



Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial

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ABSTRACT

Background: Remote ischaemic preconditioning (RIPC) induced by brief ischaemia and reperfusion of the arm reduces myocardial injury in coronary artery bypass (CABG) surgery patients receiving predominantly cross-clamp fibrillation for myocardial protection. However, cold-blood cardioplegia is the more commonly used method world wide.

Objective: To assess whether RIPC is cardioprotective in CABG patients receiving cold-blood cardioplegia.

Design: Single-centre, single-blinded, randomised controlled trial.

Setting: Tertiary referral hospital in London.

Patients: Adults patients (18–80 years) undergoing elective CABG surgery with or without concomitant aortic valve surgery with cold-blood cardioplegia. Patients with diabetes, renal failure (serum creatinine >130 mmol/l), hepatic or pulmonary disease, unstable angina or myocardial infarction within the past 4 weeks were excluded.

Interventions: Patients were randomised to receive either RIPC (n = 23) or control (n = 22) after anaesthesia. RIPC comprised three 5 min cycles of right forearm ischaemia, induced by inflating a blood pressure cuff on the upper arm to 200 mm Hg, with an intervening 5 min reperfusion. The control group had a deflated cuff placed on the upper arm for 30 min.

Main outcome measures: Serum troponin T was measured preoperatively and at 6, 12, 24, 48 and 72 h after surgery and the area under the curve (AUC at 72 h) calculated.

Results: RIPC reduced absolute serum troponin T release by 42.4% (mean (SD) AUC at 72 h: 31.53 (24.04) µg/l.72 h in controls vs 18.16 (6.67) µg/l.72 h in RIPC; 95% CI 2.4 to 24.3; p = 0.019).

Conclusions: Remote ischaemic preconditioning induced by brief ischaemia and reperfusion of the arm reduces myocardial injury in CABG surgery patients undergoing cold-blood cardioplegia, making this non-invasive cardioprotective technique widely applicable clinically.

Trial registration number: NCT00397163.

Coronary artery disease is the leading cause of death globally, and coronary artery bypass graft (CABG) surgery is one of the established procedures for the treatment of patients with severe coronary artery disease. The risk profile of patients who are referred for cardiac surgery continues to change with factors such as the ageing population, the increasing incidence of diabetes and more

complex percutaneous coronary interventions, resulting in operations being carried out on patients at higher risk.¹ Clearly, new treatment strategies are required to protect the myocardium in these higher-risk patients undergoing CABG surgery, in order to improve clinical outcomes in this patient group.

In this regard, the endogenous cardioprotective strategy of remote ischaemic preconditioning (RIPC), a phenomenon in which brief ischaemia of one organ or tissue confers protection of another organ or tissue against a sustained ischaemia-reperfusion injury insult, may be of benefit (reviewed by Hausenloy *et al*).² This phenomenon was initially described in 1993 by Przyklenk and colleagues,³ as intramyocardial protection extending from one coronary artery bed to another, but subsequent studies have demonstrated that brief ischaemia of distal organs and tissues such as the kidney,⁴ and small intestine⁵ reduce myocardial infarct size in animal hearts. Brief limb ischaemia was first used to induce RIPC in animals by Birnbaum and colleagues in 1997,⁶ who reported cardioprotection using an invasive preconditioning stimulus comprising partial reduction in femoral artery flow applied in conjunction with pacing of the lower limb muscle. Kharbanda *et al*⁷ characterised a far less invasive transient upper limb ischaemia protocol in adult human volunteers and demonstrated an improvement in endothelial function in the contralateral upper limb. This technique was used in patients for the first time in children undergoing corrective surgery for congenital heart disease, in whom it was shown to reduce troponin release 24 h postoperatively.⁸ We and others have recently demonstrated that RIPC using brief ischaemia and reperfusion of the arm or leg reduces myocardial injury in patients undergoing cardiac surgery^{9–11} or in surgical repair of an abdominal aortic aneurysm.¹⁰

For patients undergoing on-pump CABG surgery, cardioplegia or cross-clamp fibrillation are the standard techniques for protecting the heart during surgery, with the former approach in the form of cold-blood cardioplegia being predominantly used world wide. We have recently reported that RIPC reduces myocardial injury in patients undergoing elective CABG surgery in whom cross-clamp fibrillation was the predominant method used to protect the heart during the surgical procedure.⁹

Therefore, given that cardioplegia is the more commonly used method for myocardial protection during on-pump cardiac surgery,^{11, 12} in this study we examined a new cohort of patients undergoing elective CABG receiving cold-blood cardioplegia alone in order to determine whether RIPC using brief limb ischaemia confers cardioprotection in a setting that is more clinically applicable.

PATIENTS AND METHODS

The study received local ethics committee approval and was carried out in accordance with the UCL Hospitals NHS Trust guidelines.

Patient selection

Adult patients with coronary artery disease consecutively referred for elective CABG surgery with or without concomitant aortic valve replacement between February 2007 and February 2008 were recruited. Patients over 80 years of age, with unstable angina, diabetes mellitus, hepatic, renal or pulmonary disease, were excluded, as were patients with peripheral vascular disease affecting the upper limbs. Written informed consent was obtained from all patients who entered into the study. Consenting patients were randomised to receive either control or RIPC before CABG surgery.

The remote ischaemic preconditioning protocol

RIPC comprised three 5 min cycles of right upper limb ischaemia, induced by a blood pressure cuff placed on the right upper arm and inflated to 200 mm Hg, with an intervening 5 min of reperfusion during which time the cuff was deflated.⁷ Control patients had a deflated cuff placed on the right upper arm for 30 min. The RIPC protocol was applied after anaesthesia induction and before the start of surgery. Patients and the cardiac surgeons were blinded to treatment allocation, although the investigators and anaesthetists were not blinded.

Surgical methodology

Premedication comprising temazepam 10–20 mg orally was given to each patient 1 h before surgery. On arrival in the anaesthetic room, a peripheral venous cannula was inserted and patients were sedated with midazolam. An arterial cannula was inserted before induction of anaesthesia. Continuous arterial pressure monitoring was started and an infusion of Hartmann's solution was made. Anaesthesia was induced with midazolam with or without etomidate or propofol, fentanyl (5–15 µg/kg) and pancuronium (0.1 mg/kg). The trachea was intubated, mechanical ventilation started with O₂ with or without air and anaesthesia was maintained either with halogenated anaesthetics or with a propofol infusion administered by target controlled infusion to achieve a target plasma concentration of 3–8 µg/ml. Midazolam, fentanyl and pancuronium were given as required. Arterial blood pressure, central venous pressure, leads I and III of the electrocardiogram and nasopharyngeal temperature were recorded continuously.

The surgical technique used was the same for both treatment groups (the surgeons were blinded to the treatment allocation). Non-pulsatile cardiopulmonary bypass was employed using a membrane oxygenator and cardiectomy suction in a standard manner. The CABGs (left internal mammary artery or saphenous vein grafts) were constructed on cardiopulmonary bypass with each anastomosis to the coronary arteries being performed with the aorta, using intermittent antegrade and/or retrograde cold-blood cardioplegia (one part of St Thomas

cardioplegia solution mixed with four parts of blood). Cold-blood cardioplegia was instilled into the aortic root after the aortic cross clamp was applied to the ascending aorta and repeated every 20 min until the distal coronary anastomoses were performed. After the aortic cross clamp was released, the proximal anastomoses were performed by applying a side-biting clamp. After construction of all the grafts, cardiopulmonary bypass was discontinued and protamine was used to reverse the effect of heparin.

Serum troponin T measurement

Blood samples for measurement of troponin T were taken preoperatively and 6, 12, 24, 48 and 72 h after surgery. Troponin T was measured quantitatively by a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010; Roche Diagnostics, UK). The lower detection limit of this assay is 0.01 µg/l with a recommended diagnostic range of 0.03–0.09 µg/l indicating possible myocardial injury and a threshold of ≥0.1 µg/l indicating significant myocardial injury.

Statistical analysis

Data are presented as mean (SD). Comparison between treatment groups was made using the unpaired student t test. A value of $p < 0.05$ was considered significant. A sample size of at least 45 patients was determined based on the following assumptions: (a) that from our previous studies we would expect a difference in total serum troponin T release over 72 h of about 15 µg/l between treated and untreated patients⁹; (b) a power of at least 80%; (c) a standard deviation of 25 µg/l⁹ and (d) significance declared at the two-sided 5% level. After consent had been obtained for participation in the clinical trial, patients were randomly assigned to receive either RIPC treatment or control. A computer-generated table of random numbers was used for randomisation. The analysis was by intention to treat. Standard statistical methods were used to test the differences between treatment groups—the independent t test for continuous variables and the χ^2 and Fisher exact test for categorical variables. The general linear regression model was used for multivariate analysis. Statistical analysis was performed using the SPSS statistical software, version 14.0.

RESULTS

Sixty-one patients scheduled for elective CABG surgery were screened for eligibility, of whom 45 were recruited and randomised to intervention or control (fig 1). Of the 16 patients ineligible for inclusion in the study, 10 had diabetes mellitus and three had renal failure and were therefore excluded while three refused to participate. Forty-five patients who consented were recruited to the study and were randomised to receive either RIPC ($n = 23$) or control ($n = 22$) before CABG surgery. There was no difference in the baseline patient characteristics (table 1) between the two groups.

Five patients (23%) in the control group had concomitant aortic valve replacement during CABG surgery as compared with only three patients (13%) in the RIPC group (table 2). Aortic valve replacement was undertaken for severe aortic stenosis in all cases. The aortic cross-clamp time ($p = 0.098$) and bypass time ($p = 0.218$) were longer in the control group than in the RIPC group, although these differences were not statistically significant. The time taken from the termination of the RIPC protocol to the first aortic cross clamp was within 60 min for all patients. There were no untoward consequences of the RIPC protocol.

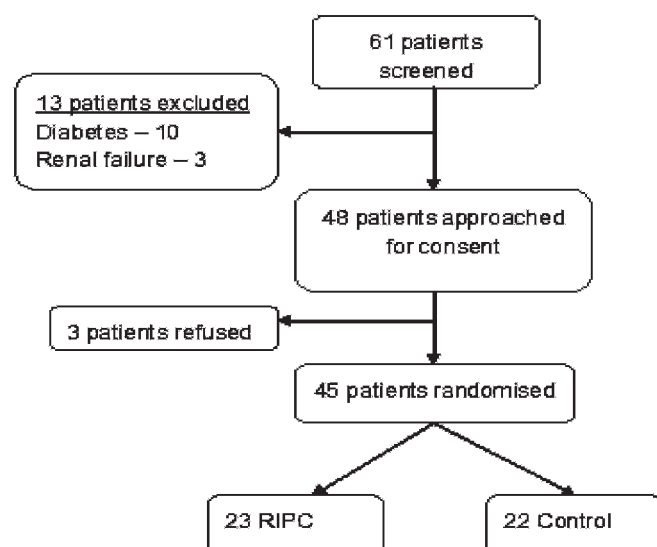


Figure 1 Clinical trial flow diagram. RIPC, remote ischaemic preconditioning.

Baseline preoperative troponin T levels were $<0.01 \mu\text{g/l}$ in both treatment groups. RIPC reduced the perioperative troponin T release over the 72 h after cardiac surgery (fig 2). The total troponin T released, expressed as the area under the curve over the 72 h after surgery, was reduced from a mean (SD) of $31.53 (24.04) \mu\text{g/l.72 h}$ in controls to $18.16 (6.67) \mu\text{g/l.72 h}$ with RIPC (mean difference $13.37 \mu\text{g/l.72 h}$, 95% CI 2.41 to $24.33 \mu\text{g/l}$, $p = 0.019$) a reduction of 42.4%. Importantly, this difference remained significant after correction for the differences in cardiac bypass time and cross-clamp time between the two groups using a general linear univariate regression model ($p = 0.017$). Of the above confounding variables, cardiac bypass time alone, which was longer in the control group, was an independent predictor of greater absolute troponin T release ($p = 0.002$).

DISCUSSION

In this clinical study, we demonstrate for the first time that RIPC induced by applying brief ischaemia and reperfusion to the forearm by a blood pressure cuff can reduce injury over and above the myocardial protection provided by the cold-blood cardioplegia. This was shown by the 42% reduction in the total serum troponin T release over the 72 h perioperative period. The magnitude of this cardioprotective effect is similar to that achieved in our recent clinical study in which we first reported cardioprotection with this RIPC protocol in a cohort of elective patients undergoing CABG receiving predominantly cross-clamp fibrillation as the method of myocardial preservation.⁹ It was essential to determine whether this non-invasive treatment strategy could confer cardioprotection over and above that offered by cold-blood cardioplegia, the technique most often used world wide for protecting the heart during on-pump cardiac surgery. In addition, since the results of conventional ischaemic preconditioning induced by aortic cross clamping are controversial in the setting of cardioplegia,^{13–18} it was important to establish the efficacy of RIPC in this clinical setting. An earlier study from our group compared the effect of invasive ischaemic preconditioning using short periods of aortic cross clamping in patients undergoing routine cross-clamp fibrillation and chemical cardioplegia during CABG and found that

Table 1 Patient characteristics

Characteristics	Control (n = 22)	RIPC (n = 23)
<i>Demographics</i>		
Age (years), mean (SD)	64 (9.0)	62 (9.7)
Male	19 (86)	19 (83)
Female	3 (14)	4 (17)
Hypercholesterolaemia	18 (82)	19 (83)
Hypertension	13 (59)	19 (83)
Previous myocardial infarction	5 (23)	5 (22)
Previous stroke	0	1 (4)
Peripheral vascular disease	1 (5)	1 (4)
<i>Smoking history</i>		
Current smokers	7 (32)	5 (22)
Ex-smokers	8 (36)	10 (43)
Never smoked	7 (32)	8 (35)
Family history of IHD	11 (50)	7 (30)
Body mass index, mean (SD)	28 (3.9)	26 (3.5)
NYHA class, mean (SD)	1.4 (0.8)	1.7 (0.8)
CCS class, mean (SD)	1.4 (0.8)	1.7 (0.9)
<i>Ejection fraction</i>		
>55%	21 (95)	20 (87)
35–55%	1 (5)	2 (9)
<35%	0	1 (4)
Euroscore, mean (SD)	2.6 (2.1)	2.1 (1.9)
<i>Drug history</i>		
Aspirin	12 (55)	10 (43)
β Blocker	16 (73)	17 (74)
Cholesterol-lowering drug	18 (82)	19 (83)
ACE-inhibitor/angiotensin receptor blocker	10 (45)	13 (57)
Nitrate	3 (14)	3 (13)

Values are presented as number (%) unless stated otherwise.

CCS, Canadian Cardiovascular Society; IHD, ischaemic heart disease; NYHA, New York Heart Association; RIPC, remote ischaemic preconditioning.

conventional preconditioning was cardioprotective in both settings.¹⁹ Therefore both conventional and remote preconditioning appear to be beneficial in the setting of cardioplegia. However, conventional ischaemic preconditioning protocols involve intermittent aortic cross clamping before the insertion of the grafts and thus have not found favour with surgeons. Therefore this non-invasive technique of remote limb preconditioning which can be performed with minimum hindrance

Table 2 Details of cardiac bypass surgery

Details	Control (n = 22)	RIPC (n = 23)
<i>Anaesthetic agent</i>		
Isoflurane/sevoflurane	17	17
Propofol	5	6
Bypass time (min), mean (SD)	97 (38)	86 (16)
Total cross-clamp time (min), mean (SD)	65 (30)	53 (14)
<i>Cardioplegia</i>		
Anterograde only	17	21
Anterograde+retrograde	5	4
<i>Number of grafts:</i>		
One	1 (5)	1 (4)
Two	5 (23)	2 (9)
Three	12 (55)	15 (65)
Four	4 (18)	5 (22)
Concomitant aortic valve replacement	5 (23)	3 (13)

Values are shown as number (%) unless stated otherwise.

RIPC, remote ischaemic preconditioning.

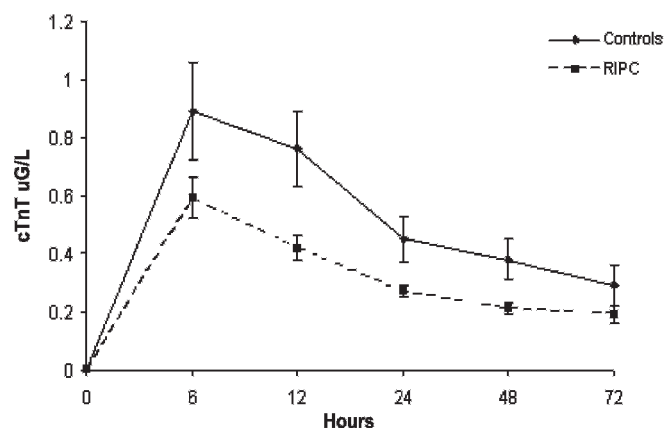


Figure 2 Remote ischaemic preconditioning (RIPC) reduced the area under the curve of troponin T over the 72 h perioperative period by 42% in adult patients undergoing elective coronary artery bypass graft surgery with cold-blood cardioplegia. Values presented are mean (SEM). * $p < 0.05$ compared with control. RIPC ($n = 23$) and controls ($n = 22$). cTnT, cardiac troponin T.

before the patient enters the operation theatre may be more widely acceptable.

Myocardial injury as indicated by the perioperative release of cardiac enzymes during cardiac surgery occurs as a result of combined ischaemia-reperfusion injury encountered during aortic cross clamping, coronary microembolisation²⁰ and direct myocardial damage from handling of the heart. Cardiac-specific markers like troponin T, troponin I and CK-MB have been used to quantify this form of myocardial injury and have been reported by several clinical studies to be associated with worse short-term and long-term outcomes.^{21–23} Lehrke and colleagues²¹ reported in a case series of 204 patients undergoing elective CABG that perioperative troponin T release was associated with worse clinical outcomes, such that a 48 h post-surgery serum troponin T level of $\geq 0.46 \mu\text{g/L}$ was associated with the greatest risk as shown by a 4.9-fold higher long-term risk for subsequent cardiac death. Indeed, the recent new universal definition of myocardial infarction has recognised the importance of post-operative enzyme release and defined this as type 5 myocardial infarction associated with poor clinical outcomes.²⁴ We have demonstrated a reduction in myocardial injury in low-risk patients undergoing cardiac surgery. High-risk patients tend to have greater myocardial injury²⁵ and therefore may derive greater benefit from RIPC, but this remains to be determined.

RIPC has been shown to have protective effects in several tissues in a number of animal studies including the liver, gut, pancreas, brain, lung (reviewed by Hausenloy *et al.*²). Therefore, it appears that applying brief ischaemia and reperfusion in one organ or tissue (in this case the upper limb) confers systemic protection in multiple organ systems against the detrimental effects of acute ischaemia-reperfusion injury. Ali *et al.*¹⁰ have recently demonstrated that intermittent lower limb ischaemia by cross clamping the iliac artery reduces both the cardiac and renal injury sustained in patients undergoing abdominal aortic aneurysm repair. Thus, in the setting of cardiac surgery, RIPC has the potential to reduce not only myocardial injury, but also renal, cerebral and pulmonary side effects, which in turn can improve short- and long-term outcomes.

The mechanisms underlying RIPC are yet to be elucidated, although animal studies have thus far implicated either a humoral or neuronal pathway as the mediator of protection. On

the one hand, the abrogation of remotely induced cardioprotection with the ganglion blocker hexamethonium²⁶ or the pretreatment of sensory nerves with capsaicin,²⁷ suggested a neuronal mechanism. On the other hand, Konstantinov *et al.*²⁸ demonstrated that RIPC can also protect the denervated transplanted heart, which would suggest a humoral mechanism. Several humoral mediators have indeed been implicated, including opioids, calcitonin gene-related peptide, insulin, bradykinin, adenosine and endocannabinoids (reviewed by Hausenloy *et al.*²). These humoral mediators may be released by the remote ischaemic tissue and be carried to the target tissue in the blood stream or be released locally in the target tissue, making them available to activate neural pathways. An interesting recent experimental study has implicated pro-survival kinase signalling within the remote preconditioning organ as a mediator of cardioprotection. Heidebreder *et al.*²⁹ reported that brief mesenteric artery occlusion reduced myocardial infarct size and that this cardioprotective effect was dependent on the phosphorylation of p38MAPK, Erk1/2 and JNK within the small intestinal tissue.

In summary, this single-blind randomised controlled clinical study was designed to determine whether RIPC using brief ischaemia of the forearm can reduce myocardial injury in elective patients undergoing CABG receiving cold-blood cardioplegia during surgery, making the positive findings more widely applicable, given that cardioplegia is the more commonly used method for myocardial preservation during cardiac surgery. We confirm that RIPC can reduce myocardial injury over and above that provided by cold-blood cardioplegia as indicated by a 42% reduction in troponin T released over the 72 h perioperative period. Further studies are underway to investigate whether this cardioprotective strategy is beneficial in patients undergoing off-pump CABG surgery. Large multicentre clinical studies are clearly required in order to determine whether the reduction in myocardial injury observed in recent clinical studies investigating this form of RIPC impacts on clinical outcomes in patients undergoing cardiac surgery.

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Competing interests: None.

Ethics approval: Local ethics committee approval received.

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