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In the Literature

Remote Ischemic Preconditioning: Would You Give Your Right 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. JAMA. 2015;313(21):2133-2141.

The incidence of acute kidney injury (AKI) following cardiac bypass surgery can be as high as 30%,[1] and even an increase in serum creatinine level smaller than the criterion for AKI after cardiac surgery is associated with increased postsurgical morbidity and mortality.[2] Although the cause of AKI following surgery is multifactorial and the precise underlying mechanisms are 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 nonlethal episodes of ischemia and reperfusion to a remote organ or tissue confer multiorgan protection against a sustained episode of ischemia-reperfusion to an organ of interest, may hold promise.[4,5] 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 the American Medical Association* has attracted significant attention.

WHAT DOES THIS IMPORTANT STUDY SHOW?

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

Participants randomly assigned to receive RIPC prior to cardiac surgery experienced a 15% absolute risk reduction in the incidence of AKI compared to the non-RIPC sham control. Among secondary end points, RIPC was associated with a 10% absolute risk reduction in renal replacement therapy and lower levels of AKI biomarkers (neutrophil gelatinase-associated lipocalin [NGAL], tissue inhibitor of metalloproteinase 2 [TIMP-2], and insulin-like growth factor binding protein 7 [IGFBP7]), although there were no differences in the incidence of myocardial infarction, 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 multicenter study that only included patients at high risk for 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. First, despite using KDIGO criteria to grade AKI,[8] Zarbock et al[6] used a cutoff of 72 hours to include patients with an increase in serum creatinine level ≥ 0.3 mg/dL from baseline, rather than 48 hours as specified by the guideline.[8] Second, they did not report on pre-existing or intraoperative use of nitrates[11] in each group, an agent that 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, follow-up time for major clinical end points was relatively short, and longer follow-up may have been more informative.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Despite intensive investigation, the mechanisms underlying organ protection elicited by limb RIPC are unclear,[4,5,13] The current paradigm suggests that a blood-borne transferrable protective factor(s) is

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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[15] (2010)	78	Adult CABG ± valve	Three 5-min arm ischemia-reperfusion vs uninflated cuff	60% volatile/40% propofol	Reduction in AKI	Diabetic patients excluded; secondary kidney end point
Zimmerman et al[28] (2011)	118	Adult CABG ± valve	Three 5-min arm ischemia-reperfusion vs no sham	100% volatile only	Reduction in AKI	Primary kidney end point
Candilio et al[12] (2015)	178	Adult CABG ± valve	Two 5-min arm and leg ischemia-reperfusion vs uninflated cuff	85% both volatile and propofol	Reduction in AKI (borderline significant $P = 0.06$)	Secondary kidney end point
Zarbock et al[6] (2015)	240	Adult CABG ± valve	Three 5-min arm ischemia-reperfusion vs low inflation pressure sham	100% volatile only	Reduction in renal biomarkers (NGAL and TIMP-2 × IGFBP7), AKI, and need for dialysis	Primary kidney end point
			Neutral Studies			
Choi et al[29] (2011)	76	Adult valve ± CABG	Three 10-min leg ischemia-reperfusion vs uninflated cuff	100% volatile	No difference in renal biomarkers (cystatin C and NGAL) or AKI	Primary kidney end point
Rahman et al[30] (2011)	162	Adult CABG only	Three 5-min arm ischemia-reperfusion vs proper sham RIPC protocol	98% volatile	No difference in serum creatinine at 4 d or dialysis	Secondary kidney end point
Young et al[31] (2012)	96	Adult CABG ± valve	Three 5-min arm ischemia-reperfusion vs proper sham RIPC protocol	Both volatile and propofol	No difference in AKI	Secondary kidney end point
Meybohm et al[32] (2014)	180	Adult CABG ± valve	Four 5-min arm ischemia-reperfusion vs proper sham RIPC protocol	100% propofol	No difference in AKI	Secondary kidney end point
Gallagher et al[33] (2014)	86	Adult CABG ± valve	Three 5-min arm ischemia-reperfusion vs uninflated cuff	87% volatile/13% ICCF	No difference in serum creatinine at 4 d or dialysis	Selected CKD patients with low eGFR (<60 mL/min/1.73 m^2); primary kidney end point

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICCF, intermittent cross-clamp fibrillation; IGFBP7, insulin-like growth factor binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; RIPC, remote ischemic preconditioning; TIMP-2, tissue inhibitor of metalloproteinase 2.

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