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Can remote ischaemic preconditioning prevent AKI?

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Abstract

A randomized multicentre controlled study of 240 cardiac surgery patients at high risk of acute kidney injury (AKI) has demonstrated that remote ischaemic preconditioning can reduce the rate of AKI and requirement for renal replacement therapy. These findings suggest this procedure could be a promising therapeutic option for this high-risk patient group.

Acute kidney injury (AKI) affects up to 30% of patients undergoing cardiac surgery, of which 1–2% will require renal replacement therapy (RRT).[1] AKI results in a marked increase in morbidity and mortality, even in cases where kidney injury is modest, with an increased risk of death in those who require acute dialysis or have a 50% reduction in glomerular filtration rate compared to those with normal kidney function.[1] Furthermore, AKI can promote the onset of chronic kidney disease (CKD) and accelerate the progression to end-stage renal disease (ESRD). Despite numerous efforts to identify appropriate treatments for AKI, no proven effective therapeutic options have been developed. To address this issue, Zarbock and colleagues performed a prospective double-blind study of 240 patients undergoing cardiac surgery at high risk of AKI (Cleveland Clinic score ≥6), in which the effect of remote ischaemic preconditioning (RIPC) on the rate and severity of AKI was compared to a sham procedure.[2] RIPC consisted of three cycles of ischaemia by arm cuff inflation to 200 mmHg (or ≥50 mmHg higher than systolic blood pressure), followed by 5 min reperfusion by cuff deflation. For the sham control group, the cuff was inflated to 20 mmHg, followed by 5 min cuff deflation. The primary end point was the occurrence of AKI (as defined by KDIGO criteria) within 72 h of cardiac surgery. All patients completed 30 days of follow-up after surgery and were analyzed by the intention-to-treat principle.

As presented at the ERA–EDTA 2015 meeting in London, UK, the researchers found the incidence of AKI to be significantly lower in the RIPC group (37.5%) compared to those in the control group (52.5%), with an absolute risk reduction of 15%.[2] When the data were stratified by AKI stage, the number of moderate and severe cases of AKI was reduced, with no difference in the rate of mild cases. Fewer patients in the RIPC treatment group received

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Competing interests

J.V.B. consults on AKI for Astellas Pharma, AbbVie, and Takeda and consults and holds equity in MediBeacon, Sentien Biotechnologies, Inc., and Thrasos Therapeutics. J.V.B. is a co-inventor on KIM-1 patents assigned to Partners HealthCare and licensed to Johnson & Johnson, Sekisui Diagnostics LLC, Novartis, Biogen IDEC, and Astute Medical. He has received grant support from Novo Nordisk and Roche. A.Z. declares no competing interests.

RRT compared to control patients (5.8% versus 15.8%, respectively) and the length of stay in the intensive care unit was shorter (3 versus 4 days, respectively). No significant effects on the secondary end points of in-hospital and 30-day mortality, mechanical ventilation, myocardial infarction, or stroke were observed. RIPC was associated with a significant reduction in urine levels of the AKI biomarkers TIMP-2 and IGFBP7, 4 h and 12 h after surgery compared to the control group. Additionally, urinary NGAL—a marker of inflammation and renal tubular injury—was significantly reduced at 4 h after cardiac surgery in those who underwent RIPC, compared to the sham control group.

The phenomenon of renal protection afforded by prior renal injury was first described >100 years ago in the setting of nephrotoxic AKI, where the rat kidney became resistant to repeated nephrotoxic insults.[3] Prior exposure to ischaemia or ureteral obstruction in rats or mice also results in renal protection when the kidneys are exposed to a subsequent ischaemic insult after 1 or 8 days.[4,5] Such protection has been shown to last up to 12 weeks depending on the length of ischaemic preconditioning time.[6] These data have led to the view that an episode of AKI imprints biologic memory on residual tubules, which reprogrammes the nephron response to further tubular injury.[4,5] Others have hypothesized that the beneficial consequences of RIPC might be associated with endothelial and hormonal responses that can affect vascular reactivity and reduce subsequent vasoconstriction.[6–8] In RIPC, ischaemia in one vascular bed can afford protection against ischaemia in another vascular bed in the same or different organ.[8] This protective effect was initially demonstrated in the heart by occluding the circumflex artery to protect the myocardium from subsequent left anterior descending coronary artery occlusion.[7] In clinical practice, the vascular bed of choice for RIPC is the upper arm where ischaemia is minimally invasive, safe, inexpensive, and easy to perform.

Although Zarbock and colleagues did not show that RIPC elicited a change in mortality or hospital length of stay,[2] the procedure might exert a long-term benefit on renal function. The presented data are provocative in demonstrating that RIPC has a beneficial effect in reducing the rate of moderate and severe AKI in high-risk patients undergoing cardiac surgery, and have important clinical implications as RIPC could be relatively easily applied in medical practice. Before widespread clinical implementation of RIPC, however, a confirmatory study would be desirable that includes a larger number of patients. Further limitations to this study should also be addressed in the design of future trials. For example, although RRT is generally associated with risk of mortality, no difference in in-hospital or 30 day mortality between the control and the RIPC group was observed, despite an absolute risk reduction of 10% for RRT in the RIPC group. This effect might be influenced by the fact that RRT was initiated at the discretion of the physician blinded to the treatment. An effect on mortality might be observed in a larger cohort, which Zarbock *et al.*[2] suggest would need to include >4,000 patients to achieve 80% statistical power. The reduction in urinary levels of renal injury biomarkers enhances our confidence in RIPC as a preventative measure for post-surgical AKI, but firm conclusions cannot be made as the markers did not predict a hard (objective) outcome, such as hospital stay or mortality. As no marked difference in the number of mild cases of AKI was observed, questions regarding the optimal procedure regimen (duration and timing of induction), and whether the treatment effect depends on the degree of renal injury, remain to be investigated.

Many factors have been implicated as protective mediators in RIPC,[6] but the mechanisms that underlie RIPC-induced protection need to be better understood to improve confidence in the results and provide further insight into additional protective pharmacological approaches. Zarbock *et al.*[2] propose that increased urinary expression of HMGB1, TIMP-2, and IGFBP7 (implicated in G1 cell cycle arrest in tubular epithelial cells) as early as 4 h after ischaemic preconditioning, might account for the observed renoprotection in treated patients. This hypothesis is supported by data from a mouse model of renal ischaemia–reperfusion injury, where preconditioning with recombinant HMGB1 elicited a renoprotective effect through negative regulation of NF-κB signalling.[9]

Clearly a definitive clinical study with adequate statistical power is required to confirm Zarbock and colleagues' findings[2] before implementation of this procedure is considered for clinical practice. Better understanding of the mechanisms responsible for improved AKI outcomes in the cardiac surgery patient population due to ischaemic preconditioning is essential.

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