BJA

British Journal of Anaesthesia, 121 (5): 1034–1040 (2018)

doi: 10.1016/j.bja.2018.07.035
Advance Access Publication Date: 18 September 2018
Cardiovascular

Remote ischaemic conditioning for prevention of acute kidney injury after valvular heart surgery: a randomised controlled trial

J. W. Song[1,2], W. K. Lee[1], S. Lee[3], J. K. Shim[1,2], H. J. Kim[1] and Y. L. Kwak[1,2,*]

[1]Department of Anaesthesiology and Pain Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Anaesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea and [3]Department of Cardiovascular Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea

*Corresponding author. E-mail: ylkwak@yuhs.ac

Abstract

Background: Repeated remote ischaemic conditioning (RIC) during weaning from cardiopulmonary bypass and in the early postoperative period may confer protection against acute kidney injury (AKI). We evaluated the effect of repeated RIC on the incidence of AKI in patients undergoing valvular heart surgery.
Methods: Patients were randomised into either the RIC (n=120) or control (n=124) group. A pneumatic tourniquet was placed on each patient's thigh. Upon removal of the aortic cross-clamp, three cycles of inflation for 5 min at 250 mm Hg (with 5 min intervals) were applied in the RIC group. Additionally, three cycles of RIC were repeated at postoperative 12 and 24 h. AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes guideline. The incidences of renal replacement therapy, permanent stroke, sternal wound infection, newly developed atrial fibrillation, mechanical ventilation >24 h, and reoperation for bleeding during hospitalisation were recorded.
Results: The incidences of AKI were not significantly different between the control (19.4%) and RIC (15.8%) groups (a difference of 3.5 percentage points; 95% confidence interval: −6.8%–13.9%; P=0.470). Perioperative serum creatinine concentrations were similar in the control and RIC groups (P=0.494). Fluid balance, urine output, blood loss, transfusion, and vasopressor/inotropic requirements were not significantly different between the groups (all P>0.05). The occurrences of a composite of morbidity and mortality endpoints were not significantly different between the control (46.0%) and RIC (39.2%) groups (a difference of 6.8 percentage points; 95% confidence interval: −6.4%–20.0%; P=0.283).
Conclusions: The results of our study do not support repeated RIC to decrease the incidence of AKI after valvular heart surgery.
Clinical trial registration: NCT02720549.

Keywords: acute kidney injury; cardiac surgery; ischaemic post-conditioning

Editorial decision: 14 July 2018; **Accepted:** 14 July 2018

Editor's key points

- Remote ischaemic conditioning, typically with a tourniquet applied briefly to a limb, has shown promise in protecting vital organs from ischaemia reperfusion injury.
- In this single-centre trial, patients undergoing valvular heart surgery were randomised to usual care or to three remote ischaemic conditioning treatments during a 24 h period after cardiopulmonary bypass.
- There was a non-significant and small decrease in acute renal failure, and a composite of major adverse outcomes in the remote ischaemic conditioning group.
- As only 244 patients were included in this trial, it remains possible that there is a small but clinically important benefit attributable to remote ischaemic conditioning, which a much larger study might detect.

Acute kidney injury (AKI) occurs in up to 30% of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), and is strongly associated with increased morbidity and mortality.[1] Despite extensive research, the prevention of AKI after cardiac surgery remains a clinical challenge.

Remote ischaemic conditioning (RIC) before CPB was proposed to be a safe, effective intervention to attenuate ischaemia/reperfusion (I/R) injury of major organs, including the prevention of AKI.[2,3] However, successful clinical translation remains controversial, as two large multicentre randomised trials demonstrated no differences in renal outcome, and in the composite of morbidity endpoints, between the control and pre-CPB RIC group.[4,5]

Heterogeneities in the timing and 'dose' of RIC, and the patients' co-morbidities and anaesthetic regimen, have been suggested to influence the protective efficacy of pre-CPB RIC.[6–9] Notably, most clinical studies have included patients with coronary artery disease,[4,5] and could have been confounded by preoperative ischaemic episodes conferring direct ischaemic conditioning.[10] Moreover, considering the limited oxygen reserve of the renal medulla, ischaemic insults to the kidney elicited by haemodynamic instability would persist into the postoperative period, with the additional burden of systemic inflammation that usually peaks several hours after CPB. Thus, in the context of AKI prevention, the repeated application of RIC after CPB might be more advantageous than pre-CPB RIC in terms of a more constant delivery of the potentially protective stimulus.

Therefore, we hypothesised that repeated application of immediate and delayed RIC during this critical period after CPB might confer a renoprotective effect via sustained conditioning and anti-inflammatory and antioxidant mechanisms.[11,12] In this randomised controlled trial, we tested whether RIC performed upon the removal of the aortic cross-clamp and repeated two times after operation (12 and 24 h) could reduce the incidence of AKI after valvular heart surgery.

Methods

Participants

This study complied with the Declaration of Helsinki, and was approved by our institutional review board and registered at clinicaltrials.gov (NCT02720549). This study was conducted in a single tertiary-care university hospital (Yonsei Cardiovascular Hospital, Seoul, South Korea) from March 7, 2016 to March 30, 2017. Written informed consent was obtained from all participants. Patients aged 19–80 yr undergoing elective valvular heart surgery without coronary revascularisation were eligible for study enrolment. The following exclusion criteria were applied: history of peripheral nerve disease or peripheral vascular disease of the lower extremities; use of nicorandil, sulphonamide, or steroids (prednisolone >10 mg day^{-1} or equivalent); infective endocarditis; aortic dissection; myocardial infarction within 3 weeks before surgery; and Stage 4 or 5 chronic kidney disease.

Study protocol

The subjects were randomly allocated to either the control or RIC group using computer-generated codes with a block size of two. An investigator who was not involved in the care or in the assessment of endpoints confirmed each subject's group assignment, which was contained in an opaque envelope, and performed the RIC or sham RIC intervention. The group assignments were concealed from the attending anaesthesiologists, surgeons, and medical staff who were involved in the perioperative care of the subjects. The other investigators and statisticians were unblinded after the data acquisition from the last participant.

RIC was performed upon the removal of aortic cross-clamp, and repeated later at postoperative 12 and 24 h. A pneumatic tourniquet was placed on the thigh of each subject. In the RIC group, three cycles of 5 min inflation at 250 mm Hg and 5 min deflation were applied. In the control group, sham RIC was performed with pseudo-ischaemia at low pressure (20 mm Hg). The operating console of a stand-alone pneumatic tourniquet with pressure adjustment and integrated timer function was located behind the anaesthesia machine to conceal the RIC or sham RIC treatment from anaesthesiologists, surgeons, and other staff. To conceal the treatment assignment in the ICU, the pneumatic tourniquet was operated behind a screen.

Anaesthesia and postoperative care in the ICU were provided according to the institutional standard of care. Briefly, anaesthesia was induced using midazolam (0.05–0.07 mg kg^{-1}) and sufentanil (1.5–2 μg kg^{-1}), and maintained using sevoflurane in oxygen (40%)/air mixture and continuous administration of sufentanil at 0.5–1.5 μg kg^{-1} h^{-1}. CPB was with non-pulsatile flow, blood-containing cold cardioplegia, and α-stat management at 32–34°C. The haematocrit was maintained at >20% during CPB with ultrafiltration or transfusion of packed red blood cells. After CPB, packed red blood cells were transfused when the haematocrit decreased to <24%. Salvaged blood from the CPB circuit was processed using a cell salvage system, and administered after CPB. Norepinephrine was used as a first-line vasopressor, and vasopressin at an infusion rate of 2.4–4 unit h^{-1} was added when norepinephrine (up to 0.3 μg kg^{-1} min^{-1}) was insufficient to maintain the target mean arterial pressure (≥65 mm Hg). Milrinone was used in cases of ventricular systolic dysfunction or pulmonary hypertension. For fluid resuscitation, balanced synthetic colloid (Volulyte; Fresenius Kabi, Bad Homburg, Germany) (up to a maximal dose of 15 ml kg^{-1} day^{-1}) and balanced crystalloid (plasma solution A; CJ, Seoul, Korea) [6–8 ml kg^{-1} h^{-1} (intraoperatively) and 2–4 ml kg^{-1} h^{-1} (after operation)] were used.

Serum creatinine concentrations were measured before operation, and at postoperative 6, 24, 48, 72, and 120 h. Subject characteristics, including preoperative co-morbid conditions, medications, and operative and perioperative data, which

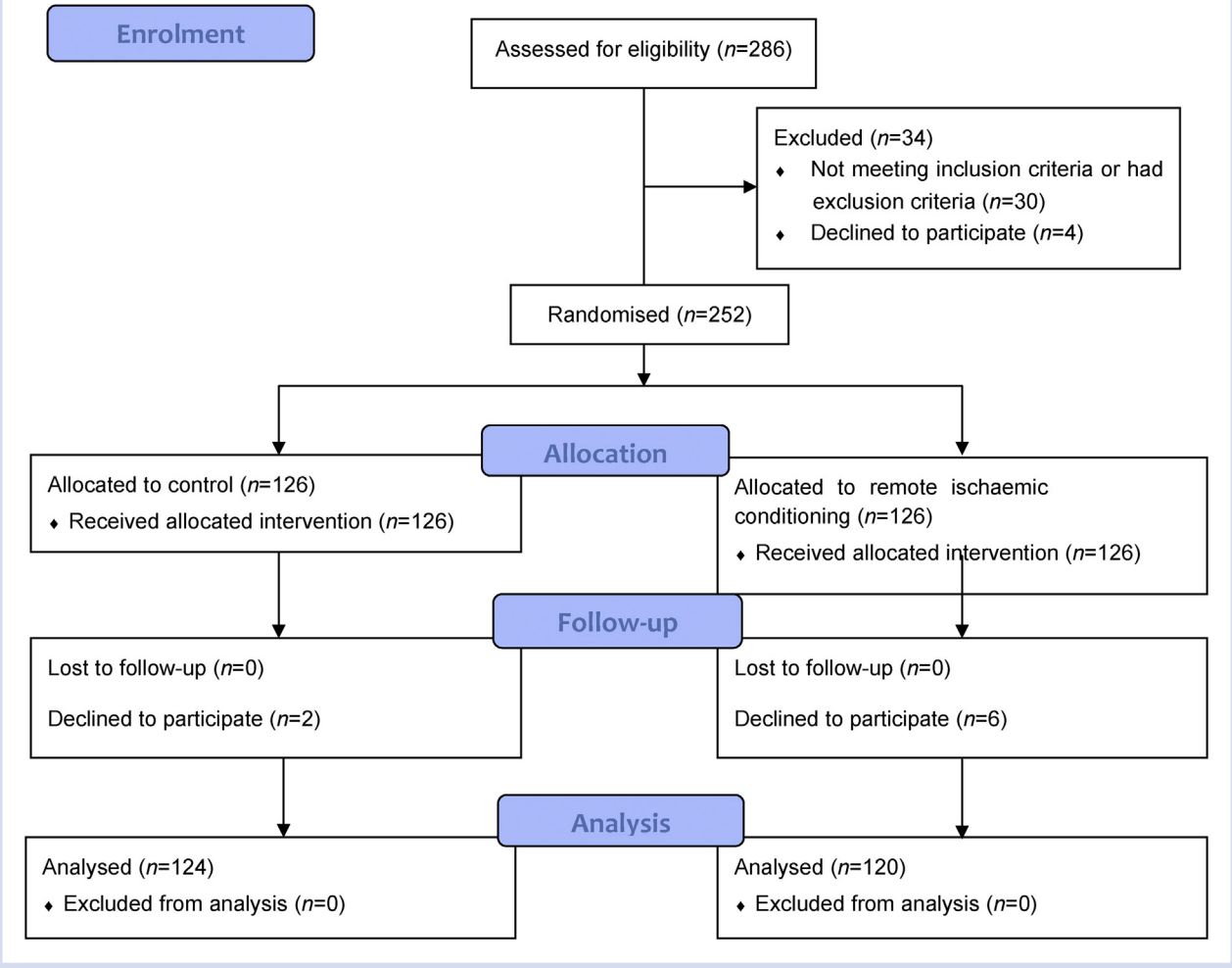

Fig 1. Consolidated Standards of Reporting Trials flow diagram.

include fluid requirement, urine output, transfusion, chest tube drainage, furosemide dose, and requirement for vasopressor/inotropes during surgery until postoperative 48 h, were recorded. Haemodynamic variables, including cardiac index, were recorded at the end of surgery, and postoperative 24 and 48 h. Creatine kinase-MB, haematocrit, leucocyte count, and serum albumin concentrations were measured before operation, and at postoperative 24 and 48 h.

Study endpoints

The primary endpoint was the incidence of AKI after surgery. According to the Kidney Disease: Improving Global Outcomes criteria,[13] AKI was defined as any of the following: increase in serum creatinine by ≥26.5 μmol L^{-1} within 48 h; or increase in serum creatinine to ≥1.5 times the baseline value, which is known or presumed to have occurred within the prior 7 days; or presence of oliguria, which is defined as urine output <0.5 ml kg^{-1} h^{-1} for 6 h within postoperative 48 h. AKI was staged as follows: Stage 1, 1.5–1.9 times the baseline or ≥26.5 μmol L^{-1} increase in serum creatinine or urine output <0.5 ml kg^{-1} h^{-1} for 6–12 h; Stage 2, serum creatinine 2.0–2.9 times the baseline or urine output <0.5 ml kg^{-1} h^{-1} for ≥12 h; and Stage 3, serum creatinine 3.0 times the baseline or increase in serum creatinine to ≥354 μmol L^{-1} or initiation of renal replacement therapy or urine output <0.3 ml kg^{-1} h^{-1} for ≥24 h or anuria for ≥12 h.

The secondary endpoints included the incidence of each stage of AKI; requirement for renal replacement therapy; incidence of a composite of morbidity and mortality endpoints consisting of permanent stroke, sternal wound infection, newly developed atrial fibrillation, mechanical ventilation >24 h, reoperation for bleeding, and in-hospital or 30-day mortality; and duration of ICU stay and hospitalisation.

Statistical analysis

According to our institutional database of electronic medical records, the incidence of AKI in the control group was expected to be 30%. Under the assumption that RIC would decrease the incidence of AKI to 15%, at least 120 patients were required per group when simulating the probability of a Type I error at 0.05 and a Type II error at 0.2. Considering a 5% dropout rate, the sample size was set at 126 patients per group.

Continuous variables were analysed using independent *t*-test or Mann–Whitney *U*-test, according to the results from

the Shapiro–Wilk test for normality. Serially measured data were analysed by repeated measures analysis of variance. Categorical variables were analysed using the χ^2 test or Fisher's exact test. *P*-values for multiple comparisons were adjusted by Bonferroni's method. All analyses were performed using SPSS 23 (IBM Corp., Armonk, NY, USA). *P*-values <0.05 were considered statistically significant.

Results

Two subjects in the control group and six subjects in the RIC group revoked their consent when they were asked whether they would continue to participate in the study before the application of RIC or sham treatment in the ICU. A total of 124 subjects in the control group and 120 subjects in the RIC group completed the study, and were included in the analysis (Fig. 1). The subjects' characteristics, including preoperative co-morbid conditions, medications, and type of operation, were comparable between groups (Table 1).

The incidence of AKI was not significantly different between the control and RIC groups [19.4% *vs* 15.8%, respectively, a difference of 3.5 percentage points; 95% confidence interval (CI): −6.8%–13.9%; *P*=0.470; Table 2]. The incidences of each stage of AKI, oliguria, and renal replacement therapy were not significantly different between the groups (all *P*>0.05). All patients who were diagnosed with AKI by urine output criteria also met the diagnosis by creatinine criteria. The mean serum creatinine concentrations throughout the study period were not significantly different (*P*=0.494) between the groups (Table 2).

The duration of surgery was significantly longer in the control group [222 (180–265) min *vs* 200 (155–250) min; Hodges–Lehmann median difference: 21 min; 95% CI: 5–37; *P*=0.016]. However, the duration of aortic cross-clamping was not significantly longer in the control group [85 (60–110) min *vs* 75 (55–103) min; Hodges–Lehmann median difference: 8 min; 95% CI: −2 to 16; *P*=0.126]. Patients in the control [309 (52–2711) μg] and RIC [168 (50–2282) μg] groups received comparable amounts of norepinephrine from the start of surgery to postoperative 48 h (Hodges–Lehmann median difference: 7 μg; 95% CI: −38 to 67; *P*=0.734). The percentage of patients who required vasopressin in the control (64.5%) and RIC (59.2%) groups did not differ significantly (a difference of 5.4 percentage points; 95% CI: −7.7 to 18.4; *P*=0.390). There was also no significant difference between the control (48.4%) and RIC (48.3%) groups in the proportion receiving inotropic support (a difference of 0.1 percentage points; 95% CI: −13.3 to 13.4; *P*=0.993). At all time points, the measured cardiac indices were similar in the two groups. Perioperative fluid balance, blood loss, and transfusion requirement were also not significantly different between the groups (Table 3). The concentrations of creatine kinase-MB, haemoglobin, white blood cell count, and albumin measured before operation and at 24 and 48 h after surgery were comparable between the two groups (Table 4).

The incidences of a composite of morbidity endpoints and mortality were not significantly different between the control (46.0%) and RIC (39.2%) groups (a difference of 6.8 percentage points; 95% CI: −6.4 to 20.0; *P*=0.283) (Table 5). The median duration of ICU stay and hospitalisation was not significantly different between the two groups (Table 5).

Table 1 Subject characteristics. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; RAS, renin–angiotensin system; RIC, remote ischaemic conditioning; SD, standard deviation

	Control (*n*=124)	RIC (*n*=120)
Age, mean (range) (yr)	58 (21–82)	59 (25–80)
Female sex, *n* (%)	64 (51.6)	63 (52.5)
Body surface area, mean (SD) (m^2)	1.67 (0.18)	1.66 (0.19)
Hypertension, *n* (%)	43 (34.7)	50 (41.7)
Diabetes mellitus, *n* (%)	10 (8.1)	11 (9.2)
COPD, *n* (%)	2 (1.6)	3 (2.5)
Cerebrovascular accident, *n* (%)	24 (19.4)	16 (13.3)
Congestive heart failure, *n* (%)	44 (35.5)	30 (25)
Atrial fibrillation, *n* (%)	56 (45.2)	44 (36.7)
Medications, *n* (%)		
Beta-blocker	41 (33.1)	45 (37.5)
Calcium channel blocker	19 (15.3)	24 (20.0)
RAS inhibitor	50 (40.3)	61 (50.8)
Statin	37 (29.8)	38 (31.1)
Anti-platelet	22 (17.7)	34 (28.3)
Diuretics	79 (63.7)	75 (62.5)
Digoxin	29 (23.4)	22 (18.3)
CKD stage 2 or 3, *n* (%)	47 (37.9)	47 (39.2)
EuroSCORE, median (inter-quartile range)	4 (2–8)	4 (2–7)
Redo surgery, *n* (%)	33 (26.6)	24 (20.0)
Type of operation, *n* (%)		
Mitral valve alone	37 (29.8)	25 (20.8)
Aortic valve alone	28 (22.6)	41 (34.2)
Double-valve surgery	42 (33.9)	45 (37.5)
Valve+aorta	9 (7.3)	4 (3.3)
Others	8 (6.5)	5 (4.2)

Discussion

RIC applied on the thigh upon the removal of the aortic cross-clamp and repeated at postoperative 12 and 24 h did not significantly reduce the incidence of either AKI or renal

Table 2 Degree of renal injury and changes in renal function. RIC, remote ischaemic conditioning

	Control (*n*=124)	RIC (*n*=120)	*P*-value
Acute kidney injury, *n* (%)	24 (19.4)	19 (15.8)	0.470
Stage 1, *n* (%)	18 (14.5)	14 (11.7)	
Stage 2, *n* (%)	3 (2.4)	3 (2.5)	
Stage 3, *n* (%)	3 (2.4)	2 (1.7)	
Oliguria, *n* (%)	4 (3.2)	2 (1.7)	0.427
Renal replacement therapy, *n* (%)	3 (2.4)	2 (1.7)	1.000
Serum creatinine, median (inter-quartile range) (μmol L^{-1})			
Baseline	66 (56–86)	69 (58–83)	0.861
Postoperative 6 h	62 (50–80)	62 (51–73)	0.783
Postoperative 24 h	69 (55–89)	68 (58–88)	0.704
Postoperative 48 h	67 (51–86)	66 (55–88)	0.903
Postoperative 72 h	62 (47–74)	60 (49–79)	0.596
Postoperative 120 h	57 (48–70)	56 (48–70)	0.642

Table 3 Intraoperative and 48 h postoperative data. RIC, remote ischaemic conditioning

	Control (n=124)	RIC (n=120)	P-value
Duration of surgery, median (inter-quartile range) (min)	222 (180–265)	200 (155–250)	0.016
Duration of aortic cross-clamp, median (inter-quartile range) (min)	85 (60–110)	75 (55–103)	0.126
Norepinephrine dose, median (inter-quartile range) (μg)	309 (52–2711)	168 (50–2282)	0.734
Patients who required vasopressin, n (%)	80 (64.5)	71 (59.2)	0.390
Patients who required inotropes, n (%)	60 (48.4)	58 (48.3)	0.993
Cardiac index, median (inter-quartile range) (L min^{-1} m^{-2})			
End of surgery	2.7 (2.1–3.1)	2.7 (2.3–3.1)	0.478
Postoperative 24 h	2.9 (2.7–3.5)	3.0 (2.5–3.5)	0.588
Postoperative 48 h	3.0 (2.4–3.4)	3.0 (2.6–3.9)	0.482
Crystalloid, median (inter-quartile range) (ml)	5334 (4571–6273)	5476 (4841–6156)	0.315
Colloid, median (inter-quartile range) (ml)	595 (475–720)	590 (490–850)	0.306
Chest tube drainage, median (inter-quartile range) (ml)	577 (420–804)	548 (369–745)	0.190
Urine output, median (inter-quartile range) (ml)	6018 (5155–6958)	6150 (5085–7245)	0.432
Packed red blood cell, median (inter-quartile range) (ml)	250 (0–505)	250 (0–500)	0.183
Fresh frozen plasma, median (inter-quartile range) (ml)	255 (0–480)	0 (0–375)	0.066
Platelet concentrate, median (inter-quartile range) (ml)	0 (0–240)	0 (0–235)	0.285
Furosemide dose, median (inter-quartile range) (mg)	73 (60–90)	73 (55–93)	0.959

replacement therapy. The overall incidences of a composite of morbidity and mortality endpoints were also not significantly different between the two groups.

Since Przyklenk and colleagues[14] discovered the possible salutary effect of RIC, numerous experimental studies consistently confirmed its protective efficacy against I/R injury.[2] RIC by way of limb I/R with a pneumatic tourniquet was rapidly translated into clinical trials. Despite some encouraging results,[3] evidence for the beneficial effects of RIC in the clinical setting remains unconvincing.[15] Two large, multicentre trials did not demonstrate a favourable renal outcome with RIC, although the impact of RIC on renal function was not the primary endpoint.[4,5] However, RIC treatment was performed only once after the induction of anaesthesia. Also, most of the enrolled patients had coronary artery disease and received propofol, which may attenuate the RIC-induced protection.[16] Additional possible explanations for the conflicting results on the renoprotective effect of RIC encompass heterogeneity in patient populations, including co-morbidities and preoperative medications, outcome measures based on diverse definitions, and varied timing and 'dose' of the conditioning stimulus.[7–9]

In comparison with previous studies using pre-CPB RIC, repeated RIC at postoperative 12 and 24 h, in addition to that given upon the removal of the aortic cross-clamp, may confer additive protection. Systemic inflammatory response after CPB and renal hypoperfusion as a result of haemodynamic deterioration during the early postoperative period are known to play important roles in the development of postoperative AKI. In experimental studies, the sustained anti-inflammatory or antioxidant effect provided by repeated RIC was suggested to provide additional long-term protection.[11,12] Thus, we hypothesised that repetition of RIC during the immediate postoperative period might extend the period of protection. Prior experimental studies performed RIC daily or twice daily.[11,12,17,18] For a more constant provision of the potentially protective stimulus during the critical period, we decided to apply the treatment upon reperfusion, and at 12 and 24 h after operation.

Despite the biological plausibility of our approach, repeated RIC did not significantly reduce the incidence of AKI, which may be attributable to several reasons. First, the organ-protective effect of RIC against I/R injury has been suggested to be more effective in moderate-to high-risk patients.[8] RIC significantly reduced AKI incidence in high-risk patients, as identified with a Cleveland Clinic Foundation score[19] of ≥6, in a recent multicentre trial by Zarbock and colleagues.[3] Notably, reduced incidence of AKI was prominent in more severe forms (AKI stages 2 and 3, and need for renal replacement therapy) in that study. In contrast, only five of our studied patients had a Cleveland Clinic Foundation score of ≥6 and the overall incidence of AKI was low, with most patients in the present study having Stage 1 disease.

Second, many studies have shown that several co-morbidities and medications can interfere with the efficacy of RIC-induced protection.[6] Some of those factors, such as diabetes, old age, beta-blockers, and statins, can be frequently found in patients undergoing cardiovascular surgery and can potentially negate the effect of RIC. We did not exclude those patients to avoid compromising the generalisability of the results.

Third, the choice of anaesthetics can also influence the effect of RIC. Propofol, which is known to attenuate the protective effect of RIC,[16] was not used in the present study. The inhalation anaesthetics and opioids used in this study are known to be protective against I/R injury via the activation of the signalling pathway involving various protein kinases and ATP-sensitive potassium channels in a similar manner to RIC.[20] When both the anaesthetic and RIC are applied simultaneously, the interaction between them is not yet elucidated. Owing to the shared signalling pathways, ischaemic- and volatile-anaesthetic-induced conditioning can act additively.[21] However, clinical studies have not found evidence for an additive effect of RIC in the presence of anaesthetic-induced conditioning.[22] In addition, a meta-analysis suggested that volatile anaesthetics might be associated with attenuated response to RIC.[23]

This study has some limitations. First, the sample-size calculation based upon both a 30% incidence of AKI and a 50% reduction in AKI with RIC was probably unrealistic. The numerical difference in the incidence of AKI in this study may be considered to be clinically relevant; however, this study

Table 4 Cardiac enzyme and haematological variables. RIC, remote ischaemic conditioning

	Control (n=124)	RIC (n=120)	P-value
Creatine kinase-MB, median (inter-quartile range) (ng ml^{-1})			
Preoperative	1.40 (1.1–1.9)	1.3 (1.0–1.9)	0.550
Postoperative 24 h	26.9 (16.0–58.6)	23.2 (14.8–45.1)	0.227
Postoperative 48 h	23.4 (14.1–47.0)	23.0 (13.7–43.8)	0.648
Haematocrit, median (inter-quartile range) (%)			
Preoperative	39 (35–43)	39 (37–43)	0.591
Postoperative 24 h	30 (27–34)	31 (28–33)	0.754
Postoperative 48 h	28 (26–31)	28 (26–31)	0.862
Leucocyte count, median (inter-quartile range) (μl^{-1})			
Preoperative	5775 (4875–7070)	6040 (4915–7365)	0.325
Postoperative 24 h	13 815 (11 252–18 075)	14 485 (11 168–17 790)	0.389
Postoperative 48 h	12 020 (10 230–15 683)	12 470 (10 275–16 650)	0.314
Albumin, median (inter-quartile range) (g dl^{-1})			
Preoperative	4.2 (3.9–4.4)	4.1 (3.9–4.4)	0.936
Postoperative 24 h	3.4 (3.2–3.6)	3.4 (3.2–3.6)	0.563
Postoperative 48 h	3.3 (3.2–3.5)	3.4 (3.2–3.5)	0.092

Table 5 Postoperative outcomes. A-fib, atrial fibrillation; RIC, remote ischaemic conditioning

	Control (n=124)	RIC (n=120)	P-value
Composite of endpoints, n (%)	57 (46.0)	47 (39.2)	0.283
Stroke, n (%)	0 (0)	1 (0.8)	1.000
Sternal infection, n (%)	1 (0.8)	1 (0.8)	1.000
Newly developed A-fib, n (%)	10 (8.1)	11 (9.2)	1.000
Haemostatic reoperation, n (%)	4 (3.2)	2 (1.7)	1.000
Mechanical ventilation >24 h, n (%)	24 (19.4)	12 (10.0)	0.273
Mortality, n (%)	3 (2.4)	1 (0.8)	1.000
Length of ICU stay, median (inter-quartile range) (day)	3 (2–3)	3 (2–3)	0.462
Length of hospital stay, median (inter-quartile range) (day)	10 (8–13)	10 (8–12)	0.209

was under-powered to detect this treatment effect. The results in this study were also imprecise (wide confidence intervals), and the statistically negative results might have been false-negative findings (or Type II error). Second, the patients were not completely blinded to the RIC procedure. The first conditioning stimulus was applied to anaesthetised patients; however, the second and third stimuli were performed at postoperative 12 and 24 h, during which most patients were fully awake and others were sedated. Different levels of sedation at postoperative 12 and 24 h might have confounded the effect of RIC, as several studies have found that pain is one of the important triggers of RIC.[24]

In conclusion, repeated RIC immediately, and 12 and 24 h after the release of the aortic clamp, did not significantly reduce the incidence and degree of AKI after valvular heart surgery. The occurrences of a composite of morbidity and mortality endpoints were also not significantly different in the RIC and control groups.

Authors' contributions

Study design: W.K.L., Y.L.K.
Data collection: W.K.L., S.L., H.J.K.
Data analysis: J.W.S., J.K.S., Y.L.K.
First drafting of manuscript: J.W.S.
Revising of manuscript: J.W.S., J.K.S., Y.L.K.

Declaration of interest

The authors declare that they have no conflicts of interest.

References

1. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol* 2006; **1**: 19–32
2. Przyklenk K, Whittaker P. Remote ischemic preconditioning: current knowledge, unresolved questions, and future priorities. *J Cardiovasc Pharmacol Ther* 2011; **16**: 255–9
3. Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015; **313**: 2133–41
4. Hausenloy DJ, Candilio L, Evans R, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* 2015; **373**: 1408–17
5. Meybohm P, Bein B, Brosteanu O, et al. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* 2015; **373**: 1397–407
6. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev* 2014; **66**: 1142–74
7. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev* 2003; **83**: 1113–51
8. Gassanov N, Nia AM, Caglayan E, Er F. Remote ischemic preconditioning and renoprotection: from myth to a novel therapeutic option? *J Am Soc Nephrol* 2014; **25**: 216–24
9. Zaugg M, Lucchinetti E. Remote ischemic preconditioning in cardiac surgery—ineffective and risky? *N Engl J Med* 2015; **373**: 1470–2

10. Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. *J Cardiothorac Vasc Anesth* 2007; **21**: 664–71
11. Drunalini Perera PN, Hu Q, Tang J, et al. Delayed remote ischemic postconditioning improves long term sensory motor deficits in a neonatal hypoxic ischemic rat model. *PLoS One* 2014; **9**, e90258
12. Wei M, Xin P, Li S, et al. Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction. *Circ Res* 2011; **108**: 1220–5
13. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013; **17**: 204
14. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893–9
15. Menting TP, Wever KE, Ozdemir-van Brunschot DM, Van der Vliet DJ, Rovers MM, Warle MC. Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. *Cochrane Database Syst Rev* 2017; **3**. Cd010777
16. Kottenberg E, Musiolik J, Thielmann M, Jakob H, Peters J, Heusch G. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2014; **147**: 376–82
17. Luca MC, Liuni A, McLaughlin K, Gori T, Parker JD. Daily ischemic preconditioning provides sustained protection from ischemia–reperfusion induced endothelial dysfunction: a human study. *J Am Heart Assoc* 2013; **2**, e000075
18. Kono Y, Fukuda S, Hanatani A, et al. Remote ischemic conditioning improves coronary microcirculation in healthy subjects and patients with heart failure. *Drug Des Devel Ther* 2014; **8**: 1175–81
19. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005; **16**: 162–8
20. Zaugg M, Lucchinetti E, Uecker M, Pasch T, Schaub MC. Anaesthetics and cardiac preconditioning. Part I. Signalling and cytoprotective mechanisms. *Br J Anaesth* 2003; **91**: 551–65
21. Toller WG, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. *Anesthesiology* 1999; **91**: 1437–46
22. Lucchinetti E, Bestmann L, Feng J, et al. Remote ischemic preconditioning applied during isoflurane inhalation provides no benefit to the myocardium of patients undergoing on-pump coronary artery bypass graft surgery: lack of synergy or evidence of antagonism in cardioprotection? *Anesthesiology* 2012; **116**: 296–310
23. Zhou C, Liu Y, Yao Y, et al. Beta-blockers and volatile anesthetics may attenuate cardioprotection by remote preconditioning in adult cardiac surgery: a meta-analysis of 15 randomized trials. *J Cardiothorac Vasc Anesth* 2013; **27**: 305–11
24. Steensrud T, Li J, Dai X, et al. Pretreatment with the nitric oxide donor SNAP or nerve transection blocks humoral preconditioning by remote limb ischemia or intra-arterial adenosine. *Am J Physiol Heart Circ Physiol* 2010; **299**: H1598–603

Handling editor: M. Avidan