However, clinical trials suggest that long-term use of celecoxib can expose patients to an additional risk of myocardial infarction.[9] Thus, although celecoxib might be beneficial even when given for a short time before and after coronary angioplasty,[11] the safety of this drug in interventional cardiology should be confirmed by studies powered to assess risk of myocardial infarction and cardiac death. Finally, we think that gastrointestinal tolerability of chronic therapy with both celecoxib and dual antiplatelet therapy (ie, treatment with aspirin and clopidogrel) might also be a drawback.

In conclusion, the study by Koo and colleagues underscores that systemic therapy might still have a role in prevention of restenosis, even in the era of drug-eluting stents. Further studies should clarify the specific role of anti-inflammatory and antiproliferative treatments in this setting, for example by comparing agents of different classes (corticosteroids, COX-2 antagonists, and other non-steroidal anti-inflammatory drugs) and by seeking to optimise the duration of therapy and benefit-to-risk ratios.

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We declare that we have no conflict of interest.

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An arm and a leg to protect the heart?

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A provocative and appealing question would be whether patients could be cardioprotected after a series of blood-pressure-cuff inflations before coronary artery bypass-graft (CABG) surgery. The answer is supplied in a study by Derek Hausenloy and colleagues in today's *Lancet*.[1]

Even in the most experienced hands, myocardial injury occurs during CABG. In its most subtle form, the injury is shown by the release of troponins, which occurs in up to 50% of patients. Such post-revascularisation leaks of cardiac protein are not benign and are associated with adverse clinical outcomes.[2] There is much current interest in the concept of conditioning to protect against acute myocardial ischaemia-reperfusion injury, and to minimise injury to cardiac myocytes.[3] Several studies have shown that patients with prodromal anginal symptoms have better survival and a reduction in infarct size after an acute myocardial infarction. Also, deliberate induction of short bouts of sublethal ischaemia and reperfusion, by intermittent occlusion of the coronary artery, renders the myocardium resistant to longer ischaemic assaults.[3] Such ischaemic preconditioning, which was first described in 1986,[4] seems to involve triggers that activate mediators, such as protein kinases, that in turn recruit effector mechanisms. Activation of these survival kinases can occur with drugs such as insulin, erythropoietin, and statins.[5]

Several small studies in patients with acute myocardial infarction have shown that, with percutaneous coronary intervention, a series of low-pressure inflations or deflations of the angioplasty balloon reduces infarct size measured by cardiac enzymes and imaging. These observations are known as ischaemic post-conditioning.

Further clinical studies have shown the cardioprotective potential of ischaemic preconditioning in patients undergoing CABG, in which cross-clamping

of the aorta was associated with reduced release of troponin T.[6] However, this intervention was impractical, and less invasive approaches were sought.

Remote ischaemic preconditioning is a technique in which brief ischaemia in one tissue or organ, such as the intestine or the kidney, protects distant tissue or organs, such as the heart, from a more sustained episode of ischaemia. This form of regional preconditioning, first described by Przyklenk and colleagues,[7] has been associated with a hormonal mediator (eg, adenosine or bradykinin) or the recruitment of a neural pathway.

Hausenloy and colleagues' proof-of-concept study describes the use of remote ischaemic preconditioning in adults undergoing elective CABG. After induction of ischaemia, remote ischaemic preconditioning was induced by three 5-min cycles of inflation of an upper arm cuff to 200 mm Hg, with an intervening 5-min of reperfusion with cuff deflation. Patients were randomised to receive either remote ischaemic preconditioning (n=27) or control (n=30; cuff positioned but no inflations). Serum troponin T was sequentially measured after surgery; the total area under the curve for concentration was reduced by 43% in the intervention recipients. None of the patients were taking drugs that could have either mimicked or inhibited ischaemic preconditioning (eg, nicorandil or glibenclamide, respectively). The investigators found a reduction in myocardial injury with transient limb ischaemia in adults undergoing CABG.

Hausenloy and colleagues' study is intriguing because they show a significant reduction in an important marker of myocyte injury. They describe how remote ischaemic preconditioning might suppress the pro-inflammatory responses to ischaemia-reperfusion injury, but provide no information on the effects this intervention might have on C-reactive protein or other inflammatory biomarkers. Similarly, we cannot infer that reduction in troponin concentrations necessarily leads to either short-term or long-term reductions in cardiovascular events, although such studies are planned. Hausenloy and colleagues' study was done in a single tertiary centre, and adult patients were recruited who were undergoing elective CABG. We do not know whether the same benefits from remote ischaemic preconditioning would be derived in patients with more severe symptoms who may require intravenous nitrates in a more acute setting. Clearly the technique for remote ischaemic preconditioning needs to be duplicated by equally skilled workers in other cardiac centres in large numbers of patients. In the meantime, if intermittent limb occlusions are consistently shown to reduce myocardial injury during cardiac revascularisation, the implications for practice are immense.

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We declare that we have no conflict of interest.

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Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial

Derek J Hausenloy, Peter K Mwamure, Vinod Venugopal, Joanne Harris, Matthew Barnard, Ernie Grundy, Elizabeth Ashley, Sanjeev Vichare, Carmelo Di Salvo, Shyam Kolvekar, Martin Hayward, Bruce Keogh, Raymond J MacAllister, Derek M Yellon

Summary

Background **Whether remote ischaemic preconditioning, an intervention in which brief ischaemia of one tissue or organ protects remote organs from a sustained episode of ischaemia, is beneficial for patients undergoing coronary artery bypass graft surgery is unknown. We did a single-blinded randomised controlled study to establish whether remote ischaemic preconditioning reduces myocardial injury in these patients.**

Methods **57 adult patients undergoing elective coronary artery bypass graft surgery were randomly assigned to either a remote ischaemic preconditioning group (n=27) or to a control group (n=30) after induction of anaesthesia. Remote ischaemic preconditioning consisted of three 5-min cycles of right upper limb ischaemia, induced by an automated cuff-inflator placed on the upper arm and inflated to 200 mmHg, with an intervening 5 min of reperfusion during which the cuff was deflated. Serum troponin-T concentration was measured before surgery and at 6, 12, 24, 48, and 72 h after surgery. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00397163.**

Findings **Remote ischaemic preconditioning significantly reduced overall serum troponin-T release at 6, 12, 24, and 48 h after surgery. The total area under the curve was reduced by 43%, from 36·12 μg/L (SD 26·08) in the control group to 20·58 μg/L (9·58) in the remote ischaemic preconditioning group (mean difference 15·55 [SD 5·32]; 95% CI 4·88–26·21; p=0·005).**

Interpretation **We have shown that adult patients undergoing elective coronary artery bypass graft surgery at a single tertiary centre could benefit from remote ischaemic preconditioning, using transient upper limb ischaemia.**

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Introduction

Several studies have shown that myocardial injury, as indicated by the release of perioperative cardiac enzymes, is associated with worse patient morbidity and mortality after coronary artery bypass graft surgery.[1–5] One potential strategy for reduction of myocardial injury sustained during this surgery is ischaemic preconditioning, which describes the cardioprotection obtained from application of one or more non-lethal episodes of myocardial ischaemia and reperfusion before the index myocardial ischaemic event.[6] However, since an ischaemic preconditioning protocol cross-clamps the aorta, this particular intervention is both invasive and impractical to apply.[7,8]

A more amenable and less invasive approach to cardioprotection might be achieved by remote ischaemic preconditioning, whereby brief ischaemia in one region or organ protects distant tissue or organs from a sustained episode of ischaemia. In 1993, Przyklenk and colleagues[9] showed that a brief circumflex artery occlusion could reduce the myocardial infarct size induced by the subsequent sustained occlusion of the left anterior descending artery. This notion was further advanced in subsequent studies which reported that brief ischaemia of non-cardiac tissue such as the kidney,[10] the intestine,[11] or skeletal muscle[12] could also protect the heart against a subsequent myocardial infarction. Remote ischaemic preconditioning induced by transient ischaemia of one arm has been shown to protect the contralateral arm against endothelial dysfunction mediated by a sustained ischaemic episode.[13,14] This particular protocol has also modified myocardial gene expression by upregulation of cytoprotective genes and suppression of proinflammatory genes that are potentially involved in the pathogenesis of ischaemia-reperfusion injury.[15,16] Furthermore, it has been used to attenuate myocardial injury in a porcine model of coronary artery bypass graft surgery[17] and in children undergoing corrective cardiac surgery for congenital heart disease.[18]

We aimed to assess whether this remote ischaemic preconditioning protocol is effective in reducing myocardial injury in adults with coronary artery disease undergoing elective coronary artery bypass graft surgery.

Methods

Patients

Between February, 2006, and February, 2007, we recruited consecutive adult patients with coronary artery disease referred for elective coronary artery bypass graft surgery. We excluded patients older than 80 years, those with unstable angina, left main stem disease, or hepatic, renal, or pulmonary disease, and those with peripheral vascular disease affecting the upper limbs. Additionally, patients

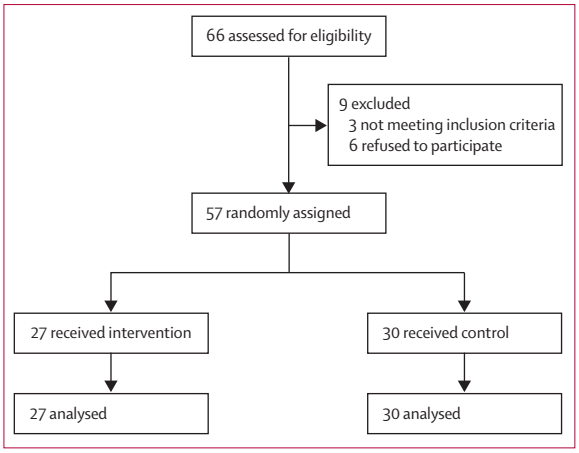

Figure 1: **Trial profile**

taking the antidiabetic sulphonylurea, glibenclamide, were excluded since this agent has been shown in experimental studies to abrogate the cardioprotection elicited by ischaemic preconditioning.[19] We obtained written informed consent from all patients entered into the study. Patients were randomly assigned to receive either control or remote ischaemic preconditioning before coronary artery bypass graft surgery. The study received local ethics committee approval and was done in accordance with the UCL Hospitals NHS Trust guidelines.

Procedures

Remote ischaemic preconditioning consisted of three 5-min cycles of right upper arm ischaemia, which was induced by an automated cuff-inflator placed on the right upper arm and inflated to 200 mm Hg, with an intervening 5 min of reperfusion during which the cuff was deflated.[13] Control patients had a deflated cuff placed on the right upper arm for 30 min. The remote ischaemic preconditioning protocol was applied after anaesthesia induction and before surgery started. Patients and the cardiac surgeons were blinded to treatment allocation.

Temazepam 10–20 mg was given orally to every patient 1 h before surgery. On arrival in the anaesthetic room, a peripheral venous cannula was inserted and patients were sedated with midazolam intravenously. An arterial cannula was inserted before anaesthesia. Arterial pressure was continuously monitored and an infusion of Hartmann's solution was started. 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 and mechanical ventilation started with oxygen with or without room air to achieve an end-tidal carbon dioxide tension of 4–5 kPa. Before cardiopulmonary bypass, anaesthesia was maintained with oxygen, without the use of isoflurane, and 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 needed. Arterial blood pressure, central venous pressure, leads I and III of the electrocardiogram, and nasopharyngeal temperature were recorded continuously.

Standard non-pulsatile cardiopulmonary bypass was used with a membrane oxygenator and cardiotomy suction in a standard manner. The coronary bypass grafts (left internal mammary artery or saphenous vein grafts) were constructed on cardiopulmonary bypass with each anastomosis to the coronary arteries being done with the aorta, with use of either intermittent cross-clamp fibrillation or cardioplegia. After construction of all the grafts, cardiopulmonary bypass was discontinued and protamine used to reverse the effect of heparin.

	Control (n=30)	RIPC (n=27)
Age (years)	67 (9·4)	67 (11·8)
Male	24 (80%)	21 (78%)
Diabetes mellitus	13 (43%)	11 (41%)
Preoperative glucose (mmol/L)	8·9 (3·2)	9·5 (4·2)
Hypercholesterolaemia	22 (73%)	20 (74%)
Hypertension	16 (53%)	19 (70%)
Previous myocardial infarction	9 (30%)	9 (33%)
Previous stroke	1 (3%)	3 (11%)
Peripheral vascular disease	2 (7%)	1 (4%)
Smoking history		
Current smokers	1 (3%)	4 (15%)
Ex-smokers	14 (47%)	18 (67%)
Never smoked	15 (50%)	5 (19%)
Family history of IHD	11 (37%)	10 (37%)
Body-mass index	28 (3·5)	28 (4·4)
NYHA class	2·0 (0·8)	2·0 (0·8)
CCS class	1·0 (0·9)	2·0 (1·2)
Ejection fraction		
>55%	18 (60%)	20 (74%)
35–55%	9 (30%)	4 (15%)
<35%	1 (3%)	1 (4%)
Not known	2 (7%)	2 (7%)
Euroscore	3·3 (2·4)	3·2 (2·6)
Drug history		
Aspirin	28 (93%)	27 (100%)
β blocker	20 (67%)	16 (59%)
Cholesterol-lowering drug	27 (90%)	27 (100%)
ACE-inhibitor/ACE antagonist	16 (53%)	19 (70%)
Long-acting nitrates	8 (27%)	1 (4%)
Antidiabetic drug		
Insulin	2 (15%)	3 (27%)
Sulphonylurea	11 (85%)	6 (55%)
Metformin	4 (30%)	3 (27%)

Data are number (%) or mean (SD). ACE=angiotensin converting enzyme. CCS=Canadian Cardiovascular Society. IHD=ischaemic heart disease. NYHA=New York Heart Association. RIPC=remote ischaemic preconditioning.

Table 1: **Patient characteristics**

Blood samples for measurement of troponin T were taken before surgery and 6, 12, 24, 48, and 72 h after surgery. Troponin-T concentrations were measured quantitatively by a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010; Roche, Basel, Switzerland). The lower detection concentration of this assay was 0·01 µg/L, with a recommended diagnostic range of 0·05–0·09 µg/L indicating possible myocardial injury and a threshold of 0·1 µg/L or more indicating myocardial injury suggestive of myocardial infarction.

Statistical analysis

Data are presented as mean (SD). Comparison between treatment groups was made with the unpaired student *t* test. A value of $p<0·05$ was regarded as significant. A sample size of at least ten patients was needed to have a power of least 90%, a SD of 0·2 µg/L,[20,21] significance at the two-sided 5% level, and on the basis that from our previous studies[20,21] we would expect a difference in serum troponin T of about 0·5 µg/L between treated and untreated patients at 72 h after coronary artery bypass graft surgery. Patients were randomly assigned to groups by random-numbers table. The analysis was by intention to treat.

This trial is registered with ClinicalTrials.gov, number NCT00397163.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Control	RIPC
Bypass-time (min)	80 (25)	76 (19)
Cross-clamp time (min)	45 (22)	36 (17)
Intermittent cross-clamp fibrillation	18 (60%)	17 (63%)
Cardioplegia	12 (40%)	10 (37%)
Number of grafts		
One	1 (3%)	1 (4%)
Two	6 (20%)	5 (19%)
Three	19 (63%)	19 (70%)
Four	4 (14%)	2 (7%)

Data are number (%) or mean (SD). RIPC=remote ischaemic preconditioning.

Table 2: **Details of cardiac bypass surgery**

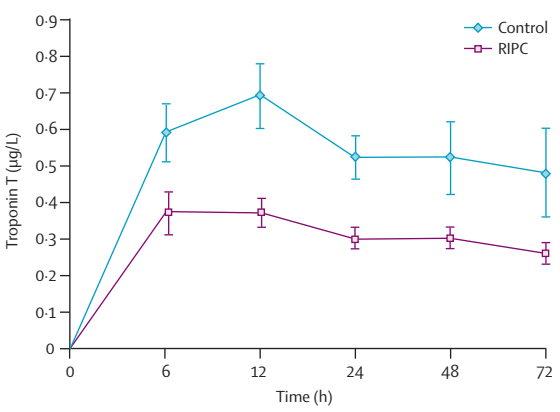

Figure 2: **Absolute serum troponin-T concentration over the 72-h perioperative patients in adult patients undergoing elective coronary artery bypass graft surgery**

Error bars show SD. RIPC=remote ischaemic preconditioning.

Results

Figure 1 shows the trial profile. 66 patients were assessed for eligibility, of whom 57 were actually recruited and randomly assigned to remote ischaemic preconditioning group (n=27) or control group (n=30). Table 1 shows baseline characteristics. There was no difference in the details of coronary artery bypass graft surgery between patients in both treatment groups (table 2). The time taken from the termination of the remote ischaemic preconditioning protocol to the first aortic cross-clamp was not more than 45 min in all patients. There were no untoward results of the remote ischaemic preconditioning protocol.

Baseline concentrations of troponin T before surgery were less than 0·01 µg/L in both treatment groups. Remote ischaemic preconditioning reduced the perioperative troponin-T release over the 72 h after cardiac surgery (figure 2). The reduction in serum troponin-T concentrations in patients treated with remote ischaemic preconditioning was significant at 6 h (0·31 µg/L [SD 0·29] with remote ischaemic preconditioning *vs* 0·59 µg/L [0·45] with control; p=0·039), 12 h (0·37 µg/L [0·19] *vs* 0·69 µg/L [0·48]; p=0·002), 24 h (0·30 µg/L [0·14] *vs* 0·52 µg/L [0·33]; p=0·003), and 48 h (0·30 µg/L [0·17] *vs* 0·52 µg/L [0·49]; p=0·036) after surgery, but not at 72 h (0·25 µg/L [0·16] *vs* 0·48 µg/L [0·64]; p=0·111; figure 2). The total troponin-T released 72 h after surgery was reduced from 36·12 µg/L (26·08) in control group to 20·58 µg/L (9·58) in remote ischaemic preconditioning group (mean difference 15·55 [SD 5·32]; 95% CI 4·88–26·21; p=0·005), which is a reduction of 43%.

Discussion

Our study has shown that remote ischaemic preconditioning, mediated by transient upper limb ischaemia, can reduce troponin T in the perioperative period in adult patients undergoing elective coronary artery bypass graft surgery.

Several studies have shown that the release of troponin T,[3,4] troponin I,[2,5] and CK-MB[1] is associated with poor short-term and long-term clinical outcomes after surgery. Lehrke and colleagues[3] reported in a case series of 204 patients undergoing elective coronary artery bypass graft surgery that perioperative troponin-T release was

associated with worse clinical outcomes; a serum troponin-T concentration of 0·46 μg/L or more 48 h after surgery was associated with a 4·9-fold increased long-term risk for subsequent cardiac death. In our study, remote ischaemic preconditioning resulted in a smaller increase in serum troponin-T concentration at 48 h after surgery, compared with the control group. One might expect that in high-risk patients for whom serum troponin-T concentrations are substantially greater,[4] remote ischaemic preconditioning might confer an even greater reduction in myocardial injury. The myocardial injury sustained during coronary artery bypass graft surgery might be due not only to acute myocardial ischaemia-reperfusion injury, but could also result from surgical manipulation or microembolisation.[22]

Birnbaum and colleagues[23] showed that remote ischaemic preconditioning by transient limb ischaemia can reduce myocardial infarct size in animals. The invasive stimulus consisted of a partial reduction in femoral artery flow applied in conjunction with electrical stimulation of the leg muscle. Subsequently, a far less invasive and simpler procedure for inducing transient upper limb ischaemia as a remote ischaemic preconditioning stimulus was done with human participants.[13] Kharbanda and colleagues[17] have shown that the remote ischaemic preconditioning protocol is capable of reducing myocardial injury as measured by troponin-I release in a porcine model of coronary artery bypass graft surgery. Furthermore, Cheung and co-workers[18] have reported that transient ischaemia of the leg reduced serum troponin-I release over 24 h after surgery in children undergoing cardiac surgery for correction of congenital heart disease. A previous negative study in a very small cohort of four patients undergoing surgery failed to find any cardioprotection with transient leg ischaemia as the remote ischaemic preconditioning stimulus.[24] However, this study was underpowered and did not measure the release of cardiac enzymes over the 72 h perioperative period. Additionally, a negative study with transient bilateral upper arm ischaemia as a remote ischaemic preconditioning stimulus did not show any cardioprotective benefit in patients undergoing low-risk elective single-vessel percutaneous coronary intervention.[25]

The actual mechanism through which remote ischaemic preconditioning protects the myocardium is unclear, although studies in animals have suggested that the protection might be mediated either via a humoral mediator[10,26,27] or the recruitment of a neuronal pathway.[11,14] Studies have shown that this protection can be abolished by the ganglionic blocker hexamethonium[11] or by the pretreatment of sensory nerves with capsaicin,[28] implicating a neuronal pathway in the protective mechanism. Several humoral mediators have been associated with this mechanism including adenosine,[10] bradykinin,[26] and opioids,[27] but whether the remote organ ischaemia generates the mediator that is then transported to the myocardium or whether a neuronal pathway is activated by ischaemia of the remote organ that releases the mediator locally into the myocardium, remains unclear. Konstantinov and colleagues[29] examined the effect of remote ischaemic preconditioing in transplanted hearts in pigs and found evidence in favour of a humoral mechanism. They reported that the application of a remote ischaemic preconditioning protocol to the recipient pig protected the donor heart against myocardial infarction, but the effect could be abolished by the non-specific ATP-sensitive potassium channel blocker glibenclamide.[29] Importantly, the remote ischaemic preconditioning stimulus also modifies gene expression and suppresses the proinflammatory response to ischaemia-reperfusion injury, which could partly contribute to its protective effect.[15]

Our clinical study was designed as a proof-of-concept study to establish whether consecutive adult patients undergoing elective coronary artery bypass graft surgery at a single tertiary centre could benefit from remote ischaemic preconditioning, irrespective of whether they received intermittent cross-clamp fibrillation or cardioplegia. We are currently undertaking a clinical study to investigate whether patients receiving only cardioplegia at the time of coronary artery bypass graft surgery accrue any benefit from this remote ischaemic preconditioning protocol.

Contributors

DJH, DMY, and RJM designed the trial. DJH and JH coordinated the trial. PKM and VV recruited patients and administered the treatment protocol. DJH and VV analysed the data. DMY was the principal investigator. MB, EG, and EA were the cardiothoracic anaesthetists. SV, CDS, SK, MH, and BK were the cardiothoracic surgeons. All authors have seen and approved the final version of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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