Promising strategies to minimize reperfusion injury in STEMI

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ABSTRACT

Morbidity in patients presenting with acute ST-segment elevation myocardial infarction remains significant despite prompt reperfusion by primary percutaneous coronary intervention. This has been partly attributed to “myocardial reperfusion injury” whereby the process of restoring coronary blood flow paradoxically induces myocardial injury and cardiomyocyte death, mitigating the full beneficial effects of reperfusion. A large number of cardioprotective therapies to reduce myocardial infarct size have been investigated in preclinical and small proof-of-concept clinical studies with mixed results. In this article, we provide an overview of the most promising cardioprotective therapies for reducing myocardial infarct size that warrant further investigation in outcome studies.

Keywords: reperfusion injury, cardioprotection, ST-segment elevation myocardial infarction, myocardial infarct size

INTRODUCTION

Timely myocardial reperfusion through primary percutaneous coronary intervention (PPCI) or thrombolysis currently remains the most effective therapy to minimize myocardial infarct (MI) size and prevent heart failure in acute ST-segment elevation myocardial infarction (STEMI) patients. However, whilst rapid reperfusion therapy decreases immediate STEMI mortality, it paradoxically results in an increased incidence of long-term heart failure.[1-3] Myocardial reperfusion has been termed “a double-edge sword”[4] due to the detrimental effects of acute ischaemia/reperfusion injury (IRI) on the heart. IRI results in cardiomyocyte death and may in fact contribute up to 50% of final MI size[5]. Four types of IRI have been recognised. So-called “myocardial stunning” and “reperfusion-induced arrhythmias” are reversible and self-limiting. The “coronary no-reflow phenomenon” and

"lethal myocardial reperfusion injury" are irreversible[5] and have been the focus of significant research over the past 3-4 decades. Despite recent advances in minimizing ischaemic injury through the use of antithrombotic agents, anticoagulants, and stent delivery in the setting of PPCI, there is currently no established therapy for minimizing IRI. In this article we provide an overview of the most promising cardioprotective therapies for reducing MI size.

BRIEF HISTORICAL PERSPECTIVE

In 1986, Murry et al[6] first showed that alternating left anterior descending (LAD) coronary artery occlusion and reflow followed by LAD occlusion for 90 minutes led to a 25% reduction in MI size in the canine heart[6]. This form of endogenous cardioprotection was termed ischemic preconditioning (IPC) and has been shown to be ubiquitous in several other organs and species[7, 8]. In 1993, Przyklenk et al[9] found that transient intermittent occlusion and reperfusion in the circumflex coronary artery was able to reduce MI size by 63% following LAD occlusion. This gave rise to the concept that cardioprotection could be induced by applying cycles of brief ischaemia and reperfusion to an organ or tissue remote from the heart in an intervention termed "remote ischemic conditioning" (RIC). It was not until 2003 that Zhao et al[10] discovered that applying three cycles of 30-seconds LAD coronary artery occlusion and reflow at the onset of myocardial reperfusion could reduce MI size by 44% in the canine heart. This phenomenon was termed 'ischaemic postconditioning' (IPost)[8] and is relevant in the context of a STEMI, where the overall ischaemic insult cannot be predicted.

OVERVIEW OF MECHANISTIC PATHWAYS

The mechanisms involved in cardioprotection are complex and not yet fully understood (comprehensively reviewed in[7, 8, 11, 12]). A simplistic representation classifies the signal

transduction into three levels: triggers (adenosine, bradykinin and opioids), intracellular mediators (protein kinases) and effectors (mitochondria, cytoskeleton). Three parallel pathways are currently understood to be involved: the Reperfusion Injury Salvage Kinase (RISK), the Survivor Activator Enhancement (SAFE) pathway, and an unnamed third pathway involving G-protein-coupled or natriuretic-peptide receptors, nitric oxide synthase, nitric oxide and protein kinase G. The underlying mechanism linking remote organs and the heart in RIC remains unknown. It has been postulated that this link may involve the release of local autocoids, which stimulate the sensory afferent neural pathway remotely, leading to the production of blood-borne cardioprotective factors (nitric oxide, MicroRNA-144, Stromal derived factor-1α) (comprehensively reviewed in[13]). The first window of protection from the conditioning stimulus occurs immediately and lasts for 2-3 hours, and the second one termed the second window of protection (SWOP) appears 12-24 hours later, and lasts up to 72 hours. Repeated RIC post-MI has also been shown to prevent left ventricular (LV) remodelling via exosome-mediated intercellular communication[14]. Increased understanding of IRI pathophysiology has helped to identify potential therapeutic targets as illustrated in **Figure 1**.

The mechanistic insights underlying ischaemic conditioning have enabled the development of pharmacological agents to mimic cardioprotection[5, 15]. A number of these including atrial natriuretic peptide (ANP)[16], exenatide[17], metoprolol[18] and adenosine[19-21] have shown promise in the clinical setting. Others, such as glucose-insulin-potassium[22 23], cyclosporine [24, 25] and erythropoietin[26-28] have failed to show consistent results (reviewed in [29]).

THERAPEUTIC INTERVENTIONS SHOWING PROMISE IN THE CLINICAL SETTING

A number of proof-of-concept studies have shown promising results in the clinical setting and some of these major studies are summarized in **Table 1**. In the next few paragraphs we will elaborate on the promising therapeutic interventions to date.

IPost

IPost was first implemented in a clinical trial in 2003 - only 2 years following its discovery. Whilst numerous clinical studies have investigated the benefit of IPost in STEMI and have produced promising results[30-32], other studies have been either neutral[33, 34] or shown the potential for clinical harm [35 36]. IPost may not benefit all patients and its clinical application is limited by its invasive nature and a minor risk of distal microembolisation[35, 37, 38]. A meta-analysis[38] of 10 trials (total of 560 patients) suggested that IPost may confer cardioprotection in terms of relatively reduced cardiac enzyme levels and increased LV function and that these effects were more pronounced among young male patients who had direct stenting. The DANAMI-3 trial[39] has completed recruitment of 2000 patients into 3 arms: conventional treatment, IPost or deferred stenting. It will hopefully provide some definite answers on whether these strategies can improve clinical outcomes at 2 years post PPCI. (**Table 2**)

Remote ischemic postconditioning (RIPost)

Several proof-of-concept studies have shown that intermittent inflation and deflation of a cuff around a limb during a STEMI leads to a reduction in infarct size[40-44] not only in patients undergoing PPCI but also in those undergoing thrombolysis[44]. The initial cohort study from Botker et al[41] was followed-up for a median of 3.8 years and fewer adverse events were observed in the RIPost group[45]. Whether RIPost can also reduce cardiac death and hospitalisation for heart failure at 1 year in PPCI patients is currently being

investigated in a joint international multicentre randomised controlled trial of 4200 patients (ERIC-PPCI and CONDI2 trials - ClinicalTrials.gov Identifier: NCT02342522 and NCT01857414) [46]. (**Table 2**)

Metoprolol

Early use of metoprolol has been shown to increase myocardial salvage in a porcine model of acute MI[47]. In the clinical setting, Ibanez et al[18] showed a 20% reduction in infarct size assessed by cardiac magnetic resonance (CMR) and LV ejection fraction (LVEF) in response to intravenous metoprolol. The pharmacological intervention was administered before reperfusion in anterior STEMI patients with Killip class II or less presenting within 6 hours of onset of symptoms. This benefit persisted at 6 months as demonstrated by an improvement in LVEF[48]. The EARLY BAMI study[49] is currently investigating early metoprolol use during ambulance transfer and will be recruiting patients within 12 hours of symptoms onset. The primary endpoint will be infarct size as measured by CMR at 30 days and it is expected to enroll 408 patients. (**Table 2**)

Exenatide

Glucagon-like peptide 1 and its analogue exenatide have been shown to reduce MI size in animal studies[50] [51]. Lonborg et al[17] demonstrated in 172 STEMI patients that exenatide administered as an infusion 15 minutes prior to reperfusion and continued for 6 hours increased myocardial salvage. In particular, there was a 30% reduction in MI size in those presenting within 132 minutes[52]. Woo et al[53] also showed a significant impact on infarct size reduction with subcutaneous exenatide in a smaller cohort of patients. Therefore there is a pressing need to perform a large randomized controlled trial to investigate whether exenatide use in STEMI also leads to an improvement in clinical outcomes.

Atrial Natriuretic Peptide

Yang et al [54] demonstrated in a rabbit model, that ANP administered just prior to reperfusion limited MI size. The cardioprotective benefit of ANP was confirmed in the J-WIND trial[16]. This was a trial of 569 STEMI patients that showed a 15% reduction in enzymatic MI size and subsequent improvement in LVEF and reduction hospitalisation for heart failure and death at 6 months in the arm receiving ANP. However, this study was not powered for clinical outcomes and these findings need to be confirmed in larger, adequately powered studies.

Adenosine

Adenosine has been extensively investigated as a cardioprotective agent in both experimental and clinical studies. In the pre-clinical setting it is generally accepted that the administration of adenosine prior to experimental IRI can reduce MI size[55]. Whether adenosine is cardioprotective when it is given at the time of reperfusion to target IRI has been unclear in experimental studies[56, 57]. A number of clinical studies have investigated the effect of adenosine when administered as an adjunct to reperfusion in STEMI patients. Many of these studies have reported beneficial effects in terms of preventing the coronary no-reflow phenomenon. Duration of symptoms may be important in explaining these experimental discrepancies. Intra-coronary adenosine has been reported to be more effective in limiting infarct size in patients receiving reperfusion within 3 hours of symptoms onset[19, 58, 59]. A recent meta-analysis[60] showed that intracoronary adenosine was associated with less heart failure in 8 randomized controlled trials however there was no difference in mortality and as such, this avenue warrants further investigation. The REFLO-STEMI trial is currently investigating the role of intra-coronary adenosine on MI

size measurement using CMR, and has been designed to address the flaws of previous studies.[61]

Combination therapy

Another approach would be to use combination therapy targeting multiple cardioprotective pathways in order to minimise IRI. Following the promising pilot studies with exenatide and RIPost in STEMI, Alburquerque-Béjar et al[62] showed an additive benefit in infarct size reduction through a combination of these 2 interventions in a porcine model. The COMBAT-MI study (ClinicalTrials.gov Identifier: NCT02404376) will be investigating the potential additive benefit of infarct size reduction in the clinical setting. The combination of RIPost and IPost has also been recently studied in a large study of 696 STEMI patients and showed better myocardial salvage in patients receiving RIPost in combination with IPost[63].

PROMISING CARDIOPROTECTIVE THERAPIES FAILING TO SHOW A BENEFIT IN THE CLINICAL SETTTING

Disappointingly, over the past 2 years there have been a number of studies reporting neutral results in several otherwise promising cardioprotective strategies. Cooling to <35°C has been shown to reduce MI size both in animal models[64, 65] and in an initial pilot study[66]. However, the CHILL-AMI study[67] (120 patients) failed to show an improvement in MI size despite achieving a temperature of <35°C prior to reperfusion by cold saline and endovascular cooling. The recently published VELOCITY study by Nichol et al[68] randomized 53 patients to peritoneal hypothermia versus control and found no benefit in infarct size reduction. Pre-clinical data has shown impressive cardioprotective benefit of sodium nitrite in the context of STEMI[69-71]. However, Siddiqi et al[72] and Jones et al[73] both

failed to show a reduction in infarct size via the intravenous and intracoronary route respectively. The NOMI study was reported at the European Society of Cardiology conference in 2014 and demonstrated that inhaled nitrous oxide did not reduce infarct size when compared to placebo[74]. Recent phase II trials investigating Delcasertib (delta-protein kinase C) in the PROTECTION-AMI study[75], TRO40303 (inhibitor of the mitochondrial permeability transition pore) in the MITOCARE study[76] and Bendavia (a mitochondria-targeting peptide) in the EMBRACE-STEMI study[77] as well as a trial investigating mangafodipir[78] (manganese dipyridoxyl diphosphate) all proved to be safe but failed to translate to a reduction in infarct size in STEMI patients when administered prior to reperfusion. The long awaited large randomized CIRCUS trial[79] comprising of 975 STEMI patients did not show a benefit in the combined primary endpoint (adverse LV remodelling, heart failure and all cause death). This failure may have been related to a novel formulation of cyclosporine (Ciclomulsion) used in the study which may have interfered with its cardioprotective benefit.[80] The failure to translate the cardioprotective benefits of these promising agents has been attributed to a number of factors such as the use of inappropriate animal models, poorly designed clinical trials, interaction of comorbidies, and polypharmacy.[81] In the next paragraph, we will explore the various factors we need to take into account when designing clinical studies in this field.

HOW TO OPTIMISE THE TRANSLATION OF CARDIOPROTECTION

The failure to translate cardioprotective therapies proven to reduce infarct size in animal models into patient benefit has been the subject of several recent articles[82-85]. There are certain factors that need to be taken into account whilst designing clinical studies in order to improve the chances of reaping their maximum benefit in the clinical environment. In the

setting of STEMI patients undergoing PPCI, these keys points need to be taken into account:

- Patients that are most likely to benefit from the cardioprotective therapy should be recruited: large area at risk (>30% of the LV)[34]; no coronary collateralisation (Rentrop<1); occluded artery prior to PPCI (TIMI 0 or 1); those presenting within 2-3 hours of symptoms onset[19 52].
- Only therapies having shown conclusive cardioprotection in pre-clinical studies should be tested.
- Therapy should be administered prior to myocardial reperfusion via PPCI.
- Confounding factors such as age, pre-infarct angina, diabetes mellitus, hypertension, dyslipidaemia and concomitant medications (nitrates, morphine, nicorandil, sulphonamides), which can interfere with cardioprotection, should be taken into consideration. [86]
- Relevant clinical endpoints for assessing cardioprotective efficacy should be selected. These include: MI size (enzymatic or CMR); myocardial salvage index (more sensitive than MI size reduction); microvascular obstruction; LV remodelling (LVH, LVEF and indexed LVEDV or LVESV); cardiac death; hospitalisation for heart failure.

Implementing the above steps should provide an optimal clinical platform to test therapies with promising preclinical results.

CONCLUSION

The field of clinical cardioprotection has a chequered history with a disappointingly large number of neutral studies in which novel cardioprotective therapies have failed to improve clinical outcomes. However numerous promising therapeutic interventions are available for

exploration, and larger trials examining outcomes are ongoing. Future studies need to be carefully designed by taking into account lessons learnt from recent studies. As such, minimising IRI may still be achievable in certain specific circumstances.

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Figure 1: Schematic representation of the main pro-survival signalling pathways and the potential sites of actions for novel therapies recently investigated in the setting of STEMI to minimize IRI.

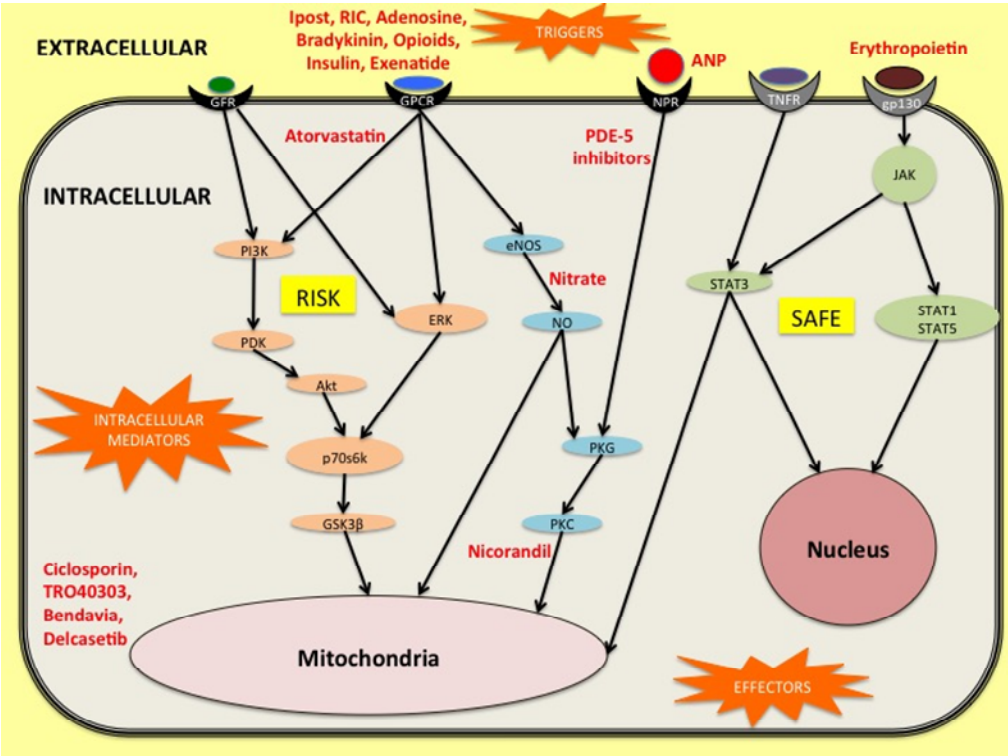

Table 1: Major promising clinical in STEMI patients

Clinical study	Therapeutic intervention	Number	Outcome	Comments
Pharmacological agents				
Kitakaze et al 2007[60] J-WIND	72 hours IV carperitide (atrial natriuretic peptide analogue) infusion started prior to PPCI	569	15% reduction in 72 hours AUC total CK 2.0% absolute increase in LVEF	Atrial natriuretic peptide targets pro-survival kinase pathways such as the cGMP and RISK pathways
Lonborg et al 2012[62]	IV infusion of exenatide started 15 minutes prior to PPCI and continued for 6 hr	107	Increase in myocardial salvage index (0.62 to 0.71) 23% reduction in MI size at 3 months on CMR Patients presenting with short ischaemic times (≤132 minutes) had greater myocardial salvage[88]	Exenatide, a GLP-1 analogue, targets pro-survival kinase pathways such as the RISK pathway
Ibanez et al 2013[63]	IV metoprolol (3x5mg) in ambulance prior to PPCI	270	Reduction in MI size by CMR at one week. Increased LVEF at 6 months Improvement in clinical outcome at 2 years Reduced: incidence of severely depressed LVEF (<35%) at 6 months by 60%; less need for ICD by 65% at 6 months and reduced HF at 2 years [89]	The mechanism of cardioprotection is not currently clear
Remote ischaemic perconditioning				
Botker et al 2010[54]	Four x 5-minutes upper arm cuff inflations/deflations in the ambulance prior to PPCI	142	Increase in myocardial salvage index at 30 days No difference in MI size (SPECT or peak Troponin)	First study to test effect of RIC in PPCI-treated STEMI patients. Reduced MI size in LAD STEMI.
Rentoukas et al 2010[55]	Three x 4-minutes cuff inflations/deflations at the hospital prior to PPCI	93	Better ST resolution and lower peak Troponin I. Synergistic effects with morphine.	
Crimi et al 2013[57]	Three x 5-minutes thigh cuff inflations/ deflations at onset of reperfusion by PPCI	100 LAD only	20% reduction in 72 hours AUC CK-MB. % reduction in myocardial oedema by CMR	First study to show effect of RIC given at onset of reperfusion via PPCI. Also, first study to report effect of RIC on enzymatic MI size and myocardial oedema.
White et al 2014[56]	Four x 5-minutes upper arm cuff inflations/deflations at the hospital prior to PPCI	197	27% reduction in MI size by CMR 19% reduction in myocardial oedema by CMR	First study to show effect of RIC given prior to PPCI on MI size and myocardial oedema by CMR
Yellon et al 2015 ERIC-LYSIS[44]	Four x 5-minutes upper arm cuff inflations/deflations at hospital prior to thrombolysis for STEMI	519	17% reduction in enzymatic MI size (CK-MB and Trop-T)	Only study to test effect of RIC in thrombolysed STEMI patients
Sloth et al 2014[86]	Four x 5-minutes upper arm cuff inflations/deflations in the ambulance prior to PPCI	251	51% reduction in all-cause mortality, nonfatal MI, TIA or stroke, HHF at 3.8 years	First study to test effect of RIC on long-term outcomes following PPCI

STEMI: ST-segment elevation myocardial infarction; IV: intravenous; AUC: area under curve; CK: creatine kinase; LVEF: left ventricular ejection fraction; cGMP: cyclic guanosine monophosphate; RISK: reperfusion injury salvage kinase; MI: myocardial infarct; CMR: cardiovascular magnetic resonance imaging; LVESV: left ventricular end-systolic volume; GLP-1: glucagon-like peptide-1; AAR: area at risk; HF: heart failure

Table 2: Ongoing clinical studies

Clinical study	Treatment protocol	Number of patients	Outcome	Comments
Ongoing studies on clinical outcomes				
Engstrom et al DANAMI-3[39]	Four x 30-seconds angioplasty balloon inflations/deflations during PPCI	2000 Completed recruitment	All-cause mortality, heart failure at 2 years Results awaited	First study which will report effects of IPost on long-term clinical outcomes
Botker CONDI-2 (NCT02342522) Hausenloy ERIC-PPCI (NCT01857414)	Four x 5-minutes upper arm cuff inflations/deflations prior to PPCI	4300 Ongoing	Primary endpoint of cardiac death and HHF at 12 months	Collaboration between UK, Denmark. First study to test effect of RIC on long-term clinical outcomes at primary endpoint following PPCI
Ongoing phase II studies				
Nazir et al[61] REFLO-STEMI	Intracoronary adenosine or sodium nitroprusside versus placebo during PPCI	240 patients Completed recruitment	Primary endpoint of infarct size by CMR at 48-72 hours post PPCI	3-arm study in 4 UK centres which also look at MVO by CMR as a secondary endpoint.
Roovlink et al[49] EARLY BAMI	Intravenous metoprolol starting as soon as possible after the diagnosis of STEMI	408 patients Ongoing	Primary endpoint of infarct size by CMR at 30 days	Multicentre study looking to start metoprolol in the ambulance and including patients with up to 12 hours of symptoms duration as compared to the recent study by Ibanez et al[47]
Halladin et al[87] IMPACT	Intracoronary and systemic administration of melatonin during PPCI	40 patients	Primary endpoint of myocardial salvage by CMR on day 3-5 post PPCI	First pilot study to investigate the cardioprotective benefit of melatonin in STEMI patients
Ishihara et al [88]	Intravenous TY-51924 prior to PPCI	100 patients	Primary endpoint of myocardial salvage by SPECT	TY-51924 is the latest sodium/hydrogen exchanger designed to improve its safety profile and this is the first study in STEMI to assess its efficacy and safety
Bulluck/ Fröhlich et al[89] MINIMISE STEMI	Intravenous spironolactone prior to reperfusion by PPCI followed by 3 months oral therapy	150 Ongoing	Primary endpoint of infarct size by CMR at 3 months	First clinical study to investigate the role of spironolactone to minimise reperfusion injury

IPost: Ischaemic postconditioning; RIC: remote ischaemic conditioning; STEMI: ST-segment elevation myocardial infarction; AUC: area under curve; CK: creatine kinase; PPCI: primary percutaneous coronary intervention; CK-MB: creatine kinase MB isoenzyme; SPECT: single-photon emission computed tomography; LVEF: left ventricular ejection fraction; PPCI: primary percutaneous coronary intervention; MI: myocardial infarct; LAD: left anterior descending artery; CMR: cardiovascular magnetic resonance imaging; Trop I: Troponin I; TIA: transient ischaemic attack; HHF: hospitalisation for heart failure;