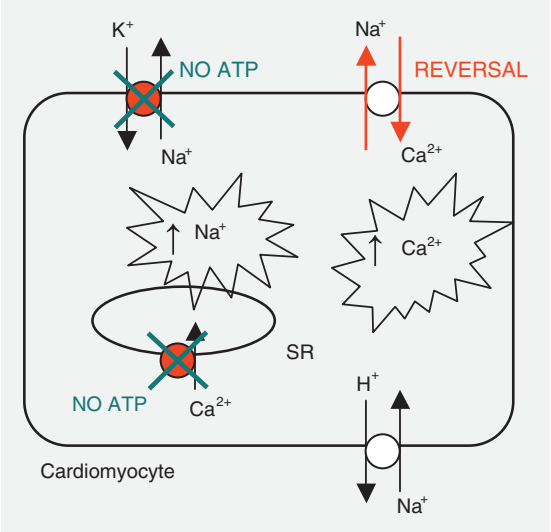

Figure 1. Pathophysiology of ischemia in the cardiomyocyte. NO, nitric oxide; SR, sarcoplasmic reticulum.

Upon reperfusion, the cardiomyocytes are subject to several abrupt biochemical changes, which include a substantial increase in the production of ROS, further exacerbation of intracellular Ca^{2+} overload, rapid restoration of intracellular pH, mitochondrial re-energization of the electron transport chain, and inflammation [30]. These processes integrate to create an intracellular environment that causes synergistic detrimental effects, and subsequently all processes converge to mediate the opening of the mitochondrial permeability transition pore (mPTP); this initiates cell death by inducing mitochondrial swelling, the uncoupling of oxidative phosphorylation, and the release of death effector proteins, including cytochrome C [31]. Intracellular Ca^{2+} overload also directly mediates both cell death via activation of proteases and hypercontracture with cytoskeletal fragility, leading to membrane rupture [30]. In addition, reperfusion subsequently causes the migration of neutrophils to infarcted tissue, which may mediate further cardiomyocyte death through vascular plugging, enzymatic degradation, and oxidative stress.

In view of the above mechanisms, the principal targets for manipulating reperfusion injury include: reduction of ROS, inhibition of the Na^+–H^+ exchanger, inhibition of opening of the mPTP, and attenuation of the delayed inflammatory response [30]. In addition to the above, basic laboratory studies have demonstrated that there are prosurvival antiapoptotic protein kinases (Akt, Erk 1/2) that are specifically activated at the time of reperfusion and may confer significant cardioprotection [32], as well as apposing kinases that aggravate injury (p38, JNK). Pharmacological agents that have shown great promise in animal studies include erythropoetin [33], adenosine [34], insulin [35], and statins [36] that, when administered specifically at the time of myocardial

reperfusion, activate survival kinases converging on the mPTP to inhibit its opening [31]. Further studies have also demonstrated the critical time window for blockade of the mPTP, as mPTP inhibitors given a few minutes after the onset of reperfusion have failed to provide any protection against reperfusion injury [37]. The key clinical studies specifically targeting the mechanisms outlined above are explained in the later section, ''Pharmacological manipulation of reperfusion injury''.

Can ischemia be protective?

The term ''ischemic preconditioning'' describes the phenomenon whereby brief periods of sublethal ischemia and reperfusion protect against a subsequent lethal ''index'' ischemia; this was first demonstrated by Murry et al [38]. Unfortunately, clinical application of ischemic preconditioning is limited because the cardioprotective stimulus must be applied before the index ischemic event. As AMI is often unheralded, the use of ischemic preconditioning is therefore restricted to elective procedures inducing ischemia-reperfusion injury, such as coronary artery bypass grafting or heart transplant surgery. Before the concept of ischemic preconditioning, Jaffe and Quinn [39] illustrated a form of innate cardioprotection in patients with coronary artery disease whereby exertional angina induced by initial exercise was greatly attenuated on second exercise if interrupted by a brief rest period; this was termed the ''warm-up phenomenon''. However, to this day, the mechanisms involved in this cardioprotective mechanism remain uncharacterized.

It has subsequently been found that brief periods of ischemia and reperfusion also protect against infarct size when applied simultaneously with the onset of reperfusion – so-called ''postconditioning'' [40]. This is an area of intensive research at present; current clinical trials [41–48] are summarized in *Table I*. Basic research data suggest that the protective mechanisms initiated by both ischemic preconditioning and postconditioning converge to target inhibition of opening of the mPTP [49]. However, postconditioning is also limited by its invasive nature, and therefore is restricted to patients with AMI undergoing PCI. Interestingly, more recent data have demonstrated cardioprotection with brief remote ischemic stimuli, which can be applied before, during, or immediately after the index ischemia; these are termed ''remote ischemic preconditioning'', ''remote preconditioning'', and ''remote postconditioning'', respectively, and they offer the opportunity for protection in all patients with AMI. Some animal studies

Table I. Cardioprotection induced by ischemia [41–48].

Trial [ref]	Location / year	*n*	Setting	Protocol (post TIMI 2)	Results (intervention vs control)
Trials / studies already completed					1st Endpoint (2nd Endpoint)
Staat et al [41]	France, 2005	27	STEMI <6 h	4 × 1 min balloon I + R	↓ CK-MB 72 h AUC ↑ Blush grade
Ma et al [42]	China, 2006	94	AMI <12 h	3 × 30 s balloon I + R	↓ CK-MB 72 h peak ↑ Flow velocity ↑ Wall motion
Yang et al [43]	China, 2007	41	AMI <6 h	3 × 30 s balloon I + R	↓ CK-MB ↓ Infarct size assessed by SPECT
Clinical trials currently in progress / recruiting patients					
POSTEMI [44]	Norway, 2009	260	AMI <6 h	4 × 1 min balloon I + R	MRI–LGE 4 months post AMI (MACE at 1 yr)
POST [45]	Korea, 2009	700	STEMI <12 h	4 × 1 min balloon I + R	Dichotomous rate ST resolution (Death / MI at 30 days and 1 yr)
POSTCON [46]	Denmark, 2009	200	STEMI <12 h	4 × 30 s balloon I + R	MRI–LGE 3 months post AMI (MACE at 1 and 15 months)
PostC in PCI [47]	Canada, 2009	?	STEMI <12 h	4 × 1 min balloon I + R	MRI–LGE 3–5 days post AMI (MR perfusion, blush grade)
Remote PostC [48]	Italy, 2009	60	STEMI <6 h	3 × 5 min I + R of lower limb (200 mm Hg)	CK-MB AUC (MRI-LGE, MACE and Mortality at 4 months)

n, Number of individuals enrolled; ↑, increased; ↓, decreased; AMI, acute myocardial infarction; AUC, area under curve; CK-MB, creatine kinase-myocardial band; I, ischemia (balloon inflation); MR perfusion, magnetic resonance perfusion imaging; MACE, major adverse cardiovascular events; MRI–LGE, magnetic resonance imaging late gadolinium enhancement; R, reperfusion (balloon deflation); STEMI, ST-segment elevation myocardial infarction.

Table II. Pharmacological manipulation of reperfusion injury [29,50–75].

Trial [ref]	Location / year	*n*	Setting	Protocol	Results (intervention vs control)
Trials / studies already completed					
Magnesium (hypothesized to reduce Ca^{2+} overload, enhance membrane stabilization, and conserve ATP)					
LIMIT2 [50]	England, 1992	2316	AMI <12 h No ECG criteria	8 mmol bolus, then 65 mmol infusion over 24 h Not specified when started	24% RRR in 28-day mortality No diff in cardiac enzyme release
ISIS-4 [29]	Multicentre, 1995	58 050	AMI <24 h	8 mmol bolus, then 65 mmol infusion over 24 h Started <2 h post STK	No diff in 5-week mortality; ↑ Incidence hypotension, bradycardia, heart failure
MAGIC [51]	Multicentre, 2002	6213	STEMI <6 h	2 g bolus, then 17 g infusion over 24 h; 95% received bolus at onset of reperfusion	No diff in 30-day mortality; No harmful effects noted
Adenosine (believed to mimic ischemic preconditioning and postconditioning, and prevent neutrophil migration and downstream inflammation)					
AMISTAD [52]	Multicentre, 1999	236	STEMI <6 h	3 h infusion given at start of reperfusion ±10 min (dose 70 μg/kg per min)	33% RRR infarct size assessed by SPECT 6 days post STEMI, and greater effect in anterior MI No diff in composite clinical endpoint
AMISTAD-2 [53]	Multicentre, 2005	2118	STEMI <6 h	3 h infusion just before thrombolysis or PCI (dose 50 or 70 μg/kg per min)	No diff in composite 1st endpoint (new CHF, death at 6 months); ↓ Infarct size (SPECT) in subgroup
PROMISE [54]	Spain, 2009	200	STEMI <6 h, undergoing PCI	Intracoronary adenosine given distal to culprit lesion just after TIMI 2 flow	Currently recruiting 1st endpoint = MRI–LGE 2 weeks and 6 months post STEMI
Na^+–H^+ Exchange inhibitor (attenuation of Na^+ accumulation and subsequent inhibition of Ca^{2+} overload)					
Rupprecht et al [55]	Germany, 2000	100	STEMI <6 h	Cariporide 40 mg bolus over 10 min just before reperfusion	Significant ↑ in LVEF and RWMA with cariporide. CK-MB, CK and LDH release significantly ↓
GUARDIAN [56]	Multicentre, 2000	11 590	NSTEMI, unstable angina PCI or CABG	Cariporide 20, 80, or 120 mg as a 60 min infusion, before PCI or CABG	No diff in death or MI at 30 days, except in CABG patients with cariporide 120 mg, in whom 10% RRR noted
ESCAMI [57]	Multicentre, 2001	978	STEMI <6 h	10 min infusion of eniporide just before reperfusion (thrombolysis or PCI)	No diff in infarct size (α-HDBH AUC) No diff in clinical outcome
EXPEDITION [58]	Multicentre, 2008	5761	High-risk CABG patients	Cariporide: 180 mg loading dose before operation, then 20 mg/h for 24 h	↓ Death or MI at 5 days; ↓ MI alone, while mortality ↑ (secondary to ↑ cerebrovascular events)
C5 complement inhibitor (potential to modulate inflammatory response during reperfusion)					
COMMA [59]	Multicentre, 2003	960	STEMI <6 h, undergoing PCI	Pexelizumab (2 mg/kg bolus just before PCI, ± 0.05 mg/kg per h for 24 h)	No diff infarct size (CK-MB AUC), or MACE at 90 days; ↓ Mortality at 90 days
APEX–AMI [60]	Multicentre, 2007	5745	STEMI <6 h, undergoing PCI	Pexelizumab (2 mg/kg bolus just before PCI, ± 0.05 mg/kg per h for 24 h)	No diff in all-cause mortality at 30 days; No diff in composite clinical outcome at 30 and 90 days
RheothRx (surfactant with antithrombotic, anti-inflammatory actions; potential to enhance fibrinolysis)					
CORE [61]	Multicentre, 1997	2948	STEMI <12 h	1 h bolus poloxamer 188, ± followed by 11 h or 23 h infusion	No diff in mortality at 35 days, or composite clinical outcome; ↑ Significant increase in renal dysfunction

Table II. (Continued)

Trial [ref]	Location / year	*n*	Setting	Protocol	Results (intervention vs control)
Trials / studies already completed					
Anti-inflammatory fibrin (competes with fibrin for vascular endothelial cadherin, deterring neutrophil migration in vitro)					
FIRE [62]	Multicentre, 2009	234	STEMI <6 h Single lesion undergoing PCI	2 × 200 mg boluses of FX06 given just before guidewire crossed occlusion	No diff in infarct size assessed by MRI–LGE at 5 days and troponin I at 4 months. No diff in clinical outcome
GIK infusion (↑ myocardial energy efficiency, reduces myocardial uptake of toxic fatty acids in vitro)					
ECLA [63]	Multicentre, 1998	268	AMI <12 h No ECG criteria	GIK (25% / 50 U / 80 mmol/L or 10% / 20 U / 40 mmol/L)	↓ Mortality in both low- and high-dose GIK. However, at 1 year no significant diff in mortality
CREATE-ECLA [64]	Multicentre, 2005	20 201	STEMI <12 h Thrombolysis or PCI	GIK 25% / 50 U / 80 mmol/L started before reperfusion	No diff in 30-day mortality or cardiac arrest or cardiogenic shock
Cyclosporin (potent inhibitor of the mPTP; significant reductions in infarct size in animal models)					
Piot et al [65]	France, 2008	58	STEMI <12 h undergoing PCI	2.5 mg/kg cyclosporin given <10 min before PCI	↓ Infarct size assessed at 5 days by MRI–LGE. No diff in troponin I, cardiac events or LVEF
Hyperoxemic reperfusion (aqueous oxygen improves recovery of ventricular function in animal studies)					
AMIHOT [66]	USA, 2007	269	STEMI <12 h Primary or rescue PCI	Aqueous oxygen perfused for 90 min with onset of reperfusion	No diff in infarct size or RWMA index at 14 days, but RWMA improved in patients with anterior MI
Selected clinical trials currently in progress / recruiting patients					1st Endpoint (2nd Endpoint)
VITAL-1 [67]	Russia, 2009	300	NSTEMI or STEMI with PCI	ARC1779 (vWF antagonist)	Timeframe 48 h post PCI bleeding
POSTCONII [68]	Denmark, 2009	100	STEMI <6 h	Exenatide (GLP-1 analogue)	Infarct size assessed by MRI–LGE at 3 months (Cardiac death 1 and 15 months)
RECREATE [69]	USA, 2009	500	AMI <24 h BM >8 mmol/L	Intensive insulin regimen targeting normoglycemia	24 h diff in mean glucose (Mortality, non-recurrent MI)
Atorvastatin [70]	Korea, 2009	300	STEMI <12 h	Atorvastatin 80 mg/day orally given before PCI	SPECT infarct size at 14 days (MRI–LGE infarct size at 14 days)
SOLSTICE [71]	Multicentre, 2009	500	NSTEMI <12 h	GW856553 (p38 MAPK inhibitor)	Troponin I AUC 72 h, hsCRP 12 weeks, MACE 14 weeks (MRI-LGE infarct size, MRI LV function 12 weeks)
Erythropoetin [72–74]	Multicentre, 2009	350	STEMI <24 h	Bolus intravenous EPO just before PCI, followed by infusion	Infarct size CK-MB, LVEF–MRI, MRI–LGE (MRI-LGE infarct size 4 days, MACE at 6 months)
KAI-9803 [75]	USA, 2009	150	STEMI <6 h	δ PKC inhibitor	Safety; no 1st endpoint specified

Route of administration of drugs is intravenous unless otherwise stated. *n*, Number of individuals enrolled; ↑, increased; ↓, decreased. AMI, acute myocardial infarction; AUC, area under curve; BM, blood glucose; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; diff, difference; ECG, electrocardiogram; EPO, erythropoetin; GIK, glucose–insulin–potassium; GLP-1, glucagon-like peptide-1; α-HDBH, alpha-hydroxybutyrate dehydrogenase; hsCRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; LVEF–MRI, left ventricular ejection fraction–magnetic resonance imaging; MACE, major adverse cardiovascular events; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MR perfusion, magnetic resonance perfusion imaging; mPTP, mitochondrial permeability transition pore; MRI–LGE, magnetic resonance imaging–late gadolinium enhancement; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PKC, protein kinase C; RRR, relative risk reduction; RWMA, regional wall motion abnormality; STEMI, ST-segment elevation myocardial infarction; STK, streptokinase; vWF, von Willebrand factor.

have failed to demonstrate cardioprotection with these remote phenomena, but this may reflect an insufficient remote ischemic stimulus.

Pharmacological manipulation of reperfusion injury

Improvement in clinical outcome with pharmacological intervention at the onset of reperfusion defines the very concept of reperfusion injury. Several mechanisms highlighted in the section above on ischemia-reperfusion have been specifically targeted, with several more potential targets yet to be tested. Space constraints prevent us, in this review, from expanding on each treatment tried to date, therefore we have produced a Table (*Table II*), which summarizes the most important clinical studies [52–75], grouped into categories based on the pharmacological intervention used. In particular, note that, despite a substantial number of adjuncts to reperfusion initially showing great promise, subsequent larger multicenter studies were unable to confirm efficacy (for examples, see [29,50,51]).

In addition to the studies outlined above, studies have also focused on other anti-inflammatory agents such as anti-CD18 and -CD11 antibodies, P-selectin antagonists, antioxidants, intravenous nicorandil (a K_{ATP} channel opener) and therapeutic hypothermia, although the larger clinical trials in these categories have also failed to show consistent benefit. With regard to the glucose–insulin–potassium debate, it remains unclear whether metabolic modulation at the moment of reperfusion can afford benefit in clinical outcome. Previous studies may have masked therapeutic potential through inadvertent hypoglycemia; further studies are needed with more intensive monitoring and maintenance of normoglycemia, and in this regard we await the results of the Researching Coronary Reduction by Appropriately Targeting Euglycemia (RECREATE) trial with anticipation.

Conclusions

To determine the efficacy of adjunctive treatments given at the onset of reperfusion, meticulous attention to study design and careful selection of end points are paramount. From the two Tables in this article alone, one can see the great variety in both of these parameters, which makes interpretation of a small but potentially invaluable effect on clinical outcome very difficult. Furthermore, established treatments have greatly reduced the morbidity and mortality from AMI, reducing the potential absolute benefit from novel therapies. A notable strength of more recent studies is the use of magnetic resonance imaging to assess infarct size with late gadolinium enhancement. This technique is particularly accurate at quantifying the region of ischemia-reperfusion injury and therefore identifying a potential therapeutic benefit. Furthermore, MRI-LGE has been shown to have a significantly higher correlation with prognosis, compared with SPECT. Hence, with an increased awareness of the importance of scrupulous study design that incorporates the use of novel techniques such as MRI–LGE as well as relevant clinical end points, we will be better able to assess the effects of new therapies, thus enabling progression along the winding road to cardioprotection. ■

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