Remote ischemic preconditioning to prevent cardiac surgery-related acute kidney injury: how far away from a breakthrough?

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Many patients undergoing cardiac surgery have pre-existent renal dysfunction or are at least burdened with specific risk factors for developing acute kidney injury (AKI). Additionally, they (may) become exposed to a myriad of renal "insults" during the peri-operative period, including the cardiopulmonary bypass (CPB) and aortic cross-clamping procedure, poly-transfusion, vasopressor and inotropic treatment, and the use of particular colloid or crystalloid solutions (1). Various culprit mechanisms are implicated in the development of cardiac surgery-related AKI (CS-AKI), including systemic inflammation, ischemia-reperfusion injury, enhanced oxidative stress, altered renal perfusion, and acute tubular damage (2). As a result, up to 30% of patients develop CS-AKI and no interventions investigated so far have been shown to reduce this risk (3).

Remote ischemic preconditioning (RIPC) is a method based on inducing brief intermittent ischemic "boosts" at a limb (arm or leg) remote from vital organs aiming to protect these organs from subsequent prolonged ischemia-reperfusion periods (4). RIPC is inexpensive, easy-to-use, and requires no particular or complex equipment. A protective effect of RIPC on myocardial tissue has been extensively documented (5). Yet, another interesting clinical application of RIPC is kidney protection during cardiac surgery. RIPC is thought to attenuate renal injury by inducing the release of endogenous thus far unidentified (neurohumoral?) signaling molecules in the circulation that activate toll-like receptors in proximal tubuli cells, harnessing them to tolerate or resist a subsequent inflammatory, oxidative, or ischemic stress (6). Some small single-center trials testing the hypothesis that RIPC decreased CS-AKI produced conflicting results (7-9) and a meta-analysis evaluating the effect of RIPC on organ function in children and adults undergoing cardiac surgery found no evidence of renal protection (10). The recently published trial by Zarbock *et al*. is the first to provide high-quality biological and clinical data on RIPC use in CS-AKI (11). In this multicenter trial, cardiac surgery patients at high risk for developing AKI were randomized to RIPC versus sham treatment. RIPC consisted of 3 cycles of 5-minute inflation of a blood pressure cuff to 200 mmHg (or at least to a pressure 50 mmHg higher than the systolic arterial pressure) to one upper arm, followed by 5-minute reperfusion with the cuff deflated. The RIPC group had a more than 15% absolute decrease in the rate of peri-operative moderate and severe AKI, needed less renal replacement therapy, and had a shorter duration of intensive care unit stay. As compared with sham therapy, RIPC resulted in an immediate urinary increase of the biomarker panel consisting of tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) and of the damage-associated molecular pattern protein, high-mobility group box 1 protein (HMGB-1). Compared with sham-treated patients, (TIMP-2) × (IGFBP-7) expression became significantly lower at 4 and 12 hours post-CBP. Early increases in (TIMP-2) × (IGFBP-7) and HMGB-1 as well as (TIMP-2) × (IGFBP-7) levels lower than 0.5 ng/mL^2/1,000, 4 hours after initiating CPB, were associated with a significantly lower risk for AKI. Limitations of the study were the relatively short follow-up time for major clinical end points, unreported pre- or peri-operative nitrate treatment in each group, and more combined (coronary bypass + valve) surgery in the control group. Obvious strengths of the study were its multicenter design, the well-documented relationship between occurrence of CS-AKI and evolution of specific "alarm" molecules, and the upfront exclusion of some confounding factors that are

known to impede or mitigate the effects of RIPC such as oral antidiabetic drugs and propofol anesthesia. The authors also used a dedicated and validated AKI risk score that permitted to select only patients at high risk for AKI while excluding those with prominent underlying chronic kidney disease. These impressive study results coupled with the excellent risk/benefit/cost profile of RIPC strongly plead for implementation of this technique in cardiac surgery protocols. However, enthusiasm became largely tempered by two subsequent recently published large, multicenter, randomized trials in cardiac surgery patients (12,13). The Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery (ERICCA) trial found no effect of RIPC on the postoperative incidence of moderate and severe AKI as compared with control treatment (12). The Remote Ischemic Preconditioning for Heart Surgery (RIP Heart) Study also reported no significant difference in occurrence of AKI between RIPC- and sham-treated patients (13). It is noteworthy that the majority of patients enrolled in these studies received propofol-induced anesthesia. Also, a dedicated score to address the patients' risk of AKI was not used. A recent systematic review and meta-analysis, including the Zarbock study as well as the ERICCA and RIP Heart trials, concluded that RIPC did not provide significant renal protection in patients undergoing cardiac surgery. RIPC also had no proven effect on postsurgical degree of AKI severity or incidence of renal replacement therapy (14). Taken together, no strong clinical evidence does actually support routine application of RIPC for prevention of CS-AKI. The study of Zarbock *et al*. underscores the validity of the FDA-approved measurement of the biomarker panel (TIMP-2) × (IGFBP-7). Both TIMP-2 and IGFBP-7 are considered to be markers of cell-cycle arrest, a natural self-defense mechanism that allows cells to stop duplicating and dividing in reaction to stress. Cells literally "shut down" until the stress trigger has expired and/or injury has been repaired (15). However, a presumed action of TIMP-2 and IGFBP-7 in inducing cell-cycle arrest at kidney level remains speculative (16) and probably explains why these markers did not increase in all patients in the Zarbock study. HMGB-1 measurement elicits even more controversy. Injured or necrotic cells passively release HMGB-1 into the extracellular milieu where it activates several pattern recognition, including toll-like, receptors that initiate cell-cycle arrest processes (3). However, HMGB-1 is also actively secreted by immune cells in response to ischemia/reperfusion in CPB-supported cardiac surgery (17) and behaves as a potent pro-inflammatory cytokine involved in delayed endotoxin lethality and systemic inflammation (18). Its aptitude to orchestrate early tissue repair must thus be weighed against potential late detrimental pro-inflammatory actions.

In conclusion, the study of Zarbock *et al*. has tremendously enhanced insight into the mechanistic and renal protective effects of RIPC in cardiac surgery patients. It has also put molecular diagnosis of CS-AKI in the spotlight. Whether biomarker assessment may affect individual treatment decisions or beneficially influence outcome at an acceptable cost/benefit ratio remains to be determined. Moreover, the exact biological role of these proteins beyond their utility as "whistle-blowers" of renal stress predicting CS-AKI should be more extensively explored as they are actively involved in a wide variety of complex cellular responses and processes (19). The scene is now set for a large randomized, controlled, and biomarker-sustained trial in a homogenous population of cardiac surgery patients (i.e., with similar AKI risk profile and subjected to similar anaesthesia, surgical, and RIPC procedures) to definitely clarify the link between RIPC and kidney protection.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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