World Journal of Cardiology

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DOI: 10.4330/wjc.v6.i6.434

World J Cardiol 2014 June 26; 6(6): 434-443
ISSN 1949-8462 (online)

TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (5): Myocardial infarction

Novel adjunctive treatments of myocardial infarction

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Author contributions: Schmidt MR drafted the manuscript; Pryds K commented and revised the manuscript; Bøtker HK provided the idea for the manuscript, and completed manuscript revision and finalized the manuscript.

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Received: December 28, 2013 Revised: January 23, 2014
Accepted: April 17, 2014
Published online: June 26, 2014

Abstract

Myocardial infarction is a major cause of death and disability worldwide and myocardial infarct size is a major determinant of prognosis. Early and successful restoration of myocardial reperfusion following an ischemic event is the most effective strategy to reduce final infarct size and improve clinical outcome, but reperfusion may induce further myocardial damage itself. Development of adjunctive therapies to limit myocardial reperfusion injury beyond opening of the coronary artery gains increasing attention. A vast number of experimental studies have shown cardioprotective effects of ischemic and pharmacological conditioning, but despite decades of research, the translation into clinical effects has been challenging. Recently published clinical studies, however, prompt optimism as novel techniques allow for improved clinical applicability. Cyclosporine A, the GLP-1 analogue exenatide and rapid cooling by endovascular infusion of cold saline all reduce infarct size and may confer clinical benefit for patients admitted with acute myocardial infarcts. Equally promising, three follow-up studies of the effect of remote ischemic conditioning (RIC) show clinical prognostic benefit in patients undergoing coronary surgery and percutaneous coronary intervention. The discovery that RIC can be performed noninvasively using a blood pressure cuff on the upper arm to induce brief episodes of limb ischemia and reperfusion has facilitated the translation of RIC into the clinical arena. This review focus on novel advances in adjunctive therapies in relation to acute and elective coronary procedures.

Key words: Myocardial infarction; Primary percutaneous intervention; Coronary artery by-pass graft; Ischemia-reperfusion injury; Ischemic preconditioning; Remote ischemic conditioning; Cyclosporine; Cooling; Exenatide

Core tip: Patients with ischemic heart disease have a high risk of developing myocardial infarction, which is associated with considerable morbidity and mortality. Limiting the detrimental consequences of myocardial infarction is a major focus of cardiovascular research. Recent clinical studies suggest that novel adjunctive therapy with pharmacological and ischemic conditioning reduce ischemia-reperfusion injury in patients during coronary procedures. In three independent randomized trials, remote ischemic conditioning (RIC) improves clinical outcome in patients undergoing acute or elective percutaneous intervention or coronary artery by-pass surgery. RIC can be performed safely and non-invasively by intermittent inflation of a blood-pressure cuff on the upper arm and is easily applicable in most clinical settings.

Schmidt MR, Pryds K, Bøtker HE. Novel adjunctive treatments of myocardial infarction. *World J Cardiol* 2014; 6(6): 434-443 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i6/434.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i6.434

INTRODUCTION

Heart disease and stroke are the leading causes of death

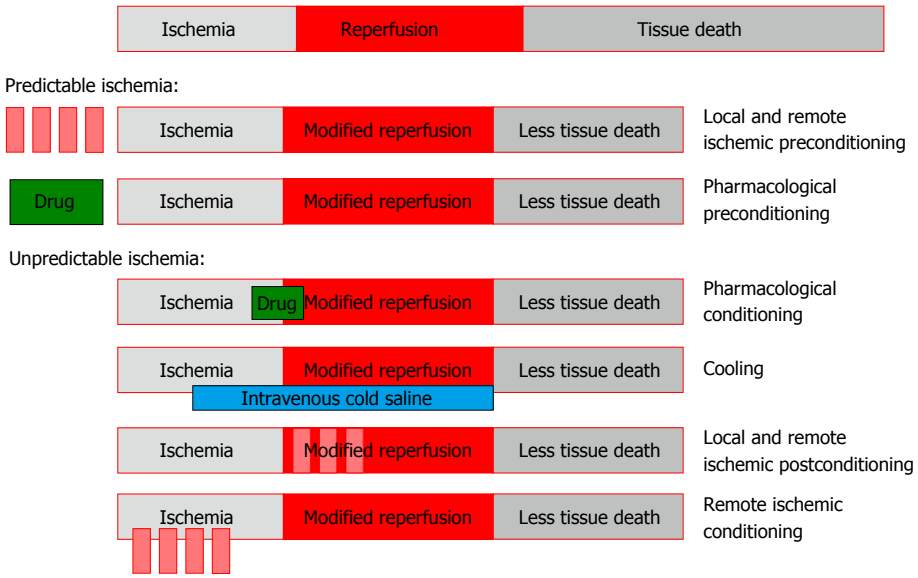

Figure 1 Overview of interventional strategies for achieving cardioprotection as adjunct to thrombolysis or primary percutaneous coronary intervention, see text for details.

worldwide[1,2]. Since 1990, more people have died from coronary artery disease than any other death cause[3,4].

In China, a staggering 230 million are estimated to suffer from cardiovascular disease, and three million Chinese die of cardiovascular disease annually, accounting for 41% of all deaths[5,6]. In the United States alone, cardiovascular diseases, including ischemic heart disease and stroke, account for more than one-third deaths and an estimated 900000 heart attacks and 800000 strokes occur each year. In the remaining parts of the world, from the Sub-Saharan developing countries over booming South America to affluent areas in Europe and Asia, similar patterns are seen[7,8].

Globally, socio-demographic factors, unhealthy life style, escalating obesity and suboptimal control of risk factors are likely to further aggravate the disease burden over the coming decades[9]. In the Western world, nearly half of the male and a third of the female population will develop coronary artery disease[10]. Partly driven by urbanization and adoption of Western life style, China undergoes a transition towards a similar health statistic[11].

The pandemic of cardiovascular disease has immense negative effects on global population health and life expectancy. While attempts to modify risk factor and life style related growth in cardiovascular disease are important and have been successful in some parts of the world[8], improved treatment of acute and chronic cardiovascular disease is also crucial to alleviate the disease burden.

This review will focus on novel advances in the treatment of coronary artery disease, particularly the recent reports of successful adjunctive therapy in relation to elective percutaneous coronary intervention (PCI), coronary artery by-pass graft surgery (CABG), and acute angioplasty (primary PCI) for ST-elevation myocardial infarction (STEMI).

PROTECTING THE HEART AGAINST ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury is the essence of myocardial infarction in relation to acute coronary events, but ischemia-reperfusion injury also occurs during planned procedures such as elective PCI and CABG, although usually to a lesser extent. As the term implies, not just the ischemia itself but also the following reperfusion harms the myocardium. Although reperfusion ultimately saves the ischemic myocardium and it may seem paradoxical that reperfusion induces myocardial injury, several biological phenomena explain for this effect [for detailed reviews, please see Hausenloy *et al*[12] (2013) and Heusch *et al*[13] (2013)]. Of potential clinical importance, ischemic and pharmacological conditioning of the myocardium can modify reperfusion injury and significantly reduce the tissue damage (Figure 1).

LOCAL ISCHEMIC CONDITIONING

Local ischemic preconditioning, induced by brief periods of ischemia before a sustained ischemic insult, has long been known to afford potent protection against ischemia-reperfusion injury[14]. However, the technique has inherent limitations as it requires interruption of blood flow to the target organ and, thus, can only be achieved in the operating room or during coronary angioplasty. Furthermore, additional time for the preconditioning procedure is required during surgery or during intervention. Preconditioning itself might cause deterioration of organ function or cause complications, such as emboli of atheroma, because of the intermittent aortic clamping or intermittent coronary balloon inflation. Hence, local ischemic preconditioning has not found widespread clinical use.

However, by instead applying the local ischemic con-

ditioning stimulus after the ischemic event (*e.g.*, at the time of reperfusion in primary PCI), so-called ischemic postconditioning, most of these obstacles for clinical use are overcome. In an experimental setting, ischemic postconditioning inhibits ischemia-reperfusion injury almost as efficiently as ischemic preconditioning[15,16]. Some clinical studies suggest that local ischemic postconditioning reduces myocardial injury in patients undergoing primary PCI for acute myocardial infarction[17,18], but another recently published trial did not confirm this effect[19]. Furthermore, a large-scale trial of 700 patients admitted with STEMI randomized to either standard primary PCI or primary PCI followed by postconditioning, failed to show any effect on myocardial reperfusion and clinical endpoints[20].

REMOTE ISCHEMIC CONDITIONING

Remote ischemic conditioning (RIC) by repeated short-lasting ischemia in a distant tissue-mostly achieved by intermittent interruption of circulation in a limb-has recently emerged as a promising adjunctive therapy to avoid organ damage, thereby improving the outcomes of well-established therapies.

From the site of the remote stimulus, through humoral[21] and neuronal[22,23] pathways, RIC activates several protective mechanisms in the target organ similar to those activated by local preconditioning. They include the reperfusion-injury salvage kinase[24] and survivor activating factor enhancement[25,26] signaling pathways. Furthermore, RIC modifies systemic inflammatory response[27,28], prevents endothelial dysfunction[29] and platelet activation[30] following ischemia-reperfusion injury.

In experimental studies, RIC has been shown to afford protection against ischemia-reperfusion in the liver[31], lung[32], kidney[33], brain[34], and heart[29].

The ability to induce organ protection by a simple, non-invasive stimulus has facilitated the translation of RIC into the clinical setting. In patients, RIC can be induced by 3-4 cycles of inflation (ischemia) and deflation (reperfusion) of a standard blood pressure cuff placed on a limb. Following the original description of the method in 1997[35] and its translation to humans in 2002[29], multiple randomized clinical trials have shown that RIC affords organ protection in many clinical ischemia-reperfusion syndromes, including the kidney[33,36], brain[37], and heart[38-41].

COOLING

Moderate hypothermia induced prior to reperfusion reduces infarct size in animal models[42-44]. A clinical pilot study has suggested that patients admitted with anterior STEMI who are rapidly cooled to a body temperature below 35 ℃ by the combination of cold saline infusion together with an endovascular cooling catheter before primary PCI develop smaller infarcts[45]. However, difficulties in applying the technique in the clinical setting without delaying treatment together with inconsistent results cause controversy about the clinical value and applicability[46], although a recent pooled analysis of two clinical trials indicate a potential beneficial effect[47]. Most recently, the CHILL-MI study, using a similar cooling technique as in the initial pilot study, showed that while cooling did not have a general cardioprotective effect, it seems to reduce infarct size in patients with anterior STEMI admitted for primary PCI within four hours of symptom onset. In addition, cooling caused a significant reduction in heart failure events[48]. A possible explanation for an overall lack of cardioprotective effect in the CHILL-MI study may be the fact that cooling below 35 ℃ was only achieved in 76% of the patients, and that sufficient cooling may be crucial for achieving cardioprotective effects.

PHARMACOLOGICAL CONDITIONING

The increasing insight into the mechanistic pathways involved in local and remote ischemic conditioning has encouraged identification of potential targets for pharmacological intervention against ischemia-reperfusion injury. A vast number of pharmacological agents have been shown to afford cardioprotection in experimental models, including adenosine[49], erythropoietin[50], rotigaptide[51], statins[52], atrial natriuretic peptide[53], glucose-insulin-potassium[54], P-selectin antagonist[55] cyclosporine[56], exenatide[57] and metoprolol[58]. A larger number of these agents have been tested in clinical studies (Table 1) with ambiguous results, the most promising being cyclosporine[64], exenatide[67] and metoprolol[75], all of which seem to consistently provide cardioprotection in the clinical setting. For a comprehensive review, please see Kloner (2013)[76]. However, an important limitation-and a potential explanation for the lack of success-of pharmacological conditioning with some drugs, is that most agents act through a single signaling pathway in the complex and interactive system of protective mechanisms activated by ischemic conditioning and cooling[13].

Cyclosporine

Cyclosporine, a widely used immunosuppressant drug, is believed to facilitate its cardioprotective effects by inhibition of mitochondrial permeability transition pore opening, thus preventing mitochondrial destruction[77]. In a study by Piot *et al*[64], administration of cyclosporine at the time of reperfusion in STEMI patients treated with primary PCI, was associated with a reduction in infarct size measured by creatine kinase and troponin I release. In a subgroup analysis, a similar reduction in infarct size was demonstrated on day 5 with cardiac magnetic resonance imaging (CMR). In a follow-up study, Mewton *et al*[78] found that this infarct-sparing effect of cyclosporine was persistent at 6 mo. However, in a more recent study, no effect was shown of early cyclosporine administration as an adjunct to thrombolysis in STEMI patients in relation to infarct size, left ventricular function, heart failure or death[65].

Table 1 Clinical studies using pharmacological adjunctive therapy in patients with acute myocardial infarction

	Intervention	*n*	Outcome
Adenosine			
Mahaffey *et al*[59], 1999 (AMISTAD)	Infusion of adenosine for 3 h as adjunct to thrombolysis	236	Reduction in infarct size
Kloner *et al*[60], 2006 (AMISTAD II)	Infusion of adenosine for 3 h	2118	No difference in death or heart failure
Atrial natriuretic peptide			
Kitakaze *et al*[61], 2007 (J-WIND)	Infusion of atrial natriuretic peptide for 3 d	569	Reduction in CK, increase in LVEF
Atorvastatin			
Kim *et al*[62], 2010 (STATIN-STEMI)	Oral atorvastatin 80 mg before primary PCI	171	No difference in death, revascularization or infarct size
Hahn *et al*[63], 2011	Oral atorvastatin 80 mg before primary PCI	173	No difference in infarct size
Cyclosporine A			
Piot *et al*[64], 2008	Infusion of cyclosporine before primary PCI	58	Reduction in infarct size
Ghaffari *et al*[65], 2013	Infusion of cyclosporine as adjunct to thrombolysis	101	No difference in infarct size, death, heart failure or LVEF
Erythropoietin			
Voors *et al*[66], 2010	Single dose erythropoietin	529	No difference in LVEF or infarct size
Exenatide			
Lønborg *et al*[67], 2012	Infusion of exenatide for 6 h	105	Reduction in infarct size
Bernink *et al*[68], 2012 (EXAMI)	Loading dose of exenatide before PCI followed by infusion for 72 h	39	No difference in left ventricular function or infarct size
Woo *et al*[69], 2013	Subcutaneously and intravenous exenatide before primary PCI followed by twice daily subcutaneous injection for 2 d	58	Reduction in infarct size and improvement of LVEF
Glucose-insulin-potassium			
Mehta *et al*[70], 2005 (CREATE-ECLA)	Infusion of GIK for 24 h	20201	No difference in mortality
Selker *et al*[71], 2012 (IMMEDIATE)	Out-of-hospital infusion of glucose-insulin-potassium	357	Reduced mortality among patients with cardiac arrest
δ-protein kinase C			
Bates *et al*[72], 2008	2 doses of KAI-9803	154	No difference in infarct size
Lincoff *et al*, 2014	Infusion of delcasertib for 24 h	1083	No difference in infarct size
P-selectin antagonist			
Mertens *et al*[73], 2006 (PSALM)	Infusion of recombinant P-selectin glycoprotein ligand-immunoglobulin as adjunct to thrombolysis	88	No difference in ST-segment resolution or LVEF
Tardif *et al*[74], 2013 (SELECT-ACS)	Infusion of inclacumab before PCI in NSTEMI patients	322	Reduction in troponin I and creatine kinase
Metoprolol			
Ibanez *et al*[75], 2013 (METOCARD-CNIC)	Infusion of metoprolol before primary PCI	220	Reduction in infarcts size and improvement of LVEF

LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; CK: Creatine kinase; NSTEMI: Non-ST-elevation myocardial infarction.

Exenatide

Exenatide, a glucagon-like peptide-1 analog, is primarily used as an anti-diabetic drug for patients with type 2 diabetes. However, in addition to its beneficial metabolic effect, exenatide is believed to induce cardioprotection through activation of ischemia-reperfusion injury survival pathways[79]. Lønborg *et al*[67] found that in STEMI patients, a 6 h infusion of exenatide started prior to primary PCI was associated with increased myocardial salvage measured by CMR. This increase in myocardial salvage from exenatide infusion translated to a reduction in final infarct size, although reserved for patients with short system delay (< 132 min from first medical contact to first balloon inflation)[80]. In a recent study by Woo *et al*[69], subcutaneous injection together with intravenous infusion of exenatide as adjunct to primary PCI followed by twice daily subcutaneous injections of exenatide for another two days, was associated with both a reduction in infarct size and improvement of left ventricular function.

Metoprolol

Most randomized clinical trials investigating potential infarct sparing effects of betablockers in STEMI patients have been conducted in the pre-reperfusion era, and only a few studies have evaluated the cardioprotective effect of beta-blockage as an adjunct to thrombolysis or primary PCI. However, recently, the METOCARD-CNIC trial demonstrated that intravenous metoprolol administrated to STEMI patients prior to primary PCI was associated with significantly smaller infarct size measured by CMR compared to primary PCI treatment alone. In addition, early metoprolol administration increased left ventricular function[75].

IMPROVING THE OUTCOME OF MYOCARDIAL INFARCTION IN PATIENTS

The translation of cardioprotective strategies to counter the detrimental consequences of ischemia-reperfusion in-

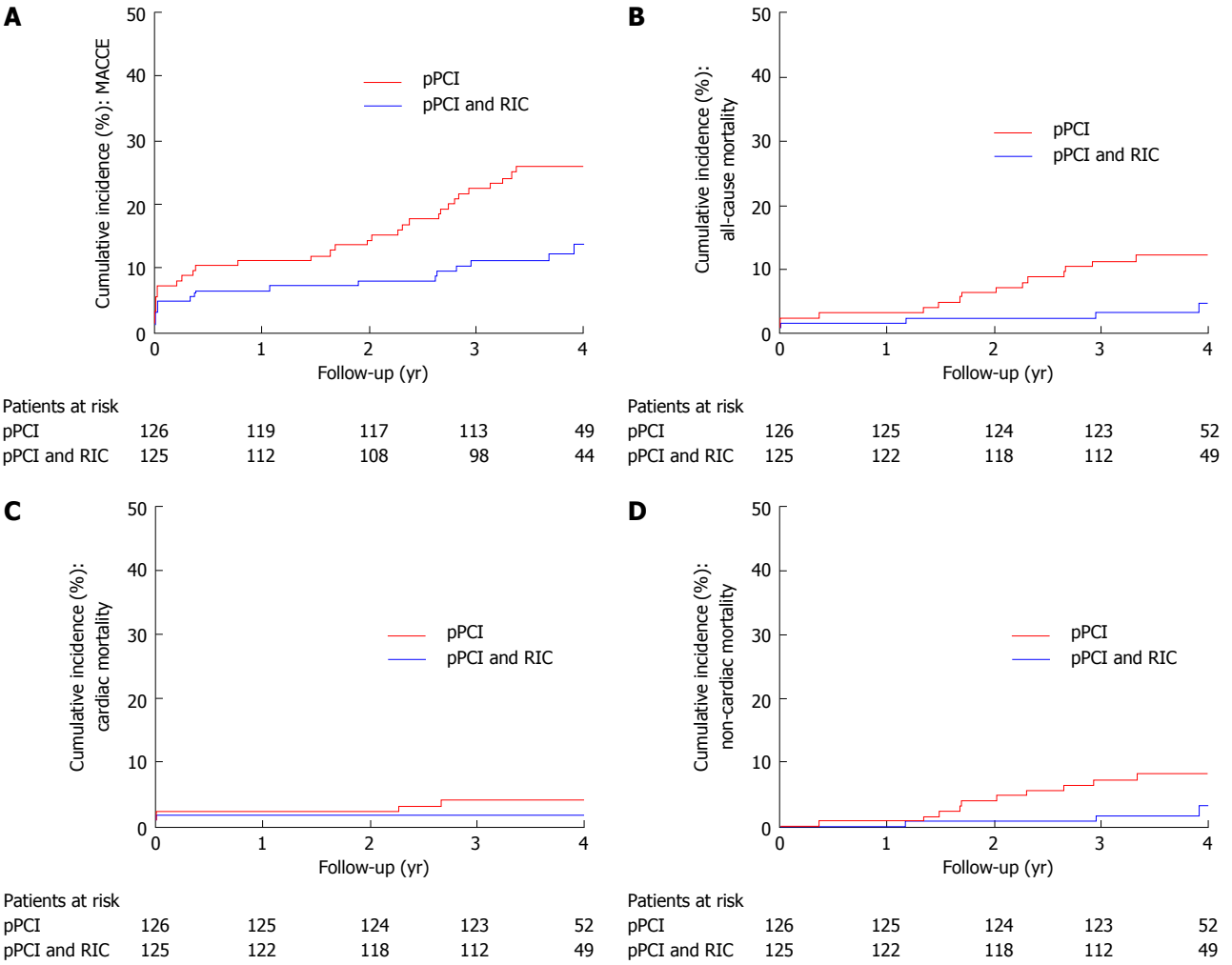

Figure 2 Effect of remote ischemic conditioning on long-term clinical outcome in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. Cumulative incidence (%). A: Of major adverse cardiac and cerebrovascular events (MACCE) by year since randomization (per-protocol analysis). P = 0.010; B: Of all-cause mortality by year since randomization (per-protocol analysis). P = 0.019; C: Of cardiac mortality (%) by year since randomization (per-protocol analysis). P = 0.248; D: Of non-cardiac mortality (%) by year since randomization (per-protocol analysis). P = 0.045. Modified from Sloth *et al*[89]. Eur Heart J (2014) 35: 168-175. pPCI: Primary percutaneous intervention; RIC: Remote ischemic conditioning.

jury is still in its infancy, and large-scale multicenter trials to show real-world clinical impact are lacking. However, recently published long-term clinical data on the use of RIC provide reason for optimism about a prognostic benefit of adjunctive therapy beyond opening the coronary artery.

REMOTE ISCHEMIC CONDITIONING IN PREDICTABLE ISCHEMIA

Predictable cardiac ischemia-reperfusion injury occurs in both elective PCI and CABG, and procedural tissue injury-as measured by biomarkers-is correlated to clinical outcome. Mid-scale clinical studies have shown that RIC applied prior to CABG[39,81] and PCI[38] reduces surrogate markers of myocardial injury, but until recently, the clinical relevance of these findings was questionable. However, two recent publications strongly suggest, that RIC should find a place as standard adjunctive therapy in elective PCI and CABG.

In a single center, randomized controlled trial, Davies *et al*[82] investigated the long-term clinical outcomes of 192 patients undergoing elective coronary angioplasty randomized to RIC or standard treatment. While their original study showed a significant reduction in troponin release in the RIC group[38], the follow-up study revealed that this translated into a reduced major adverse cardiac and cerebrovascular events (MACCE) rate up to 6 years after the coronary intervention.

In another single center, double-blinded trial, Thielmann *et al*[83] studied 329 low-risk patients undergoing elective isolated on-pump first-time CABG randomized to either standard CABG or CABG preceded by RIC. Besides reduced perioperative troponin I release as also shown previously by others[84], the authors found a reduction in all-cause and cardiac mortality as well as MACCE in the intervention group during the follow-up period that was a mean of 1.5 year. During the follow-up period, MACCE occurred 23 times in the control group *vs* 8 times in the RIC group (P = 0.011). The authors observed 11 deaths in the control group and only 3 deaths in the RIC group (P = 0.046). The combined endpoint

(death, MACCE and repeat revascularization) yielded a HR of 0.38 (0.21-0.70) in favor of RIC. Interestingly, Thielmann *et al*[83] also found that RIC reduced the occurrence of sepsis, stroke and non-cardiac deaths, which adds to the speculation that RIC could confer systemic beneficial effects beyond the organ exposed to ischemia-reperfusion injury.

REMOTE ISCHEMIC CONDITIONING IN UNPREDICTABLE ISCHEMIA

In unpredictable ischemic events, like myocardial infarction and stroke, rapid restoration of blood flow to the ischemic territory has been the primary focus. Optimization of prehospital admission logistics to reduce any delay improves outcome[85] and decreases mortality[86]. While acute thrombolysis and primary PCI have improved outcome, recent studies show that further injury occurs early after reperfusion and can continue long afterwards[87,88] emphasizing the need for therapies limiting clinical reperfusion injury in acute ischemic events.

In a study of 333 patients admitted with STEMI for primary PCI and randomized to either standard treatment or RIC performed in the ambulance during transportation to primary angioplasty, we showed, that RIC improves myocardial salvage index (0.75 in the RIC group *vs* 0.55 in the control group, $P = 0.033$) as measured by single-photon emission computed tomography[40]. Recently, Sloth *et al*[89] published 4-year follow-up data on our original study, showing that the improved myocardial salvage translates into clinical prognostic benefit, as MACCE occurred for 17 (13.5%) patients in the RIC treated group compared with 32 (25.6%) patients in the control group, yielding a HR of 0.49 (95%CI: 0.27-0.89, $P = 0.018$). Furthermore, only 5 deaths (4%) occurred in the intervention group compared with 15 (12%) in the control group, yielding a HR of 0.32 (95%CI: 0.12-0.88, $P = 0.027$) (Figure 2)[89]. Specific evaluation of death causes suggested a reduction in both cardiac and non-cardiac mortality, although only the latter was statistically significantly reduced (and most likely arose by chance). However, even when excluding non-cardiac deaths, MACCE was still reduced in the RIC group.

CONCLUSION

The globally increasing burden of cardiovascular disease calls for improved prevention and treatment. Acute and chronic coronary artery disease constitute the leading death cause in the World, and adjunctive therapies to limit the morbidity and mortality related to myocardial infarction may have major impact on global health. Pharmacological adjunctive therapy and rapid cooling decrease infarct size in some clinical studies but have yet to prove convincing clinical benefit. Remote ischemic conditioning-a low-cost, non-invasive and easily applicable adjunctive therapy-may confer prognostic benefit for patients undergoing coronary artery by-pass surgery and elective and acute percutaneous coronary interventions. Large-scale studies with clinical endpoints, such as the ERICCA trial (ClinicalTrials.gov NCT01247545), the RIPHeart-study (ClinicalTrials.gov NCT01067703) and the CONDI 2 trial (ClinicalTrials.gov NCT01857414) are, however, needed to confirm the clinical effect, before RIC should be applied as standard adjunctive therapy. Similarly, as an adjunctive therapy to primary PCI the CIRCUS trial (Clinicaltrials.gov NCT01502774) will clarify the potential clinical benefit of cyclosporine A, and the DANAMI-3 trial (Clinicaltrials.gov NCT01435408) the potential clinical efficacy of ischemic postconditioning.

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