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Remote ischaemic pre-conditioning does not affect clinical outcomes following coronary Artery bypass grafting. A systematic review and meta-analysis

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ABSTRACT

Background: Trials of remote ischemic pre-conditioning (RIPC) have suggested this intervention reduces complications of angioplasty and coronary artery by-pass grafting (CABG). The aim of this work was to conduct a systematic review and meta-analysis of the effects of RIPC on mortality and myocardial damage in patients undertaking coronary artery bypass grafting with/without valve surgery.
Methods: A systematic review and subsequent meta-analysis of randomized controlled trials of RIPC versus usual care or sham RIPC was performed.
Results: Eighteen studies, totalling 4551 participants were analysed. RIPC reduced post troponin release as indicated by area under the curve at 72 h ($\mu g \cdot L^{-1}$) Mean Difference (MD) −3.72 (95% CI −3.92 to −3.53, $p < 0.00001$). However there was no significant difference between RIPC and control when mortality odds ratio (OR) 1.27 (95% CI 0.87 to 1.86, $p = 0.22$); the incidence of new onset atrial fibrillation OR 0.82 (95% CI 0.67 to 1.01, $p = 0.06$); inotropic support OR 1.27 (95% CI 0.84 to 1.91, $p = 0.25$); intensive care unit stay in days MD −0.02 (95% CI −0.12 to 0.07, $p = 0.61$); Hospital stay in days MD 0.18 (95% CI −0.30 to 0.66, $p = 0.47$) and serum creatinine MD −0.00 (95% CI −0.07 to 0.07, $p = 0.97$) were compared.
Conclusions: RIPC reduces does not confer any clinical benefit in patients undertaking CABG with/without valve surgery.

1. Introduction

Remote ischaemic pre-conditioning (RIPC) is a novel prophylactic treatment during which brief periods of ischaemia in a remote vascular bed provides protection against a subsequent longer bout of ischaemia in the heart. Initially demonstrated in a separate cardiovascular bed [1], it was later shown that protection could also be achieved by preconditioning in a remote organ [2] or in a remote limb [3]. Transfer of the signalling stimulus to the heart is thought to involve the somatosensory system, the spinal cord, the autonomous nervous system and humoral elements. Candidates for the humoral signal include nitric oxide, MicroRNA-144, and stromal derived factor-1α [4]. A further complex signal transduction occurs in the heart possibly involving the reperfusion injury salvage kinase (RISK) pathway [4]. Since the early animal studies [1–3], RIPC has been shown to reduce myocardial injury in patients undergoing both elective [5] and primary percutaneous interventions [6] as well as coronary artery bypass grafting (CABG) [7]. In addition to these cardioprotective effects, RIPC has also been used in the management of blood pressure [8], improvement of endothelial function and blood flow [9], and neuroprotection [10].

There have been a number of meta-analyses that have investigated the effects of remote ischaemic preconditioning during open heart surgery. An early study conducted in 2008 only managed to pool data from four studies [11]. Later studies conducted in 2012 predominately focussed on myocardial injury as indicated by troponin release [12–15] and there are many more clinical outcomes that were not assessed. To some extent this was addressed in a recent meta-analysis by Deng et al. [16] who compared aortic cross-clamping versus remote ischaemic preconditioning, however they did not investigate important clinical outcomes such as inotrope use and post-discharge mortality. Since then another six randomized trials have been published including 2 recent large scale multicentre trials [17–22], which also suggest another look is justified.

The aims of this work were to; (i) examine the effects of RIPC on a range of clinical outcomes and markers of myocardial and renal damage in patients undertaking coronary artery bypass grafting with/without valve surgery; (ii) relate these findings to established thresholds of clinical significance and provide an evidence based context for RIPC use.

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Table 1
Characteristics of included studies.

Study	RIPC protocol	Comparator	N RIPC (control)	Population	Age RIPC (control)	Male % RIPC (control)	All outcome measures
Ahmad et al., 2014 [17] Pakistan	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	35 (32)	Triple vessel CABG	54.46 ± 8.83 (55.16 ± 10.95)	77 (78)	CK-MB Creatinine IABP Inotropic support Mortality
Ali et al., 2010 [23] Pakistan	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	50 (50)	Double/triple vessel CABG	56.02 ± 8.24 (51.6 ± 9.58)	94 (84)	CK-MB IABP Inotropic support
Candilio et al., 2015 [7] UK	Upper and lower limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	89 (89)	Single-quadruple vessel CABG and/or valve surgery	65 ± 10 (66 ± 10)	81 (75)	AF Creatinine hsTnT ICU stay Inotropic support MACE Mortality
Gedik et al., 2014 [18] Germany	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	10 (10)	Double/triple vessel CABG	62.6 ± 3.4 (65.5 ± 4.2)	90 (80)	Autophagy markers cTnI Signalling markers
Hausenloy et al., 2007 [24] UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (30)	Single-quadruple vessel CABG	67 ± 11.8 (67 ± 9.4)	78 (80)	cTnT
Hausenloy et al., 2015 [21] UK	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	801 (811)	CABG and valve surgery	76.1 ± 6.1 (76.3 ± 7)	70.4 (72.7)	Acute kidney injury cTnT Hospital stay ICU stay Inotropic support MACE
Holmberg et al., 2014 [19] Denmark	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	20 (21)	CABG and valve surgery	68 ± 11 (72 ± 9)	75 (67)	AF cTnT CK-MB Hospital stay ICU stay Inotropic support
Karuppasamy et al., 2011 [25] UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (27)	Double-quintuple vessel CABG	66.9 ± 11.2 (67.3 ± 10.3)	81 (85)	BNP cTnI CK-MB Cytokines Growth factors Hospital stay Inotropic support ICU stay
Kottenberg et al., 2012 [26] Isoflurane anaesthetic Propofol anaesthetic Germany	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	20 (19) 14 (19)	Triple vessel CABG	64 ± 9 (65 ± 9) 65 ± 15 (64 ± 12)	95 (84) 64 (84)	cTnI Creatinine
Lomivorotov et al., 2012 [27] Russia	Upper limb 3 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	40 (40)	Mean 2.7 vessel CABG	56.5 ± 8.7 (58.1 ± 6.4)	90 (93)	cTnI CK-MB ICU stay Inotropic support Mortality
Lucchinetti et al., 2012 [28] Canada	Lower limb 4 × 5 min & 5 min reperfusion	Sham (Cuff deflated)	27 (28)	Mean 3.6 vessel CABG	59 ± 7 (62 ± 10)	96 (86)	AF Creatinine hsCRP hscTnT Mortality NT-proBNP S100
Meybohm et al., 2013 [29] Germany	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Cuff inflated to 20 mm Hg)	90 (90)	CABG and valve surgery	70 (68)	77 (86)	AF cTnT Hospital stay Neurocognitive changes
Meybohm et al., 2015 [22] Germany	Upper limb 4 × 5 min & 5 min reperfusion	Sham (Dummy arm)	692 (693)	CABG and valve surgery	65.8 ± 10.7 (66 ± 10)	73.4 (75)	AF AKF Mortality MI Stroke
Rahman et al., 2010 [30]	Upper limb 3 × 5 min &	No RIPC	80 (82)	Triple to quadruple vessel CABG	63 (65)	89 (88)	AF cTnT