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Remote Ischemic Preconditioning: Would you give your right to arm to protect your kidneys?

(Commentary on 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. (1538-3598 (Electronic)).)

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The incidence of acute kidney injury (AKI) following cardiac bypass surgery can be as high as 30%[1] and even a rise in serum creatinine smaller than the criterion for AKI after cardiac surgery is associated with an increased post-surgical morbidity and mortality[2]. While the etiology of AKI following surgery is multi-factorial and the precise underlying mechanisms remain unclear, acute tubular injury is the predominant pathology in severe cases of AKI. Although numerous strategies have been investigated to minimize AKI during cardiac surgery, there is currently no effective renoprotective intervention in clinical use[3].

In this context, remote ischemic preconditioning (RIPC), which refers to the phenomenon whereby transient non-lethal episodes of ischemia and reperfusion to a remote organ or tissue confer multi-organ protection against a sustained episode of ischemia/reperfusion to an organ of interest, may hold promise[4,5]. The results of studies investigating the potential for RIPC, performed using transient limb ischemia and reperfusion, to reduce the incidence of AKI following cardiac surgery have been inconsistent. It is therefore not surprising that the recently published study titled “Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial” by Zarbock et al[6] in the Journal of American Medical Association has attracted significant attention.

WHAT DOES THIS IMPORTANT STUDY SHOW?

This multi-center study by Zarbock et al[6] investigated the effect of RIPC on AKI in 240 patients undergoing on-pump cardiac bypass surgery. Only patients with chronic kidney disease at high-risk of developing AKI (as defined

by a Cleveland Clinical Foundation score[7] of ≥ 6) were eligible. The RIPC protocol comprised of 3 cycles of 5-minute upper arm cuff inflations/deflations. The study primary endpoint was the incidence of AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[8] within the first 72 hours. Secondary endpoints included renal replacement therapy (RRT), myocardial infarction (MI), stroke, in-hospital and 30-day mortality; duration of intensive care unit and hospital courses; and changes in kidney injury biomarkers.

Participants randomized to receive RIPC prior to cardiac surgery experienced a 15% absolute risk reduction in the incidence of AKI when compared to the non-RIPC sham control. Among secondary endpoints, RIPC was associated with a 10% absolute risk reduction in RRT and lower levels of AKI biomarkers (Neutrophil Gelatinase-Associated Lipocalin [NGAL] and Tissue Inhibitor of MetalloProteinases-2 [TIMP-2] and Insulin-Like Growth Factor Binding Protein 7 [IGFBP7]), although there were no differences in the incidence of MI, stroke or mortality at 30 days. Finally, although RIPC reduced the duration of intensive care unit stay, there was no difference in the overall length of hospital stay.

There are several strengths to the study: (1) this was a multi-center study which only included patients at high-risk of AKI (as reflected by a high incidence of AKI of 52.5% in the control arm); (2) patients were administered volatile anesthesia instead of propofol, given the potential confounding effects of the latter on RIPC cardioprotection in the setting of cardiac surgery[9,10]; and (3) investigators attempted to maintain blinding of the treatment allocation by using a low cuff inflation sham RIPC protocol.

Despite its numerous strengths, there are several minor limitations. Firstly, despite using the KDIGO criteria to grade AKI[8], Zarbock et al[6] used a cut-off of 72 hours to include patients with an increase in serum creatinine by ≥ 0.3mg/dl from baseline rather than 48 hours as specified by the guideline[8]. Secondly, they did not report on the pre-existing use or intra-operative use of nitrates[11] in each group, an agent which may have the potential to interfere with RIPC cardioprotection during cardiac surgery[12]. Finally, although the incidence of AKI was very high in the control arm, the follow-up time for major clinical endpoints was relatively short, and a longer duration of follow-up may have been more informative.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Despite intensive investigation the actual mechanisms underlying organ protection elicited by limb RIPC remain unclear[4,5,13]. The current paradigm suggests that a blood-borne transferrable protective factor(s) is released in response to the limb RIPC stimulus[5]. The identity of the factor(s) remains unknown, although it is believed to be a peptide of less than 30 KiloDaltons in size - its release into the blood stream is dependent on an intact neural pathway to the RIPC-treated limb[5,14].

The first study to investigate the effect of RIPC on the incidence of AKI following cardiac surgery was by Venugopal et al[15] in 2010, which reported a lower incidence of AKI in patients undergoing CABG±valve surgery. However, subsequent studies investigating the potential renoprotective effects of RIPC in the setting of cardiac bypass surgery have produced mixed results (Table 1). A recent meta-analysis of these randomized clinical trials did show a

benefit of RIPC on kidney outcomes following cardiac surgery, although the included studies used an array of different kidney outcomes[16].

The positive trial by Zarbock et al[6] of 240 patients is the largest study to prospectively investigate the effect of RIPC on the incidence of AKI in the setting of cardiac surgery, and it was sufficiently powered for this outcome; in contrast, many of the previous studies had fewer patients and kidney outcomes were not primary endpoints. Zarbock et al[6] specifically selected patients with chronic kidney disease, a population that would be expected to be at highest risk of developing post-surgical AKI, whereas other studies have not restricted the study population based on the level of pre-operative kidney function. In the study by Zarbock et al[6], volatile anesthesia was used instead of the intravenous anesthetic, propofol. It has been suggested in one small 72 patient study that RIPC may not reduce peri-operative myocardial injury during cardiac surgery[9,10] in the presence of propofol. Whether the use of propofol is enough to explain the neutral results observed in some of the past studies investigating the effect of RIPC on AKI is not clear, given that there appears to be no obvious correlation between the use of propofol and the absence of RIPC-associated benefits in prior trials (Table 1).

Whether the benefits observed in some of the phase II studies can translate to an improvement in clinical outcome in larger studies remains to be tested. However, the long-awaited ERICCA trial[17], announced at the latest American College of Cardiology Scientific Session, showed that RIPC did not improve one-year clinical outcomes (cardiovascular death, MI, revascularization and stroke) in a cohort of 1612 patients. Importantly, RIPC had no effect on the incidence of AKI during cardiac surgery (a secondary

endpoint). The results of the RIPHeart trial, in which AKI was a component of the primary endpoint, are eagerly awaited[18].

Interestingly, RIPC has been reported to confer renoprotection in several other clinical settings including major vascular surgery[19,20], elective percutaneous coronary intervention for stable coronary artery disease[21,22], primary PCI for ST-segment elevation myocardial infarction patients[23,24], and kidney transplantation[25], although again not all studies have been positive[26,27].

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Strategies to protect against AKI during cardiac surgery have remained elusive. RIPC may be a feasible and low-cost therapeutic intervention meeting this need that could potentially confer additional neuroprotective and cardioprotective benefits. To date, no significant adverse effects have been reported with RIPC, and the discomfort associated with cuff inflation is not an issue in anesthetized patients.

Currently, RIPC cannot be routinely recommended for kidney and heart protection during cardiac surgery as there is no evidence that it improves clinical outcome in this clinical setting. However, the study by Zarbock et al[6] has set the scene for a large scale randomized controlled trial, which accounts for patient risk factors and the choice of anesthetic agent, to confirm if RIPC can reduce the incidence of AKI and assess whether RIPC can improve clinical outcomes in patients undergoing cardiac bypass surgery.

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Table 1 Major studies investigating renoprotective effect of RIPC during cardiac surgery

Study	N	Clinical setting	RIPC protocol	Anesthesia	Result	Notes
Positive studies						
Venugopal et al 2010[15]	78	Adult CABG ± valve	Three-5 min arm I/R vs un-inflated cuff	60% volatile/40% propofol	Reduction in AKI	Diabetic patients excluded. Secondary renal endpoint
Zimmermann et al 2011[28]	118	Adult CABG ± valve	Three-5 min arm I/R vs no sham	100% volatile only	Reduction in AKI	Primary renal endpoint
Candilio et al 2015[12]	178	Adult CABG ± valve	Two-5 min arm and leg I/R vs un-inflated cuff	85% both volatile and propofol	Reduction in AKI (borderline-significant P=0.06)	Secondary renal endpoint
Zarbock et al 2015[6]	240	Adult CABG ± valve	Three-5 min arm I/R vs low inflation pressure sham	100% volatile only	Reduction in renal biomarkers (NGAL and TIMP-2 × IGFBP7), AKI and need for dialysis	Primary renal endpoint
Neutral studies						
Choi et al 2011[29]	76	Adult valve ± CABG	Three-10 min leg I/R vs un-inflated cuff	100% volatile	No difference in renal biomarkers (cystatin C and NGAL) or AKI	Primary renal endpoint
Rahman et al 2011[30]	162	Adult CABG only	Three-5 min arm I/R vs proper sham RIPC protocol	98% volatile	No difference in serum Cr at 4 days or dialysis	Secondary renal endpoint
Young et al 2012[31]	96	Adult CABG ± valve	Three-5 min arm I/R vs proper sham RIPC protocol	Both volatile and propofol	No difference in AKI	Secondary renal endpoint
Meybohm et al 2014[32]	180	Adult CABG ± valve	Four-5 min arm I/R vs proper sham RIPC protocol	100% propofol	No difference in AKI	Secondary renal endpoint
Gallagher et al 2014 [33]	86	Adult CABG ± valve	Three-5 min arm I/R vs un-inflated cuff	87% volatile/13% ICCF	No difference in serum Cr at 4 days or dialysis	Selected CKD patients with low eGFR (<60) Primary renal endpoint

I/R= Ischemia/Reperfusion; AKI=acute kidney injury; CABG=coronary artery bypass graft; Cr=creatinine; eGFR=estimated glomerular filtration rate; ICCF=Intermittent cross-clamp fibrillation; RIPC=remote ischemic preconditioning; CKD=chronic kidney disease