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Remote ischemic preconditioning in isolated aortic valve and coronary artery bypass surgery: a randomized trial.

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Visual abstract

Key question:

Does RIPC confer cardioprotection in patients undergoing CABG or AVR surgery?

Key findings:

RIPC does not ameliorate cardiac injury, metabolic stress, and inflammatory response during CABG or AVR surgery.

Take home message

This trial supports the view that RIPC does not confer additional cardioprotection in patients undergoing isolated CABG or AVR surgery.

ABSTRACT

Objective: This trial was designed and started recruiting at a time when the benefits of remote ischemic preconditioning during open-heart surgery were still controversial. We focused on a homogeneous patient's population undergoing either isolated aortic valve replacement (AVR) or coronary artery bypass graft surgery (CABG) by investigating cardiac injury, metabolic stress and inflammatory response.

Methods: A two-centre randomised controlled trial recruited a total of 124 patients between February 2013 and April 2015. Of these 64 patients underwent CABG and 60 patients AVR. Patients were randomized to either sham or preconditioning. Remote ischemic preconditioning was applied following anesthesia and before sternotomy. Myocardial injury and inflammatory response were assessed by serially measuring cardiac troponin I, and IL-6, 8, 10 and TNF-α. Biopsies from left and right ventricles were harvested after ischemic reperfusion injury for nucleotides analysis.

Results: Application of remote ischemic preconditioning did not alter troponin I release, levels of inflammatory markers and cardiac energetics in both CABG or AVR groups.

Conclusions: Preconditioning did not confer any additional cardioprotection in terms of troponin I, inflammatory markers reduction, and left and right ventricle energy metabolites preservation in patients undergoing isolated coronary artery bypass grafting or aortic valve surgery.

Key words: remote ischemic preconditioning; coronary artery bypass grafting; aortic valve replacement; cardiac injury.

INTRODUCTION

Two recent large randomized trials have shown neither troponin reduction nor clinical benefit in patients undergoing cardiac surgery after upper limb remote ischemic preconditioning (RIPC)[1-2]. Different confounders, heterogeneous population of patients with different pathologies and a variety of comorbidities may have significantly biased the efficacy of the intervention[3].

The mechanisms underlying RIPC protection in experimental models and clinical setting are still poorly understood[4]. Work in experimental models has monitored changes in cardiac metabolites in ventricular biopsies to help understand how this intervention is working[5]. Additionally, knowledge of potential RIPC-induced changes in systemic stress (e.g. inflammatory response) would also help in elucidating the effects of RIPC during cardiac surgery[4].

Thus, the aim of this trial was to investigate the effect of upper limb RIPC in patients undergoing isolated coronary artery bypass grafting (CABG) and aortic valve replacement (AVR) on cardiac injury, metabolic stress and inflammatory response.

PATIENTS AND METHODS

Trial Design

A two-centre randomised controlled trial investigating the effects of RIPC in patients undergoing: a) isolated CABG and b) isolated AVR with cardiopulmonary bypass (CPB) and cardioplegic arrest. The research objectives were addressed by randomising participants within each of four patient's strata to RIPC or SHAM control. The randomisation was carried out by the research nurse, who carried out both interventions in theatre. Participants, clinicians and trial personnel were blinded to which group a participant was assigned. The study was conducted at the Hammersmith Campus of Imperial College Healthcare NHS Trust and the University Hospitals of Bristol NHS Foundation Trust. The study was approved by the London-Harrow Research Ethics Committee (reference No. REC No: 12/LO/1361), and registered to the International Standard Randomized Controlled Trial Number (ISRCTN)

registry with the ID 33084113 (DOI 10.1186/ISRCTN33084113) and to the UK controlled randomized trial number (UKCRN) registry ID 13672. The study was sponsored by the Imperial College of London and funded by the British Heart Foundation (BHF) and Biomedical Research Unit (BRU)[6]. The recruitment was carried out from February 2013 till April 2015 (CONSORT checklist on line supplement).

Participant and RIPC protocol

Inclusion, exclusion criteria and trial conduct were published before[6] (supplementary data). RIPC was induced as described by others[1,7]. Briefly, RIPC comprised four 5 min cycles of upper limb ischemia, induced by a blood pressure cuff inflated to 200 mm Hg, with an intervening 5 min of reperfusion by deflating the cuff.

Outcomes

The study's primary end point was: troponin I (cTnI) measured at base line (before the operation) and 6, 12, 24, 48, 72, hours after aortic cross clamp release. Secondary outcomes were: myocardial metabolites measured in snap-frozen biopsies obtained with tru-cut needle from the left and right ventricle 20 minutes after index ischemia (aortic cross clamp); blood inflammatory markers: interleukin (IL)-6, 8, 12 and tumor necrosis factor (TNF)-α; blood pH; systemic metabolic stress assessed by lactate and serum creatinine level. Inflammatory markers, lactate and pH were measured at the same time points as for cTnI; serum creatinine was measured at baseline and from post-operative day 1 to day 7. Relevant clinical outcomes and serious adverse events (SAEs) were also recorded.

Sample size and statistical analysis

Sample size was estimated from our previous work[6] (supplementary data). Analyses were performed on an intention-to-treat basis. Shapiro-Wilk test was used to check for the normality of data in groups before further analysis. Continuous data are summarized as mean ± SD or median (interquartile range) if distributions are skewed. Categorical data are

summarized as number and percentage. Repeated measures (troponin, inflammatory markers, pH, lactate, creatinine) were compared using mixed model, with RIPC as the reference group. ~~Model validity was checked using standard methods; if a model fitted poorly, transformations were explored~~. Outcomes analyzed on a logarithmic scale were transformed back to the original scale after analysis and results presented as geometric mean ratios (GMR). Ventricle biopsies were compared using unpaired, two tailed, t-test or Wilcoxon rank sum test; $P < 0.05$ was considered significant. Energy charge was calculated as follow: Energy charge = ATP + (0.5 * ADP)/ ATP + ADP + AMP[5].

The trial was not powered to detect differences in clinical outcomes and their frequencies are tabulated descriptively. All analyses and plotting were performed in: R Core Team (2014); R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org (packages used: 'aov', 'graphics', 'lmer', 'stat').

Anaesthesia and surgical management

Anaesthetic, CPB, cardioplegia, and surgical techniques and any other aspect of pre and post-operative management were in accordance with existing protocols in use at both centres (supplementary data) as previously reported[6].

RESULTS

Recruitment

Between February 2013 and April 2015, 316 patients were screened at the Hammersmith Hospital and Bristol Royal Infirmary Hospital for inclusion in the trial. Sixty-four were ineligible (see CONSORT diagram, supplementary figure S1). Of the 252 eligible patients, 124 agreed to participate to the study; 64 and 60 patients respectively formed the CABG and AVR population that was randomized to RIPC / SHAM. The primary analysis includes all randomized participants. Participants were followed for 3 months after randomization. Safety data at 3 months were available on all participants.

Baseline data

Overall baseline data are reported in table 1. In the CABG group, patients allocated to SHAM when compared with those allocated to RIPC included more individuals with previous myocardial infarction (40.6% vs 9.3%), type 2 diabetes mellitus (NIDDM) (40.6% vs 15.6%) and higher creatinine (95.1 ± 20.7 and 82 ± 14). In the AVR group patients allocated to RIPC compared with those allocated to SHAM had slightly higher creatinine (87.3 ± 22 and 78.6 ± 16.2). Four patients underwent unplanned concomitant CABG. The surgeons performing the procedures on reviewing the coronary angiogram after randomization, felt that the degree of coronary stenosis was significant, hence the need for additional CABG. Those patients were included as per intention to treat analysis (3 in RIPC group and 1 in SHAM group). Preoperative medications are reported in supplementary table T1.

Operative details

Operative details are illustrated in table 2. In both CABG and AVR there was no difference in RIPC or SHAM group in cross-clamp, CPB time and the overall duration of the surgical procedure. There was no in-hospital mortality. Post-operative complications are described in table 3 and 4. No serious adverse events were recorded.

cTnI release

CABG group: Troponin I concentrations are illustrated in Figure 1a and summarized in supplementary table T2. Preoperative concentrations were similar in the 2 groups (30 out of 32 [93.7%] below the detectable limit, median concentration 0.25 ng/L among participants with detectable concentrations in the RIPC group vs 30 out of 32 [93.7%] and 0.007 ng/L in the SHAM group). Cardiac troponin I concentrations rose following surgery peaking at 6 hours and were, on average, 8% lower in the RIPC group (geometrical mean ratio GMR 0.92 (0.78,0.98), p=0.24).

Creatinine, pH and lactate concentration are also illustrated in figure 1 (b/c/d). Postoperative creatinine, lactate concentrations and blood pH did not significantly differ between the

groups; postoperative creatinine concentration was lower in the RIPC group (GMR, 0.85; 95% CI, 0.83-0.86; P=0.74); pH was slightly lower in the SHAM group (MD, 1; 95% CI, 0.99 to 1; P=0.26) and lactate were, on average, 7% lower in the RIPC group (GMR, 0.93; 95% CI, 0.87-0.99; p=0.9). No serious adverse events were recorded.

AVR group: Troponin I concentrations are illustrated in Figure 2a and summarized in supplementary table T3. Preoperative concentrations were similar in the 2 groups (31 out of 31 [100%] below the detectable limit in the RIPC group, vs 28 out of 29 [96.5%] in the SHAM group). Cardiac troponin I concentrations rose following surgery peaking at 6 hours and were, on average, 10% lower in the SHAM group (geometrical mean ratio GMR 1.1 (0.65,1.44), p=0.65).

Postoperative creatinine, blood pH and lactate concentrations were similar in both groups (Figure 2 b/c/d); as was postoperative creatinine concentration (GMR, 1.07; 95% CI, 0.97-1.17; P=0.56); pH was, on average, 10% lower in the RIPC group (MD, 0.9; 95% CI, 0.89-1; p=0.85), while lactate was slightly lower in the SHAM group (GMR, 1.01; 95% CI, 0.89-1.27; P=0.63).

Inflammatory markers

The expression of relevant cytokines was assessed using the MILLIPLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel (supplementary data).

CABG group: Interleukin 6, 8, 10 and TNF-α baseline and post-operative values for both groups are depicted in figure 3 a-d. There were no statistically significant differences for each inflammatory marker considered (P=0.62, 0.72, 0.73 and 0.81, IL-6, 8, 10 and TNF-α RIPC vs SHAM respectively).

AVR group: Interleukin 6, 8, 10 and TNF-α baseline and post-operative values for both groups are depicted in figure 4 a-d. There were no differences for each inflammatory marker considered (P=0.84, 0.43, 0.5 and 0.28, IL-6, 8, 10 and TNF-α RIPC vs SHAM respectively).

Cardiac metabolites

The metabolites measured were: ATP (adenosine triphosphate), ADP adenosine diphosphate, AMP (adenosine monophosphate). They were measured using high-performance liquid chromatography (HPLC) as previously described[5] (supplementary data). The specimens were all of high quality with wet weight 2.6 (1.8) and 2.9 (2) mg for CABG and AVR respectively.

CABG group: The analysis of the adenine nucleotides of the left and right ventricle biopsies are illustrated in supplementary figure S2 and summarized in supplementary table T4. No statistical difference was observed at the level of the left and right ventricles in terms of phosphorylation potential (P=0.84, 0.76, 0.71, 0.92, ATP/ADP, ATP/AMP, left and right ventricle RIPC vs SHAM respectively) and cardiomyocytes energy charge between RIPC/SHAM group after ischemic reperfusion injury (P=0.65, 0.88, left and right ventricle RIPC vs SHAM respectively).

AVR group: The analysis of the adenine nucleotides of the left and right ventricle biopsies are illustrated in supplementary figure S3 and summarized in supplementary table T4. No statistical difference was observed at the level of the left and right ventricles in terms of phosphorylation potential (P=0.74, 0.67, 0.50, 0.89, ATP/ADP, ATP/AMP, left and right ventricle RIPC vs SHAM respectively) and cardiomyocytes energy charge between RIPC/SHAM group after ischemic reperfusion injury (P=0.96, 0.78, left and right ventricle RIPC vs SHAM respectively).

DISCUSSION

To the best of our knowledge this is the first study in human that investigate the effect of RIPC on troponin, inflammatory markers and myocytes metabolites of left and right ventricle in two different cardiac pathologies.

Preconditioning did not to confer any additional cardio-protection in term of troponin I, inflammatory markers reduction, and left and right ventricle energy metabolites preservation. These findings are in line with the report of the two largest prospective trials on RIPC in cardiac surgery[1,2].

The ERICCA trial recruited high-risk patients undergoing CABG ± AVR and failed to detect any benefit in the group randomized to RIPC[1]. The RIPHeart study led to the same conclusions[2]. Same neutral findings were reported by the most recent meta-analysis by the Remote reconditioning Trialists' Group, which included 23 trials of RIPC with a total of 2200 patients undergoing cardiovascular surgery[8].

Coronary artery and aortic valve disease are associated with specific disease-induced cellular remodeling, since they may exhibit specific cellular proteome and may response differently to ischemic reperfusion injury[9]. Similarly, left and right ventricle may have, as previously demonstrated, different protein profile[9]. Different Authors [10-12], upon calculating markers of ischemic stress including phosphorylation potential and energy charge, found RIPC to have significant effect. On the contrary we previously reported that RIPC was associated with lower phosphorylation potential compared to control in mice, after RIPC but before ischemic reperfusion injury[5].

Neutral results were observed in our study in both diseases in left and right ventricle biopsies questioning the uncritical interpretation of results from experimental clinical models to the clinical scenario.

Ischemic reperfusion injury and CPB used during cardiac surgery elicit systemic inflammatory responses that may ultimately contribute to myocardial dysfunction and postoperative complications[13]. Accordingly, it has been proposed that RIPC confers systemic protection by eliciting an anti-inflammatory response and anti-apoptotic gene activation[13-15]. In our study we did not find any significant differences in terms of pro and anti-inflammatory cytokines in both pathologies.

There are many confounders that may undermine the effect of RIPC[4]. Patients with coronary disease may be already 'naturally preconditioned' by previous episode of transient ischemia. There are evidences that both propofol and volatile (e.g. sevoflurane) anesthetic regime used in heart surgery may elicit cardio-protection[16]. As the ERICCA trial, we included both anesthetic regimens while in the RIPHeart only propofol based anesthesia was used.

It may be plausible that RIPC may be associated with some harmful events[17]. We did not find any difference in clinical outcomes but our study was not powered to achieve this.

This study had several strengths. It was a two-centred prospective double-blinded randomised trial that used a sham control (inflation of the cuff under the surgical drape beside the patient) to prevent surgeon or physician bias. It included 2 different populations with specific diseases; in the AVR stratum, patients had normal coronary artery physiology with no anticipated natural preconditioning, whereas a certain degree of natural preconditioning phenomena was expected in the CABG group due to previous angina. It also investigated the effect of RIPC in two different proteonomic scenarios (coronary disease and aortic valve disease) in left and right ventricles biopsies. Furthermore, the study has strong elements of novelty: it compares blood (troponin) and myocardial biomarkers of injury (inflammatory response, energy charge, phosphorylation potential) in humans.

Perhaps the biggest study limitation was the use of both propofol and volatile (sevoflurane) anaesthesia regimens during surgery. Both anaesthetic regimens can potentially interfere with preconditioning effects. There was also a certain level of heterogeneity with more patients with diabetes and history of MI in the SHAM CABG group. Lastly, mid- and long-term follow-ups were not conducted in this study; however, survival after surgery has been shown to correlate with early troponin release, which was no different in both groups of our study

CONCLUSION

In patients undergoing isolated CABG or AVR, preconditioning did not seem to confer any additional cardioprotection in term of troponin I, inflammatory markers reduction, and left and right ventricle energy metabolites preservation.

Conflict of interest: There are no conflicts of interest for this research.

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FIGURE LEGEND

Figure 1 a-d. CABG: Concentration over time. Geometric mean and 95% confidence interval (CI) at each study time point by group, and geometric mean ratio (GMR) and 95% CI for the effect of RIPC versus SHAM on a) troponin, b) creatinine, c) pH and d) lactate. Mean and standard deviation (SD) at each study time point by group, and mean difference (MD) and 95% CI for the effect of RIPC versus SHAM on pH level. CABG: Coronary artery bypass grafting. Pre: Preoperative. RIPC: Remote ischemic preconditioning.

Figure 2 a-d. AVR: Concentration over time. Geometric mean and 95% confidence interval (CI) at each study time point by group, and geometric mean ratio (GMR) and 95%CI for the effect of RIPC versus SHAM on a) troponin, b) creatinine, c) pH and d) lactate. Mean and standard deviation (SD) at each study time point by group, and mean difference (MD) and 95% CI for the effect of RIPC versus SHAM on pH level. AVR: Aortic valve replacement. Pre: Preoperative. RIPC: Remote ischemic preconditioning.

Figure 3 a-d. CABG: Concentration over time. Geometric mean and 95% confidence interval (CI) at each study time point by group, and geometric mean ratio (GMR) and 95% CI for the effect of RIPC versus SHAM on a, b, c) IL-6, 8, 10 and d) TNF-α. CABG: Coronary artery bypass grafting. IL: Interleukin. Pre: Preoperative. RIPC: Remote ischemic preconditioning. TNF: Tumor necrosis factor.

Figure 4 a-d. AVR: Concentration over time. Geometric mean and 95% confidence interval (CI) at each study time point by group, and geometric mean ratio (GMR) and 95% CI for the effect of RIPC versus SHAM on a, b, c) IL-6, 8, 10 and d) TNF-α. AVR: Aortic valve replacement. IL: Interleukin. Pre= Preoperative. RIPC: Remote ischemic preconditioning. TNF: Tumor necrosis factor.

TABLE 1. Baseline characteristics

	CABG			AVR			ALL
	RIPC (n=32)	**SHAM (n=32)**	**Overall (n=64)**	**RIPC (n=31)**	**SHAM (n=29)**	**Overall (N=60)**	**n=124**
Age (y/o)	63.4±8.9	62.9±16.3	64.1±10.3	71.4±16.8	66.2±12.6	68.9±15	66.4±13
Male, n (%)	28(87.5)	27(84.3)	55(85.9)	19(61.3)	20(69)	39(65)	94(75.8)
Body mass index	28.2±4.5	29.2±5.6	28.7±5.1	29.2±6.8	28.7±5.5	29±6.2	28.8±5.6
NYHA I, n (%)	10(31.2)	12(37.5)	22(34.4)	19(61.3)	20(69)	39(65)	61(49.2)
NYHA II, n (%)	17(53.1)	18(56.2)	35(54.7)	4(12.9)	2(6.9)	6(10)	41(33)
NYHA III, n (%)	4(12.5)	2(6.2)	6(9.3)	17(54.8)	19(65.5)	36(60)	42(33.9)
NYHA IV, n (%)	1(3.1)	0	1(1.6)	10(32.2)	8(27.6)	18(30)	19(15.3)
CCS I, n (%)	9(28.1)	8(25)	17(26.6)	4(12.9)	6(20.7)	10(16.6)	27(21.7)
CCS II, n (%)	17(53.1)	19(59.4)	36(56.2)	10(32.2)	7(24.1)	17(28.3)	53(42.7)
CCS III, n (%)	5(15.6)	3(9.3)	8(12.5)	2(6.4)	0	2(3.3)	10(8)
CCS IV, n (%)	0	0	0	0	1(3.4)	1(1.6)	1(0.8)
Previous MI, n (%)	3(9.3)	13(40.6)	16(25)	2(6.4)	0	2(3.3)	18(14.5)
AF, n (%)	0	0	0	2(6.4)	1(3.4)	3(5)	3(2.4)
Permanente pacemaker, n (%)	1(3.1)	1(3.1)	2(3.1)	1(3.2)	1(3.4)	2(3.3)	4(3.2)
LV good >50%, n (%)	26(81.2)	23(71.8)	49(79.6)	26(83.9)	26(89.6)	52(86.6)	101(81.4)
LV moderate <50 > 30%, n (%)	6(18.7)	9(28.1)	15(23.4)	4(12.9)	3(10.3)	7(11.6)	22(17.7)
LV less < 30%, n (%)	0	0	0	1(3.2)	0	0	1(0.8)
Smoking, n (%)	15(46.9)	17(53.1)	32(50)	15(48.4)	10(34.5)	25(41.6)	57(46)
Ex smoking, n (%)	5(15.6)	2(6.2)	8(12.5)	1(3.2)	6(20.7)	7(11.6)	15(12)
Family history CAD, n (%)	24(75)	23(71.8)	47(73.4)	12(38.7)	13(44.8)	25(41.6)	72(58)

Hypercholesterolemia, n (%)	29(90.6)	31(96.9)	60(93.7)	16(51.6)	17(58.6)	33(55)	93(75)
Hypertension, n (%)	26(81.2)	30(93.7)	56(87.5)	23(74.2)	20(68.9)	43(71.6)	99(79.8)
Hypothyroidism, n (%)	0	1(3.1)	1(1.6)	3(9.7)	3(10.3)	6(10)	7(5.6)
COPD, n (%)	5(15.6)	7(21.9)	12(18.7)	3 (9.7)	3 (10.3)	6 (10)	18(14.5)
CVA/TIA's (%)	4(12.5)	1(3.1)	5(7.8)	3(9.7)	3(10.3)	6(10)	11(8.9)
Neurological dysfunction, n (%)	0	0	0	0	1(3.4)	1(1.6)	1(0.8)
IDDM, n (%)	1(3.1)	3(9.3)	4(6.25)	0	1(3.4)	1(1.6)	5(4)
NIDDM, n (%)	5(15.6)	13(40.6)	18(28.1)	4(12.9)	4(13.8)	8(13.3)	26(21)
Extracardiac arteriopathy, n (%)	1(3.1)	0	1(1.6)	1(3.2)	2(6.9)	3(5)	4(3.2)
Creatinine, mg/dl	82±14	95.1±20.7	88.6±18.7	87.3±22	78.6±16.2	83.1±19.7	85.9±19.3
Number of CABG	2.7±0.5	2.7±0.5	2.7±0.5	0.1±0.7	0±0	0.08±0.5	1.4±1.4
Elective, n (%)	28(87.5)	30(9.4)	58(90.6)	29(936)	27(93.1)	56(93.3)	114(92)
Urgent, n (%)	4(12.5)	2(6.2)	6(9.4)	2(6.4)	2(6.9)	4(6.6)	10(8)

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). AVR: Aortic valve replacement. CABG: Coronary artery bypass grafting. CAD: Coronary artery disease. CCS: Canadian Cardiovascular Society. CVA: Cerebral vascular accident. COPD: Chronic obstructive pulmonary disease. IDDM: Insulin dependent diabetes mellitus. LV: Left ventricular function. MI: Myocardial infarction. NIDDM: Non-insulin dependent diabetes mellitus. NYHA: New York Heart Association. TIA= Transient ischemic attack. RIPC: Remote ischemic preconditioning.

TABLE 2. Intraoperative details

	CABG			AVR		
	RIPC (n=32)	**SHAM (n=32)**	**Overall (n=64)**	**RIPC (n=31)**	**SHAM (n=29)**	**Overall (n=60)**
Operation duration (h) (IQR)	3.6(3-4)	3.7(3.3-4.1)	3.7(3.2-4.1)	3.1(2.9-3.5)	3.1 (2.9-3.4)	3.1(2.9-3.4)
CCT (min) (IQR)	40.5(32.5-49.5)	42 (33-49)	42 (32.5-49.5)	66(55-79)	63 (52-85)	64 (52-81)
CPB (min) (IQR)	77.5(71.5-85.5)	85(68.5-95)	79.5(70.5-94)	93(75-112)	91(80-110)	93(77.5-111)
DC shock after CC release, n (%)	3 (9.3)	1 (3.1)	4 (6.2)	6 (18.7)	7 (24.1)	13 (21.6)
SR after CC release, n (%)	28 (87.5)	28 (87.5)	56 (87.5)	20 (64.5)	20 (68.9)	40 (66.6)
IABP, n (%)	1 (3.1)	0	1(1.5)	1 (3.2)	1 (3.4)	2 (3.3)
Use of tranex, n (%)	23 (71.8)	23 (71.8)	46 (71.8)	27 (87)	25 (86.2)	52 (86.6)
Intraop RBC	0.06±0.3	0.6±1	0.3±0.8	0.2±0.6	0.03±0.1	0.1±0.3
Noradrenalin, n (%)	14 (43.7)	11 (34.3)	25 (39)	6 (19.3)	5 (17.2)	11 (18.3)
Dobutamine, n (%)	0	0	0	0	0	0
Enoximone, n (%)	1 (3.1)	0	1 (1.5)	3 (9.6)	2 (6.9)	5 (8.3)
Needs for pace maker, n (%)	1 (3.1)	1(3.1)	2 (3.1)	5 (16.1)	6 (20.6)	11 (18.3)
Number of CABG	4.4±0.8	4.1±0.9	4.2±0.9	-	-	-

Values are presented as median (1st and 3rd interquartile range), mean ± standard deviation, or n (%). AF: Atrial fibrillation. AV: Atrio-ventricular. AVR: Aortic valve replacement. CC: Cross clamp. Cryo: Cryoglobulin. CCT: Cross clamp time. CPB: Cardio pulmonary bypass. FFP: Fresh frozen plasma. IABP: Intra-aortic balloon pumping. PLT: Platelets. RBC: Red blood cells. RIPC: Remote ischemic preconditioning. VF: Ventricle fibrillation. VT: ventricle tachycardia

TABLE 3 CABG: Postoperative details

	Randomised to RIPC (n = 32)	Randomised to SHAM (n = 32)	Overall (n = 64)
Total ventilation time (h) (IQR)	8 (6–12)	7.5 (5–10)	7.7 (5–12)
Time in ICU (h) (IQR)	15 (12–18)	9 (3.6–14.4)	12 (8.1–17.1)
Time on ward (h) (IQR)	3 (2–5)	4 (3–5)	3 (3–5)
Length of hospital stay (days) (IQR)	6.5 (6–8)	6.5 (6–8)	6.5 (6–8)
In hospital mortality, n (%)	0	0	0
Myocardial infarction, n (%)	1 (3.1)	0	1 (1.5)
ST/AF, n (%)	5 (15.6)	5 (15.6)	10 (15.6)
VF/VT, n (%)	0	0	0
Pacing permanent (%)	0	0	0
Reopening for bleeding (%)	0	1 (3.1)	1 (1.5)
Inotropes used, n (%)	17 (53.1)	15 (23.4)	(50)
IABP, n (%)	0	0	0
Vasodilators used, n (%)	8 (25)	6 (18.7)	(21.8)
Low cardiac output, n (%)	0	0	0
Re-intubation, n (%)	0	0	0
Tracheostomy, n (%)	0	0	0
C-PAP mask, n (%)	9 (28.1)	6 (18.7)	15 (18.7)
Pneumothorax/effusion, n (%)	2 (6.2)	3 (9.3)	5 (7.8)
Respiratory infection, n (%)	1 (3.1)	1 (3.1)	2 (3.1)
Hemofiltration/dialysis (%)	0	0	0
Permanent stroke/TIA, n (%)	0	0	0

Values are presented as median (1st and 3rd interquartile range), or n (%). There were no missing data.

AF: Atrial fibrillation. IABP: Intra-aortic balloon pump. ICU, intensive care unit; RIPC: Remote

ischemic preconditioning. TIA, transient ischaemic attack. VF: Ventricle fibrillation. VT: Ventricle tachycardia.

TABLE 4. AVR: Postoperative details

	Randomised to RIPC (n = 31)	Randomised to SHAM (n = 29)	Overall (n = 60)
Total ventilation time (h) (IQR)	8 (4–12)	7.2 (5–13)	7.5 (4–13)
Time in ICU (h) (IQR)	13.2 (9–24)	12 (4.5–20)	12 (6.6–21)
Time on ward (h) (IQR)	3.5 (3–6)	3 (2–5)	3 (2.5–6)
Length of hospital stay (days) (IQR)	7 (6–9)	6 (5–8)	7 (6–8.5)
In hospital mortality, n (%)	0	0	0
Myocardial infarction, n (%)	0	0	0
Tachycardia/AF, n (%)	18 (58)	12 (38.7)	30 (50)
VF/VT, n (%)	0	0	0
Pacing permanent, n (%)	2 (6.4)	0	2 (3.3)
Reopening for bleeding, n (%)	1 (3.2)	0	1 (1.6)
Inotropes used, n (%)	15 (48.3)	17 (58.6)	(53.3)
IABP, n (%)	0	0	0
Vasodilators used, n (%)	13 (41.9)	10 (34.4)	23 (38.3)
Low cardiac output, n (%)	1 (3.2)	0	1 (1.6)
Re-intubation, n (%)	0	1 (3.4)	1 (1.6)
Tracheostomy, n (%)	0	1 (3.4)	1 (1.6)
C-PAP mask, n (%)	5 (16.1)	1 (3.4)	6 (10)
Pneumothorax/effusion, n (%)	1 (3.2)	1 (3.4)	2 (3.3)
Respiratory infection, n (%)	4 (12.9)	4 (13.7)	8 (13.3)
New hemofiltration/dialysis, n (%)	0	0	0
Permanent stroke/ TIA, n (%)	0	0	0

Values are presented as median (1st and 3rd interquartile range), or n (%). There were no missing data. AF: Atrial fibrillation. IABP: Intra-aortic balloon pump. ICU: intensive care unit; RIPC: Remote ischemic

preconditioning. TIA: Transient ischaemic attack. VF: Ventricle fibrillation. VT: Ventricle tachycardia.

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