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Conditioning the heart to prevent myocardial reperfusion injury during PPCI

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Abstract

For patients presenting with a ST-segment elevation myocardial infarction (STEMI), early myocardial reperfusion by primary percutaneous coronary intervention (PPCI) remains the most effective treatment strategy for limiting myocardial infarct size, preserving left ventricular systolic function, and preventing the onset of heart failure. Recent advances in PCI technology to improve myocardial reperfusion and the introduction of novel anti-platelet and anti-thrombotic agents to maintain the patency of the infarct-related coronary artery continue to optimize PPCI procedure. However, despite these improvements, STEMI patients still experience significant major adverse cardiovascular events. One major contributing factor has been the inability to protect the heart against the lethal myocardial reperfusion injury, which accompanies PPCI. Past attempts to translate cardioprotective strategies, discovered in experimental studies to prevent lethal myocardial reperfusion injury, into the clinical setting of PPCI have been disappointing. However, a number of recent proof-of-concept clinical studies suggest that the heart can be 'conditioned' to protect itself against lethal myocardial reperfusion injury, as evidenced by a reduction in myocardial infarct size. This can be achieved using either mechanical (such as ischaemic postconditioning, remote ischaemic preconditioning, therapeutic hypothermia, or hyperoxaemia) or pharmacological (such as cyclosporin-A, natriuretic peptide, exenatide) 'conditioning' strategies as adjuncts to PPCI. Furthermore, recent developments in cardiac magnetic resonance (CMR) imaging can provide a non-invasive imaging strategy for assessing the efficacy of these novel adjunctive therapies to PPCI in terms of key surrogate clinical endpoints such as myocardial infarct size, myocardial salvage, left ventricular ejection fraction, and the presence of microvascular obstruction or intramyocardial haemorrhage. In this article, we review the therapeutic potential of 'conditioning' to protect the heart against lethal myocardial reperfusion injury in STEMI patients undergoing PPCI.

Keywords

Ischaemic postconditioning, myocardial reperfusion injury, primary percutaneous coronary intervention, remote ischaemic perconditioning, ST-segment elevation myocardial infarction

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Introduction

Coronary heart disease is the leading cause of morbidity and mortality in Europe and Worldwide. Its major emergent manifestation is a ST-segment elevation myocardial infarction (STEMI), which accounts for 800 hospital admissions every year per million population in Europe.[1] For STEMI patients, early myocardial reperfusion using primary percutaneous coronary intervention (PPCI) remains the most effective treatment strategy for reducing myocardial infarct (MI) size, preserving left ventricular (LV) ejection fraction, and preventing the onset of heart failure. The total ischaemic time (a key determinant of MI size) has been dramatically reduced by improvements in patient flow through the STEMI chain of survival,[2] resulting in shortened symptom-onset to balloon times. Furthermore, recent developments in PCI technology (thrombus aspiration, novel stents), anti-platelet agents (Abciximab, Prasugrel, Ticagrelor), and anti-thrombotic agents (Bivalirudin) continue to optimise

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the process of myocardial reperfusion by maintaining the patency of the infarct-related coronary artery after PPCI. However, despite these improvements, the mortality of STEMI patients undergoing PPCI in Europe remains significant (3−7% in-hospital mortality depending on the country).[1] One major contributing factor has been the inability to protect the myocardium against the detrimental effects of lethal myocardial reperfusion injury during the PPCI procedure.

Although myocardial reperfusion is clearly essential for salvaging viable myocardium in STEMI patients, the actual process of restoring coronary blood flow to acutely ischaemic myocardium can paradoxically induce cardiomyocyte death in itself − a phenomenon which has been termed 'lethal myocardial reperfusion injury.[3,4] The existence of lethal myocardial reperfusion injury as an independent mediator of cardiomyocyte death has been surrounded by controversy.[3,4] Evidence supporting its existence as a cause of cell death distinct from acute myocardial ischaemia has been recently provided by experimental and more recently clinical studies reporting that MI size can be reduced by a therapeutic intervention given solely at the onset of myocardial reperfusion.[4] These studies suggest that lethal myocardial reperfusion injury accounts for 40−50% of the final MI size and its presence, therefore, mitigates the full benefits of reperfusion in terms of myocardial salvage.[4] There currently exists no effective therapeutic strategy for preventing lethal myocardial reperfusion injury in STEMI patients undergoing PPCI. Therefore, novel cardioprotective strategies, which can be administered to STEMI patients prior to or at the time of PPCI to prevent lethal myocardial reperfusion injury, are required to reduce MI size and preserve LV ejection fraction. In this regard, it is possible to 'condition' the heart to protect itself against acute ischaemia-reperfusion injury (IRI), through the activation of pro-survival intracellular signal transduction pathways which converge and protect against mitochondrial dysfunction during myocardial reperfusion.[5,6] In this article, the therapeutic potential of 'conditioning' as a strategy for protecting the heart against lethal myocardial reperfusion injury in STEMI patients undergoing PPCI is reviewed.

Conditioning the heart to protect itself against ischaemia-reperfusion injury

A landmark experimental study published in 1986 by Murry et al.[7] first introduced the concept of ischaemic preconditioning (IPC) as a powerful endogenous therapeutic strategy for rendering the myocardium resistant to MI. These authors made the intriguing discovery that the canine heart could be protected against MI by subjecting it to four 5-min cycles of alternating occlusion and reflow of the left anterior descending (LAD) coronary artery (to induce episodes of brief myocardial ischaemia and reperfusion).[7] The IPC stimulus is believed to put the heart into a protected state through the activation of a number of complex intracellular signalling pathways, many of which converge on the mitochondria.[5,6] However, the need to apply the IPC stimulus prior to the index myocardial ischaemic event and the requirement to apply the IPC stimulus to the heart directly has hampered its translation into the clinical setting. These obstacles have been overcome by the introduction of ischaemic postconditioning,[8] an endogenous cardioprotective strategy which can be applied at the time of myocardial reperfusion, and remote ischaemic perconditioning,[9] an endogenous cardioprotective strategy which can be applied after the onset of myocardial ischaemia to an organ or tissue remote from the heart, facilitating the translation of 'ischaemic conditioning' to STEMI patients undergoing PPCI.

Ischaemic postconditioning: cardioprotection at the time of reperfusion

In 2003, Zhao et al.[8] first introduced the concept of ischaemic postconditioning (IPost), an endogenous cardioprotective intervention which could be applied at the onset of myocardial reperfusion immediately following the index myocardial ischaemic event. Using the in-situ canine heart subjected to 60 minutes of LAD occlusion, these authors demonstrated that interrupting myocardial reperfusion with three 30-second cycles of LAD re-occlusion and reflow reduced MI size by 43%.[8] The fact that an intervention applied at the onset of myocardial reperfusion could limit MI size by over 40% confirmed the existence of lethal myocardial reperfusion injury and suggested that the latter was responsible for over 40% of the final MI size. Curiously, the term 'ischaemic postconditioning' was actually first mentioned in the research literature in 1996 by Na et al.[10] who first reported that ventricular premature beat-driven intermittent reperfusion could reduce reperfusion-induced ventricular fibrillation following myocardial ischaemia in feline hearts. Similarly, the idea of modifying the conditions of reperfusion to alleviate the detrimental effects of lethal myocardial reperfusion injury had been initially explored in the 1980s with controlled, gradual, or gentle reperfusion.[11,12] All things considered, IPost, as a form of modified reperfusion, has regenerated interest in the reperfusion phase as a target for cardioprotection.

Only 2 years after its initial description, the concept of IPost was successfully translated into the clinical setting by Staat et al. in 2005.[13] In this first proof-of-concept clinical study, 30 carefully selected STEMI patients who were eligible for PPCI were randomised to receive either an IPost or sham protocol immediately following direct stenting to the infarct-related artery[13] (Table 1). For those patients treated with IPost, the coronary angioplasty balloon was pulled

Table 1. Major studies investigating ischaemic postconditioning as adjunct to primary percutaneous coronary intervention

Study	Patients	Patient eligibility: (1) STEMI type; (2) Presentation time (3) TIMI flow (4) Rentrop	Ischaemic time (min); AAR (%LV)	IPost protocol	Outcome measures	Notes
Staat et al. (2005)[13]	30	LAD/RCA STEMI	331 C	Four 60-s inflations/ deflations	36%↓ in 72 h AUC CK	First application of IPost in STEMI patients
		<6 h	318 IPost		34% ↓ in peak CK	
		TIMI 0 flow	34% C		MBG ↑ 1.7 to 2.4	
		Rentrop <1	37% IPost			
Laskey et al. (2005)[52]	17	All STEMI	286 C	Two cycles of 1.5 min inflation/3−5 min deflations	Improved coronary blood flow	
		NA	341 IPost		Better ST-segment resolution	
		All TIMI flow	NA			
		Collaterals included				
Ma et al. (2006)[53]	94	All STEMI	426 C	Three 30-s inflations/ deflations	28% ↓ peak C	
		<12 h	395 IPost		32% ↓ peak CK-MB	
		All TIMI flow	NA		↓ serum MDA	
		Collaterals included			Improved coronary blood flow	
					Better endothelial function	
					Better WMSI at 8 weeks	
Yang et al. (2007)[54]	41	All STEMI	264 C	Three 30-s inflations/ deflations	27% ↓ 72 h AUC total CK	First study to show ↓ MI size by imaging
		NA	312 IPost		27% ↓ MI size at 7 days by SPECT	
		TIMI 0 flow	NA			
		Rentrop <1				
Laskey et al. (2008)[55]	24	LAD STEMI	222 C	Two cycles of 1.5 min inflation/4−5 min deflations	19% ↓ peak total CK level	
		<6 h	228 IPost		Improved coronary flow velocity reserve	
		TIMI 0−1 flow	NA		Better ST-segment resolution	
		No collateral flow				
Thibault et al. (2008)[56]	38	LAD/RCA STEMI	297 C	Four 60-s inflations/ deflations	40% ↓ 72 h AUC CK	First study to demonstrate long-term cardioprotection with IPost
		<6 h	283 IPost		41% ↓ 72 h AUC CK-MB	
		TIMI 0 flow	39% C		39% ↓ MI size at 6 months by SPECT	
		Rentrop <1	40% IPost		7% ↑ EF by echo at 1 year	

(Continued)

Table 1. (Continued)

Study	Patients	Patient eligibility: (1) STEMI type; (2) Presentation time (3) TIMI flow (4) Rentrop	Ischaemic time (min); AAR (%LV)	IPost protocol	Outcome measures	Notes
Zhao et al. (2009)[57]	75	All STEMI	268 C	Three 30-s or 60 s inflations/deflations	↓ in plasma apoptotic marker sFas	Three 60-s IPost protocol more effective
		<6 h	288 IPost			
		TIMI 0–1 flow				
		Rentrop <2				
Lonborg et al. (2010)[58]	118	All STEMI	255 C	Four 30-s inflations/ deflations	No difference in troponin T or LVEF	Largest IPost study to date
		<12 h	241 IPost		19% ↓ MI size at 3 months by CMR	First to use CMR to assess IPost
		TIMI 0 flow	29% C		31% ↑ in myocardial salvage index	
		Collaterals included	29% IPost		Less heart failure (27% vs. 46%)	
Xue et al. (2010)[59]	43	All STEMI	324 C	Four 60-s inflations/ deflations	Better ST-segment resolution	
		<12 h	246 IPost		26% ↓ 72 h AUC CK-MB	
		TIMI 0 flow			46% ↓ in MI size at 7 days by SPECT	
		Rentrop <2			↓ levels of hs-C-reactive protein	
					10% ↑ in EF	
Lin et al. (2010)[60]	74	All STEMI	NA	Three 30-s or 60 s inflations/deflations	↑ in EF and WMSI at 1 year	Three 60-s IPost protocol more effective
		<12 h			↓ levels of tumour necrosis factor α	
		TIMI 0 flow				
		Rentrop <2				
Fan et al. (2010)[61]	50	All STEMI	268 C	Three 30-s inflations/ deflations	↓ inducible nitric oxide synthase activity in white blood cells	
		NA	288 IPost		Decreased plasma nitrotyrosine	
		TIMI 0–1 flow			Improved cardiac function	
		Rentrop <2				
Sorensson et al. (2010)[17]	76	All STEMI	185 C	Four 60-s inflations/ deflations	No difference in 48 h AUC CK-MB and troponin T	First negative study, although IPost effective in those patients with large AAR (>30%) or LAD infarcts
		<6 h	165 IPost		No difference in myocardial salvage by CMR at day 7–9	
		TIMI 0 flow	23% C		Significant increase in myocardial salvage in patients with large AAR (>30% of LV)	
		Rentrop <2	30% IPost			

(Continued)

Table 1. (Continued)

Study	Patients	Patient eligibility: (1) STEMI type; (2) Presentation time (3) TIMI flow (4) Rentrop	Ischaemic time (min); AAR (%LV)	IPost protocol	Outcome measures	Notes
Garcia et al. (2010)[62]	43	All STEMI	270 C	Four 30-s inflations/ deflations	11% ↓ peak CK	
		<12 h	270 IPost		20% ↓ peak CK-MB	
		TIMI 0 flow			Increased MBG	
		Rentrop <1			9% ↑ in EF	
Limalanathan et al. (2010) [63]POSTEMI		All STEMI		Four 60-s inflations/ deflations	Ongoing	
		<6 h				
		TIMI 0 flow				
		Rentrop <1				
Tarantini et al. (2010)[64] (POST-AMI)	78	All STEMI	NA	Four 60-s inflations/ deflations	Ongoing	
		<6 h			Endpoints include AUC or peak troponin I	
		TIMI 0 flow			MI size at 30 d by CMR with IPost	
		Rentrop <1				
Engstrom et al. (DANAMI-3)	2000	All STEMI	NA	Four 30-s inflations/ deflations	Ongoing	Large outcome-based study
		<12 h			Primary combined endpoint is cardiac death, re-infarction, and heart failure at 3 years	
Ovize et al. (PRIME)	72	LAD/RCA STEMI	NA	Four 60-s inflations/ deflations	Ongoing	Tests if IPost is effective in patients who spontaneously reperfuse
		<12 h			Primary endpoint is MI size by CMR at 5 d	
		TIMI 2–3 flow				
		Rentrop <1				

AUC, area under the curve; AAR, area at risk; C, control; CK, creatine kinase; CMR, cardiac MRI; EF, ejection fraction; IPost, ischaemic postconditioning; LAD, left anterior descending coronary artery; LV, left ventricular; MBG, myocardial blush grade; MDA, malondialdehyde; MI, myocardial infarct; RCA, right coronary artery; SPECT, single photon emission CT; STEMI, ST-segment elevation MI; TIMI, thrombolysis in myocardial infarction; WMSI, wall motion score index.

immediately upstream of the stent and inflated to a low pressure (4−6 atm) for 60 seconds and then deflated for 60 seconds, a cycle which was repeated four times in total. Interrupting myocardial reperfusion in the infarct-related coronary artery in this way was shown to reduce 72 h total creatine kinase area under the curve by 36%.[13] This landmark clinical study confirmed the existence of lethal myocardial reperfusion injury in man and suggested that the latter may contribute up to 40% of the final MI size in STEMI patients undergoing PPCI. Since the publication of this small initial clinical study, several other studies have been published confirming the beneficial effects of IPost both acutely and in the long-term using SPECT[56], cardiac MRI[58], and echocardiography[56] (Table 1). However, a couple of recent clinical trials have been negative (Table 1). The reason for the discordant findings in the recently published studies is not clear, although it may be attributed to a number of factors including:

(1) Comorbidities: In the experimental literature, it has been suggested that presence of certain comorbidities such as diabetes, hypertension, age, and dyslipidaemia can attenuate the efficacy of IPost.[14] Whether this phenomenon occurs in the clinical setting is unclear at present and needs to be addressed in a large multicentre randomised clinical trial of IPost;
(2) Ischaemic time; It is not clear whether IPost is more effective in STEMI patients presenting with total ischaemic times (symptom-onset to balloon) of short (<3 h) or long (>3 h) duration. In other words, how the magnitude of lethal myocardial reperfusion injury varies with the preceding duration of ischaemia is not known. The experimental literature has reported that, in the rat MI model at least, IPost may actually be harmful following short ischaemic times (15−20 minutes) and only protective after longer durations of ischaemia (45−60 minutes).[15] Whether, a similar phenomenon is observed in the clinical setting is unknown;
(3) Thrombolysis in myocardial infarction (TIMI) flow in the infarct-related coronary artery: It is vital that IPost is administered to those STEMI patients in which myocardial reperfusion has already not taken place spontaneously (i.e. TIMI flow within the infarct-related artery should be 0 at the time of PPCI). It has been estimated that 25−30% of patients treated by PPCI may have already undergone spontaneous lysis prior to coronary angiography;[16]
(4) Coronary collateralisation: It is essential that STEMI patients with significant collateralisation to the area at risk are excluded at the time of coronary angiography as their presence would be expected to reduce MI size and may dilute the effect of IPost;
(5) Area at risk(AAR): It is essential that the AAR of myocardial infarction is measured at the time of PPCI so that the efficacy of IPost can be assessed in terms of myocardial salvage, a measure which takes into account the differing sizes of the AAR between patients in the IPost and sham groups;
(6) The size of the AAR: By including STEMI in all coronary territories there is a risk of diluting the beneficial effect of IPost. Ongoing clinical studies of IPost and other reperfusion treatment strategies have suggested that those STEMI patients presenting with a large AAR (>30% of LV) are most likely to accrue any benefit from IPost.[17] Similarly, patients with an AAR of <20% LV are unlikely to benefit from a cardioprotective intervention applied at PPCI.[17] Proximal LAD occlusions and some large right coronary artery (RCA) occlusions are most likely to have AAR >30% LV and these are the patients which should be targeted by IPost;
(7) The delivery of the IPost protocol: Care must be given when applying the IPost protocol particularly in the presence of obvious thrombus in the infarct-related coronary artery, as this could easily cause coronary embolization and worsen microvascular obstruction. For this reason, it is essential that the IPost protocol is performed upstream of the stent and not inside it.

Overall, the evidence suggests that IPost is cardioprotective in STEMI patients treated with PPCI. However, whether IPost can improve clinical outcomes in this patient group remains to be investigated in a large adequately powered multicentre clinical trial. In this regard, the DANAMI-3 trial (www.clinicaltrials.gov: NCT01435408), which is scheduled to report in 2014, is currently investigating whether IPost can improve clinical outcomes in PPCI patients (Table 1).

The disadvantages of IPost include: it prolongs the PPCI procedure, it requires a specific and carefully delivered protocol, and it can only be implemented in STEMI patients undergoing PPCI. Most importantly, IPost requires an interventional procedure being applied to the heart directly. This can be avoided by using a related endogenous cardioprotective strategy termed remote ischaemic conditioning, which was actually first described in 1993,[18] but has only been translated into the clinical setting in the last few years.

Remote ischaemic perconditioning in STEMI patients undergoing PPCI

In 1993, Przyklenk et al.[18] first demonstrated that applying four 5-minute cycles of occlusion and reflow to the circumflex coronary artery could reduce MI generated by a sustained occlusion in the LAD coronary artery, demonstrating for the first time that cardioprotection could be transferred from one region of the heart to another. This concept was quickly extended beyond the heart with the demonstration

that the myocardium could be protected against MI by applying the preconditioning stimulus to either the kidney or intestine,[19] confirming that the heart could be protected at a distance. Remote ischaemic preconditioning, as it became termed, offered inter-organ protection from acute IRI.[20] Despite intensive investigation, the mechanistic pathway linking the preconditioning organ or tissue to the heart is unknown but it has been attributed to a neurohormonal pathway.[20–22]

The next major development in the experimental literature was the discovery that the heart could be protected remotely by applying the remote ischaemic preconditioning (RIPC) stimulus to the lower limb,[23,24] providing a non-invasive and practical approach for remotely protecting the heart. In 2002, Kharbanda et al.[25] first pioneered a non-invasive RIPC protocol in human volunteers, in which a standard blood pressure cuff was placed on the upper arm and inflated to 200 mmHg to and deflated to 0 mmHg to induce three 5-min cycles of ischaemia and reperfusion to the skeletal tissue of the lower arm, using flow mediated dilatation as the read-out. Furthermore, it was found that the remote ischaemic conditioning stimulus could be applied either prior (RIPC) to, or after the onset of (RIPerC) the index myocardial ischaemia[9] or even at the onset of myocardial reperfusion (RIPost),[26] facilitating its application to a wide variety of clinical settings of IRI,[20] including cardiac bypass[27,28] and abdominal aortic aneurysm surgery,[29] elective percutaneous coronary intervention,[30] and most recently, STEMI patients undergoing PPCI.[31–33]

At the beginning of 2010, two independent clinical studies were published investigating the effect of RIPerC in STEMI patients undergoing PPCI.[31,32] In the study by Rentoukas et al.,[31] 96 STEMI patients were randomised at the hospital to receive control (three 4-min inflations to 20 mmHg below diastolic blood pressure and deflations to 0 mmHg of upper arm cuff started 10 min before reperfusion), RIPerC (three 4-min inflations to 20 mmHg above systolic blood pressure and deflations to 0 mmHg of upper arm cuff started 10 min before reperfusion) or RIPerC+morphine (5 mg intravenous infusion initiated 5 min before reperfusion). Interestingly, patients receiving RIPerC+morphine prior to PPCI had better ST-segment resolution, lower peak tropinin I levels compared to control patients. In those STEMI patients who received RIPerC alone, there was a non-significant trend to benefit when compared to control patients.[31] In the larger study by Botker et al.,[32] the STEMI patients were randomised in the ambulance to receive control (a deflated cuff placed on the upper arm for 40 min) or RIPerC (four 5-min inflations to 200 mmHg and deflations to 0 mmHg of upper arm cuff). Because patients in the ambulance were randomised prior to coronary angiography and as the primary endpoint was myocardial salvage index at 30 days post PPCI estimated by gated single photon emission CT (SPECT), although 333 patients were randomised, only 142 patients were analysed for the primary endpoint of myocardial salvage.[32] Those patients randomised to RIPerC had a greater myocardial salvage index when compared to control (0.75 vs. 0.55, p=0.0333), although there was no significant difference in final MI size at 30 days (4% vs. 7% of LV, p=0.1).[32] However, in those patients presenting with LAD STEMI and complete occlusion in the infarct-related coronary artery (TIMI 0 flow), in whom the AAR was greater, there was a greater reduction in final MI size at 30 days in those patient treated with RIPC when compared to control (8% vs. 16% of LV with LAD STEMI, p=0.01 and 9% vs. 13% of LV with TIMI 0, p=0.06), despite there being little difference in the myocardial salvage index.[32] It is important to note there were no significant differences in important secondary outcomes including peak tropinin T, ST-segment resolution, LVEF at 30 days,[32] although a post-hoc analysis did observe a modest improvement in LVEF at 30 days in those patients with AAR >35% or those with LAD infarcts.[33]

How the timing of the RIPerC protocol impacts on the cardioprotective effects of RIPerC is unclear. In the study by Rentoukas et al.,[31] the RIPerC protocol was initiated in the cardiac catheter laboratory 10 minutes prior to the first angioplasty balloon inflation and it overlapped with reperfusion. In contrast, in the study by Botker et al.,[32] the RIPerC protocol was delivered in the ambulance by paramedics, as the transit times are longer in Denmark, one may expect the earlier application to be more effective, which may in part explain the different in results between the two studies. Further studies are needed to confirm the cardioprotective benefits of RIPerC particularly in those patients most likely to benefit. Whether, the improved myocardial salvage conferred by RIPerC translates into improved clinical outcomes post PPCI remains to be determined in a large multicentre randomised clinical trial. Furthermore, whether RIPerC is effective in STEMI patients undergoing myocardial reperfusion using thrombolytic therapy, a group of patients not amenable to IPost, is unknown at present.

Several other mechanical cardioprotective strategies, which also recruit some of the signalling pathways utilized in IPost, and which have shown therapeutic potential when applied as adjuncts to PPCI, include therapeutic hypothermia and hyperbaric hyperoxaemia (Table 2). Of these two, therapeutic hypothermia is currently been investigated in the ongoing CHILL-MI study (www.clinicaltrials.gov: NCT01379261).

Pharmacological conditioning as an adjunct to PPCI

A number of pharmacological agents designed to prevent lethal myocardial reperfusion injury by targeting one of its individual components have been investigated as adjuncts to PPCI. Unfortunately, the results from the vast majority of these clinical studies have been hugely disappointing. The reasons for this are multifactorial and include inconclusive

Table 2. Novel interventional adjuncts to primary percutaneous coronary intervention with clinical potential

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Outcome measures
Therapeutic hypothermia				
Dixon et al. (2002)[65]	42 patients	Experimental data suggests that lowering myocardial temperature during ischaemia but not reperfusion can limit MI size by reducing metabolic demand	Cooling using the Radiant SetPoint Endovascular Temperature Management System to lower body core temperature to 34°C (mean temperature at reperfusion of 34.7±0.9°C)	Major adverse cardiac events occurred in (0% vs. 10% control, $p>0.05$)
	Ant/Inf STEMI			Median MI size at 30 d by SPECT (2% vs. 8% control of LV, $p>0.05$)
	<6 h			Endovascular cooling safe
	All TIMI flow			
	Collaterals included			
O'Neill et al. (2003)[66] (COOL-MI)	325 patients		Cooling using the Radiant SetPoint Endovascular Temperature Management System to lower body core temperature to 34°C (mean temperature at reperfusion of 34.7±0.9°C)	No difference in MI size at 30 d by SPECT (13.8% control vs. 14.1%, $p>0.05$)
	Ant/Inf STEMI			Longer door-PCI time in treated group (92±47 min vs. 110±41 min, $p=0.0003$)
	<6 h			Ant MI patients in whom temperature lowered to 35°C MI size was significantly reduced
	All TIMI flow			Plan to organize COOL-MI II trial
	Collaterals included			
Grines et al. (2004)[67] (ICE-IT-1)	224 patients		Cooling using the Philips Innercool Celsius Control System to lower body core temperature	No difference in MI size at 30 d by SPECT (10.2% control vs. 13.2%, $p=0.14$)
	Ant/Inf STEMI			Only one-third of patients achieved 35°C by reperfusion
	<6 h			Plan to organize ICE-IT-2 trial
	All TIMI flow			
	Collaterals included			
Dixon et al. (2007) (COOL-MI; IINCT00248196)	225 patients		Cooling using the Radiant Reprieve Endovascular Temperature Therapy System to lower body core temperature for 30 min prior to PPCI	Primary endpoint has been MI size by SPECT
	Ant/Inf STEMI			Study aborted 2008
	<6 h			
	All TIMI flow			
	Collaterals included			

(Continued)

Table 2. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Outcome measures
Gotberg et al. (2010)[41] (RAPID-MI-ICE)	20 patients	Cooling by infusion of cold saline endovascular cooling achieved 35°C without significant delay in door-PCI time	Cooling by IV infusion of 1−2 litres of cold saline and central venous catheter cooling with Philips InnerCool RTx Endovascular System prior to PPCI achieved core body temperature of 35°C without delaying door-PPCI time	Significant reduction in MI size as % of AAR on CMR at 4 d (29.8±12.6% vs. 48.0±21.6%, p=0.041)
	Ant/Inf STEMI			Significant reduction (43%) in peak and cumulative tropinin T release
	<6 h			Plan to organise CHILL-MI trial
	All TIMI flow			
	Collaterals included			
Erlinge et al. (CHILL-MI; NCT01379261)	120 patients		Cooling by IV infusion of 1−2 litres of cold saline and central venous catheter cooling with Philips InnerCool RTx Endovascular System prior to PPCI and continued for 1 h after	Ongoing multicentre study will investigate whether cooling prior to PPCI reduces MI size (as a % of AAR) by CMR at 4 days
	Ant/Inf STEMI			Scheduled to complete recruitment by May 2012
	<6 h			
	All TIMI flow			
	Collaterals included			
Therapeutic hyperoxaemia				
Dixon et al. (2002)[68]	29 patients	Experimental data suggests that hyperbaric oxygen reduces MI size by decreasing tissue oedema, reducing formation of lipid peroxide radicals, altering NOS expression and inhibition of leukocyte adherence, and plugging in the microcirculation	IC hyperbaric hyperoxaemic reperfusion started after PPCI and continued for 60−90 min	No adverse events
	Ant/Inf STEMI			Improved WMSI at 24 h
	<24 h			Trend to increased LVEF
	All TIMI flow			Therapeutic hyperoxaemia safe
	Collaterals included			Plan for AMIHOT trial

(Continued)

Table 2. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Outcome measures
O'Neill et al. (2007)[69] (AMIHOT I)	269 patients		IC hyperbaric hyperoxaemic reperfusion started after PPCI and continued for 90 min	No difference in primary endpoints (14 d MI size
	Ant/Inf STEMI			No difference in 30 d major adverse cardiac events (5.2% vs. 6.7%, p=0.62)
	<24 h			Ant STEMI patients <6 h had greater improvement in WMSI, smaller MI size and improved STR
	All TIMI flow			Plan for AMIHOT-II trial
	Collaterals included			
Stone et al. (2009)[70] (AMIHOT II)	281 patients		IC hyperbaric hyperoxaemic reperfusion started after PPCI and continued for 90 min	No adverse events
	Ant STEMI			No difference in MI size by SPECT at 14 d or peak CK-MB or tropinin
	<6 h			No difference LVEF
	All TIMI flow			Pooled analysis of AMIHOT I and II trials suggested beneficial effects on MI size and major adverse cardiovascular events
	Collaterals included			

AAR, area at risk; CMR, cardiac MRI; LV, left ventricular; MI: myocardial infarct; PPCI: primary percutaneous coronary intervention; SPECT, single photon emission CT; STEMI: ST-segment elevation MI; STR: ST-segment resolution; TIMI, thrombolysis in myocardial infarction; WMSI, wall motion score index.

experimental studies, the timing of the intervention, and the patient selection (issues that are discussed in Table 3 and a later section). However, the elucidation of the signal transduction pathways underlying IPost have identified several novel targets for cardioprotection, a few of which have shown benefit in initial proof-of-concept clinical studies (Table 4). The most promising of these pharmacological adjuncts include natriuretic peptide,[34] cyclosporin A,[35] and exenatide.[36] Further studies are required to confirm the efficacy of these therapeutic agents and to determine whether they can improve clinical outcomes in STEMI patients undergoing PPCI. In this regard, the CIRCUS study will investigate whether cyclosporin A can improve clinical outcomes in this patient group.

Cardiac MRI for assessing efficacy of adjunctive therapy in PPCI patients

Cardiac magnetic resonance (CMR) imaging of STEMI patients after they have undergone PPCI which is safe in the first week following PPCI, has emerged as an important imaging modality. From a clinical perspective in the first 2−3 days post PPCI, the CMR scan can be used to exclude LV thrombus, measure acute MI size, LV chamber size and ejection fraction, and assist in the diagnosis of troponin-positive chest pain where the coronary angiogram is normal such as in myocarditis. Repeated imaging at 3−6 months post PPCI permits the assessment of final MI size and ejection fraction after post MI remodelling. CMR imaging can also be used to detect the presence of microvascular obstruction[37] and intramyocardial haemorrhage,[38] key features of lethal myocardial reperfusion injury, which are associated with worse clinical outcomes following PPCI.

Crucially, CMR can be used to assess myocardial salvage of novel cardioprotective strategies given as adjuncts to PPCI. Experimental animal studies have shown that 2 days following reperfusion of an acute MI in the canine heart, the area of myocardial oedema detected by T2-weighted CMR imaging corresponded to the AAR, assessed by the gold-standard technique of fluoroscopic microspheres.[39] In PPCI patients, the increase in signal intensity detected by T2-weighted CMR imaging in the first week following the STEMI, corresponded to the AAR delineated by myocardial nuclear scanning,[40] the current gold-standard technique for assessing AAR in the clinical setting. A couple of clinical studies have already applied T2-weighted imaging for the assessment of the AAR in order to index infarct size to the AAR[41] or to estimate myocardial salvage[36] when investigating novel adjuncts to PPCI. This area of research is not without controversy with experimental animal studies suggesting that T2-weighted CMR imaging overestimates the AAR;[42] questions over the validity of using an indirect measure such as myocardial oedema to depict the AAR; and whether the T2-weighted CMR imaging technique is robust enough in the acutely unwell PPCI patient to measure AAR. Whether the development of more robust T2 mapping CMR sequences[43,44] or other novel CMR sequences[45] will facilitate use of CMR to retrospectively determine the AAR and therefore be used to measure myocardial salvage in PPCI patients remains to be determined.

Improving the translation process for clinical cardioprotection

Apart from early myocardial reperfusion, there is no other therapeutic strategy for limiting MI size in STEMI patients. Since the possibility of infarct-size limitation was first proposed in the late 1960s, a vast number of therapeutic agents have been identified in experimental studies to limit MI size. However, the vast majority of these treatments have not been translated into the clinical setting (Table 3). There are many reasons for this failure to translate cardioprotective therapies from the experimental setting to the clinical arena, and many of these have been discussed in the published literature[46–50] and reviewed in the section on ischaemic postconditioning. To summarize the key issues, the main obstacles to translation include the use of experimental animal MI models which poorly represent the STEMI patient undergoing PPCI, the failure to thoroughly test the novel treatment agent in the preclinical setting before moving onto clinical studies, and finally the design of the clinical studies. In 2004, the National Heart, Lung, and Blood Institute (NHLBI) first convened a workshop to discuss this issue,[46] and in 2010 proposed the formation of the US multicentre Consortium for Preclinical Assessment of Cardioprotective Therapies (CAESAR), which was set up to test novel cardioprotective strategies in small and large animal MI models using a multicentre randomised controlled 'clinical' trials approach.[51] This initiative will hopefully result in only the most robust cardioprotective strategies reaching the clinical setting.

Conclusions

Despite early reperfusion and improvements in anti-platelet and thrombotic therapy, the mortality of STEMI patients undergoing PPCI remains significant. One major contributing factor is the inability to protect the heart against the detrimental effects of lethal myocardial reperfusion injury, which occur on restoring blood flow to the acutely ischaemic myocardium. Previous attempts to prevent lethal myocardial reperfusion injury using pharmacological adjuncts to PPCI have been disappointing. However, a number of novel therapeutic strategies, which have been demonstrated in experimental studies to 'condition' the heart to protect itself against lethal myocardial reperfusion injury, have been reported in clinical proof-of-concept studies to prevent lethal myocardial reperfusion injury, as evidenced by reduced MI size and improved LV function. The more

Table 3. Major studies investigating pharmacological adjuncts to primary percutaneous coronary intervention

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Results
Anti-inflammatory agents				
Granger et al. (2003)[71] (COMMA)	960 patients	Pexelizumab is an anti-inflammatory antibody which has been reported to reduce MI size by binding to and inhibiting the C5 component of complement pathway	Intravenous pexelizumab 2 mg/kg bolus only given prior to PPCI. Or bolus followed by 0.05 mg/kg/h infusion for 24 h	No difference in primary endpoint of AUC CK-MB
	All STEMI			However, the 90-d mortality rate was significantly lower with pexelizumab bolus plus infusion (1.8% vs. 5.9% with placebo, p=0.014)
	<6 h			Therefore, APEX-MI planned
	All TIMI flow			
	Collaterals included			
Armstrong et al. (2007)[72] (APEX-MI)	5745 patients		Intravenous pexelizumab 2 mg/kg bolus given over 10 min prior to PPCI followed by 0.05 mg/kg/h infusion for 24 h	No difference in primary endpoint of 30 day death (pexelizumab 4.1% vs. 3.9% placebo)
	All STEMI			
	<6 h			
	All TIMI flow			
	Collaterals included			
Atar et al. (2009)[73] (F.I.R.E.)	232 patients	FX06 is a cleavage product of fibrin which inhibits inflammation by preventing the activation of endothelial VEcadherin	IV bolus of FX06 (200 mg) immediately prior to guidewire crossing obstruction and then repeated 10 min later	No difference in MI size by CMR at 5 days or 4 months
	All STEMI	Animal studies report MI reduction with FX06		No difference in MI size by tropinin
	<6 h			
	All TIMI flow			
	Collaterals included			
Adenosine				
Ross et al. (2005)[74] (AMISTAD II)	2118 patients	Adenosine has been reported to protect the heart in experimental studies by activating pro-survival kinases and anti-inflammatory mechanism	Intravenous infusion of adenosine 50 or 70 μg/kg/min for 3 h. Started after PPCI	No difference in primary endpoint of primary end point was new CHF beginning <24 h after randomization, or the first re-hospitalization for CHF, or death from any cause within 6 months
	Ant STEMI	However, whether it was effective at reperfusion was inconclusive		Subsequent post-hoc analysis suggested that in patients presenting within 3.17 h there was a beneficial effect with adenosine
	<6 h			Experimental evidence inconclusive
	All TIMI flow			
	Collaterals included			

(Continued)

Table 3. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Results
Glucose insulin potassium (GIK) therapy				
Mehta et al. (2005)[75] (CREATE-ECLA)	20,201 patients	GIK therapy reported in experimental studies to limit MI size via the activation of pro-survival kinases	IV infusion of GIK (25% glucose, 50U/l insulin, 80 mEq/lof potassium to be infused at a rate of 1.5 ml/kg/h) for 24 h. Started after reperfusion in majority of patients	No difference in 30 d mortality (9.7% placebo vs. 10.0% GIK)
	All STEMI	Initial promising clinical studies		Majority of patients treated by thrombolysis and not PPCI
	Most patients received thrombolysis			GIK administered prior to reperfusion in only 1437 patients
	<12 h			
	All TIMI flow			
	Collaterals included			
Nicorandil				
Kitakaze et al. (2007)[34] (J-WIND)	545 patients	Nicorandil is an anti-anginal which is also known to limit MI size via the activation of the mitochondrial KATP channel and the release of nitric oxide, both of which are known mediators of IPost	IV bolus of nicorandil (0·067 mg/kg) followed by infusion at 1·67 μg/kg/min for 72 h. Started after PPCI	No difference in MI size or LVEF
	All STEMI			Nicorandil was given after PPCI
	<12 h			Inconclusive whether nicorandil administered at reperfusion was protective in experimental studies
	All TIMI flow			
	Collaterals included			
Erythropoietin				
Ferriario et al. (2009)[76]	30 patients	EPO is a haemopoietic cytokine which is also known to limit MI size at reperfusion via the intracellular activation of the RISK pathway (a known mediator of IPost)	IV EPO 33,000 iU prior to PPCI repeated 24 and 48 h later	30% reduction in 120 h AUC CK-MB but no difference in MI size using CMR at 3 days and 6 months
	All STEMI	Large animal studies inconclusive		
	<6 h			
	All TIMI flow			
	Collaterals included			
Suh et al. (2010)[77]	57 patients		IV EPO 50 iU/kg prior to PPCI	No beneficial effects on MI size (assessed by 72 h AUC CK-MB and CMR at 4 days)
	Ant STEMI			
	<12 h			
	TIMI 0 flow			
	Collaterals included			

(Continued)

Table 3. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Results
Ozawa et al. (2010)[78] (EPO-AMI-1)	36 patients		IV EPO epoetin-beta 12,000 iU after (within 24 h) PPCI	Increase in LVEF at 6 months
	STEMI			
	<24 h			
	All TIMI flow			
	Collaterals included			
Voors et al. (2010)[79] (HEBE-III)	529 patient		IV EPO epoetin-alpha 60,000 iU after (within 3 h) PPCI	No difference in primary endpoint of LVEF at 6 weeks
	STEMI			No difference in MI size (AUC CK-MB or tropinin T)
	<12 h			More major adverse cardiac events occurred with EPO
	All TIMI flow			
	Collaterals included			
Tanaguichi et al. (2010)[80] (EPOC-AMI)	35 patients		IV EPO epoetin-alpha 6000 iU after (within 3 h) PPCI repeated 24 and 48 h later	Improvement in LVEF and smaller MI size at 4 days and 6 months by SPECT
	STEMI			
	<12 h			
	All TIMI flow			
	Collaterals included			
Ott et al. (2010)[81] (REVIVAL-3)	138 patients		IV EPO epoetin-beta 33,000 iU immediately after PPCI repeated 24 and 48 h later	No difference in LVEF at 6 months assessed by CMR (primary endpoint)
	STEMI			No difference in MI size (5 days and 6 month CMR)
	<12 h			
	All TIMI flow			
	Collaterals included			
Ludman et al. (2011)[82]	52 patients		IV EPO epoetin-beta 50,000 iU prior to PPCI repeated 24 h later	No difference in MI size at 3 days using CMR and troponin T
	All STEMI			Doubling of incidence of MVO on CMR
	<12 h			
	All TIMI flow			
	No collaterals			
Rao et al. (2011) (REVEAL, unpublished)	138 patients		IV EPO epoetin-beta 60,000 iU immediately after PPCI repeated 24 and 48 h later	No difference in MI size on CMR within 6 days and 3 months

(Continued)

Table 3. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Results
	STEMI			Trend to increased adverse events in patients over 70 years old
	<8 h			
	All TIMI flow			
	Collaterals included			
Protein kinase C-δ inhibitor				
Bates et al. (2008)[83] (DELTA-MI)	154 patients	A drug which is known to limit MI size by inhibiting the pro-apoptotic protein kinase, PKC-δ. This mechanism also contributes to IPost	Intracoronary KAI-9803 (delcasertib) at different doses (0.05, 0.5, 1.25 and 5.0 mg) administered in two divided doses prior to and after PPCI	Safe, efficacy not primary endpoint but non-significant reductions in MI size by CK-MB and SPECT
	Ant STEMI			
	<6 h			
	All TIMI flow			
	No collaterals			
Lincoff et al. (2011) (PROTECTION-AMI, unpublished)	1083 patients		Intravenous KAI-9803 (delcasertib) at different doses 50, 150, and 450 mg/h) for 24 h started prior to PPCI	No difference on primary endpoint of infarct size as assessed by CK-MB AUC
	Ant/Inf STEMI			Takes 5–30 min to reach steady state after infusion begun
	<6 h			
	All TIMI flow			
	No collaterals			
Atorvastatin				
Kim et al. (2010)[84] STATIN STEMI	171 patients	A variety of pleiotropic effects including MI size reduction via the direct intracellular activation of the RISK pathway (a known mediator of IPost)	Atorvastatin 80 mg versus atorvastatin 10 mg prior to PPCI	No effect on primary endpoint of (death, MI, revasc)
	STEMI			No difference in MI size (CKMB max)
	<12 h			Improved myocardial perfusion (blush grade, STR)
	All TIMI flow			
	No collaterals			

AUC, area under the curve; CHF, congestive heart failure; CK, creatine kinase; CMR, cardiac MRI; EPO, erythropoietin; IPost, ischaemic postconditioning; LVEF, left ventricular ejection fraction; MI, myocardial infarct; MVO, microvascular obstruction; PPCI, primary percutaneous coronary intervention; SPECT, single photon emission CT; STEMI, ST-segment elevation MI; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction.

Table 4. Novel pharmacological adjuncts to PPCI with clinical potential

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Outcome measures
Atrial natriuretic peptide				
Kitakaze et al. (2007)[34] (J-WIND)	569 patients	A natriuretic peptide which is also known to limit MI size via the intracellular activation of the RISK pathway (a known mediator of IPost)	IV carperitide infusion at 0.025 μg/kg per min for 3 days started after PPCI	14.7% reduction in MI size (total CK AUC)
	All STEMI <12 h			2.5% increase in LVEF at 6–12 months
Cyclosporin-A				
Piot et al. (2008)[58]; Mewton et al. (2010)[35,85]	58 patients	An immunosuppressive agent which is also known to inhibit the opening of the mitochondrial permeability transition pore (a known mediator of lethal myocardial reperfusion injury and a target of IPost)	IV CsA (2.5 mg/kg) 10 min prior to PPCI	44% reduction in MI size (72 h AUC total CK)
	Ant/Inf STEMI			20% reduction in MI size (CMR in subset of 27 patients)
	<12 h			Non-significant 13% reduction in MI size (72 h AUC tropinin I)
	TIMI 0 flow			28% reduction in MI size and smaller LVESV on CMR at 6 months
	Collaterals included			
Ovize et al. (CIRCUS)	?1000 patients		IV CsA (2.5 mg/kg) 10 min prior to PPCI	Ongoing multicentre clinical trial investigating whether CsA can improve clinical outcomes in PPCI patients
	Ant/Inf STEMI <12 h TIMI 0 flow No collaterals			
Glucagon-like peptide 1				
Nikolaides et al. (2004)[86]	22 patients	GLP-1 is an insulin incretin which is also known to limit MI size via the direct intracellular activation of the RISK pathway (a known mediator of IPost)	IV infusion of GLP-1 (1.5 pmol/kg per minute) for 72 h started 2 h after PPCI	Improved LVEF, better regional wall motion at 6–12 h
	All STEMI LVEF <40% <6 h			

(Continued)

Table 4. (Continued)

Study	Patients	Mechanism of cardioprotection	Therapeutic strategy	Outcome measures
Lonborg et al. (2011)[36]	107 patients	Exenatide is an analogue of GLP-1 which is also known to limit MI size via the direct intracellular activation of the RISK pathway (a known mediator of IPost)	IV infusion of exenatide (25 mg in 250 ml saline) started 15 min prior to PPCI at a flow rate of 72 ml/h for 15 min then maintained at 26 ml/h for 6 h	Increase in myocardial salvage index at 90 d by CMR (0.71 vs. 0.62, p=0.003)
	All STEMI			Reduced MI size as % of AAR at 90 d by CMR (0.30 vs. 0.39, p=0.003)
	<12 h			Trend to smaller MI size at 90 d by CMR (13 g vs. 17 g, p=0.11)
	TIMI 0 flow			No difference in LVEF at 90 d by CMR, peak tropinin T, 30 d clinical events
	Collaterals included			
TRO40303				
Atar et al. (MitoCare; NCT01374321)	180 patients	TRO40303 is a drug which indirectly inhibits the opening of the mitochondrial permeability transition pore (a known mediator of lethal myocardial reperfusion injury and a target of IPost)	Peripheral IV infusion (35 ml/min) of TRO40303 of 6 mg/kg of TRO40303 at 5–15 min prior to PPCI	Ongoing phase 2 clinical trial to investigate whether TRO40303 reduces MI size (72 h AUC CK and tropinin I)
	All STEMI			
	<6 h			
	TIMI 0–1 flow			
	Collaterals included			
Nitrites				
Frennaux et al. (NIAMIIS; RCTN 57596739)	200 patients	Experimental studies have shown that administration of sodium nitrite reduces MI size	Intravenous bolus of sodium nitrite given 5 min prior to PPCI	Ongoing study
	All STEMI			Primary endpoint is MI size as a % of AAR at 10–14 d by CMR
	<12 h			Expected to complete by 30 January 2013
	TIMI 0–1 flow			
	Collaterals included			

AAR, area at risk; AUC, area under the curve; CK, creatine kinase; CMR, cardiac MRI; IPost, ischaemic postconditioning; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarct; PPCI, primary percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation MI; TIMI, thrombolysis in myocardial infarction.

promising amongst these include mechanical 'conditioning' strategies such as ischaemic postconditioning, remote ischaemic perconditioning, therapeutic hypothermia or hyperoxaemia, and pharmacological 'conditioning' strategies such as natriuretic peptide, cyclosporin-A, and exenatide. Large multicentre studies are now required to investigate preventing lethal myocardial reperfusion injury using these novel therapeutic strategies improve clinical outcomes in STEMI patients undergoing PPCI.

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