The Devil Is in the Detail

Remote Ischemic Preconditioning for Perioperative Kidney Protection

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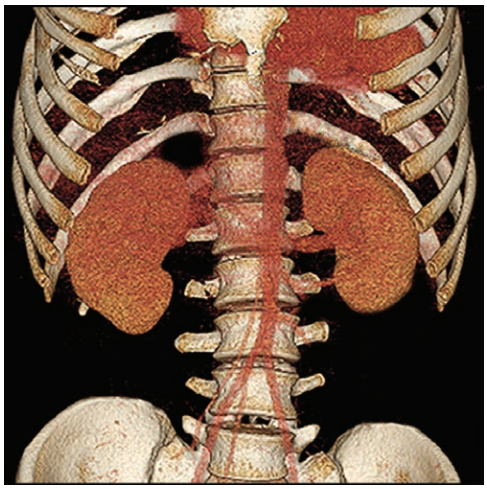
ACUTE kidney injury (AKI) is a leading postoperative complication and is associated with higher mortality and higher morbidity.[1] Even minor postoperative creatinine increases below AKI criteria are associated with adverse outcome in both noncardiac surgery[2] and cardiac surgery patients.[3] Hence, a method for the effective prevention of AKI is important and will eventually lead to the improvement of postoperative outcome. In the past, a variety of pharmacologic agents have been trialed for perioperative renoprotection (*e.g.*, fenoldepam, statins, human atrial natriuretic peptide, and nesiritide) but without conclusive evidence supporting their use.[1] In this issue of Anesthesiology, Zarbock *et al.*[4] present data on the long-term renoprotective effect of remote ischemic preconditioning (RIPC). The authors show that RIPC significantly reduced major adverse kidney events at 90 days after cardiac surgery in patients at high risk for AKI. The results of this follow-up analysis of the effects of remote ischemic preconditioning on kidney injury in high-risk cardiac surgery patients (RenalRIP) trial deliver strong evidence that RIPC provides additional long-term kidney protection. In the primary analysis of their trial, Zarbock *et al.*[5] had demonstrated RIPC to deliver short-term postoperative kidney protection: RIPC significantly reduced the rate of AKI and the use of renal replacement therapy compared to no ischemic preconditioning. RIPC could therefore be a promising method for protecting the kidney from ischemia-reperfusion injury.



"…the evidence on remote ischemic preconditioning and kidney protection is still inconclusive.…A likely reason...could be that the [most effective] exact conditions…are difficult to identify in humans."

RIPC is an experimental therapeutic strategy to protect organs against the harmful effects of ischemia-reperfusion injury by beforehand applying cycles of brief, nondetrimental ischemia and consecutive reperfusion in a distant organ (fig. 1).[6] Kharbanda *et al.*[7] were among the first to describe a noninvasive approach that was later translated to clinical use: by applying short cycles of ischemia and reperfusion to a skeletal muscle—conducted by simply inflating and deflating a standard blood pressure cuff placed on the leg—the researchers could reduce subsequently induced myocardial infarction size in pigs. Cheung *et al.*[8] subsequently demonstrated the clinical application in a proof-of-concept study in humans: the authors reported that RIPC (four 5-min cuff inflations and deflations on the thigh to 15 mmHg above systolic blood pressure) before cardiac surgery in 37 children reduced perioperative myocardial injury by less troponin I release, lowered inotrope requirements, and reduced airway pressure.

Researchers in the field have since been working on the elucidation of the underlying pathways. The stimulation with cycles of ischemia and reperfusion ultimately leads to transcriptional responses, such as the stabilization of hypoxia-induced factors (HIFs): HIF1A and HIF2A.[9,10] These changes are then signaled to other organs *via* blood-borne factors in humoral pathways. Candidates to mediate distant organ protection could potentially include soluble mediators as adenosine, soluable nucleotidases, interleukin-10, micro-RNAs, or microvesicles, leading to the activation of a protective intracellular signal transduction cascade in the target organ.[6,11–13] By this means, RIPC attenuates the detrimental effects of an upcoming ischemic event in distant organs such as the heart, the lungs, the

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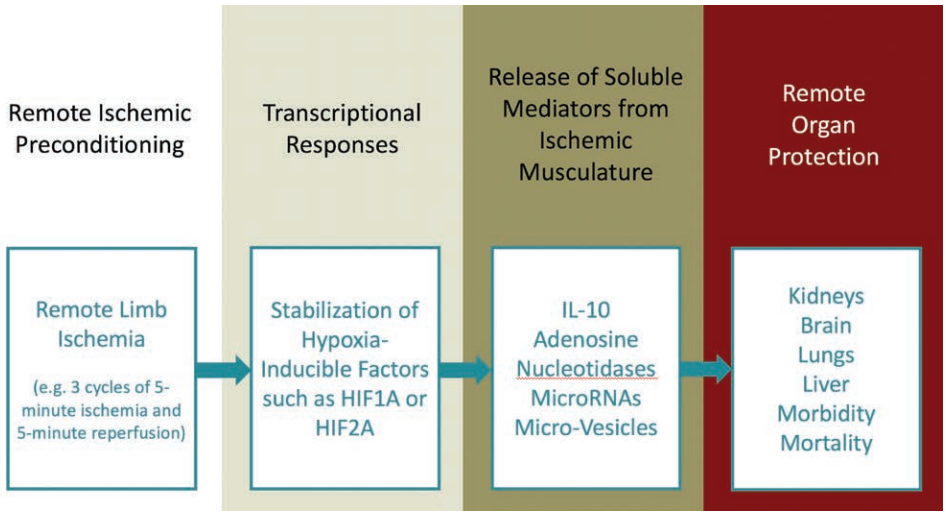

Fig. 1. Remote ischemic preconditioning (RIPC) represents an experimental approach to provide organ protection. Mechanistically, short cycles of nondetrimental ischemia and reperfusion are applied to the arm or the leg. This approach is thought to drive the stabilization of transcription factors such as hypoxia inducible factors (HIF; *e.g.*, HIF1A or HIF2A).[11] This transcriptional program mediates the release of soluble mediators from the ischemic musculature into the systemic circulation. Such mediators could potentially include cytokines (*e.g.*, interleukin [IL]-10), adenosine, circulating nucleotidases, micro-RNAs, or microvesicles. Signaling effects of these soluble mediators on remote organs such as the heart or the kidneys could then provide remote organ protection. In the current issue of Anesthesiology, Zarbock *et al*.[4] show that RIPC provides long-term kidney protection by reducing persistent renal dysfunction and renal replacement therapy dependence in cardiac surgery patients at high risk for acute kidney injury.

liver, or the kidneys and therefore may eventually reduce not only organ injury but also morbidity and mortality.

In this issue, Zarbock *et al*.[4] present the follow-up results of their randomized controlled clinical RenalRIP trial.[5] The multicenter, double-blinded trial demonstrated short-term postoperative kidney protection by RIPC in patients undergoing cardiac surgery and at high risk for AKI. RIPC reduced the rate of AKI within the first 72 h after surgery, reduced the need for renal replacement therapy, and reduced the intensive care unit stay. In the current follow-up analysis, the authors show that RIPC also causes long-term kidney protection and the enhanced renal recovery of those patients who did have postoperative AKI. The authors could show that RIPC reduced the frequency of the composite endpoint major adverse kidney events (consisting of mortality, the need for renal replacement therapy, and persistent renal dysfunction) at 90 days after surgery. When analyzing the components of major adverse kidney event at 90 days, RIPC significantly reduced persistent renal dysfunction (absolute risk reduction of 13%) and renal replacement therapy dependence (absolute risk reduction 7%) at 90 days after surgery but did not influence mortality. Intriguingly, of those patients who did develop AKI within 72 h after cardiac surgery, fewer suffered from persistent renal dysfunction or dialysis dependence at day 90 if they were treated with RIPC before surgery. These results provide strong evidence supporting the concept that RIPC delivers kidney protection in patients at high risk for AKI.

Despite these promising results, the evidence on RIPC and kidney protection is still inconclusive. Two additional multicenter studies by Meybohm *et al*.[14] (remote ischemic preconditioning for heart surgery [RIPHeart] trial) as well as Hausenloy *et al*.[15] (effect of remote ischemic preconditioning on clinical outcomes in patients undergoing coronary artery bypass graft surgery [ERICCA] trial) investigated the effect of RIPC on postcardiac surgery outcome. While the Zarbock *et al.* study's primary endpoint was postoperative renal function, the primary composite endpoints of both the RIPHeart and ERICCA trials were focusing on postoperative cardiovascular complications and death. Interestingly, the results of both Meybohm *et al*.[14] and Hausenloy *et al*.[15] did not show any effect of RIPC, neither on the primary composite endpoints (as well as on any of its individual components), nor on the secondary endpoints. In particular regarding postcardiac surgery renal function, both trials did not show any renoprotective effects for RIPC (postoperative renal function was a secondary endpoint in both the RIPHeart and the ERICCA trials), contrasting the results of RenalRIP. The differences in the results may be explained by the different patient populations. The RenalRIP trial included only high-risk patients, while both the RIPHeart and ERICCA trials included low-risk patients.

A likely reason for the contradicting results could be that the exact conditions for the most effective RIPC are difficult to identify in humans. Animal studies have revealed that this is in fact a challenging task. For example, an experimental study designed to define optimal conditions for myocardial ischemic preconditioning in mice examined numerous different preconditioning regimens. Protocol optimization in this study included different cycle numbers, body temperatures, ischemia

times, *etc*., before the authors were able to identify a regimen that reliably produced organ protection.[16] Both the RIPHeart and ERICCA trials used a sequence of four times 5-min ischemia, with 5 min of reperfusion in-between, whereas the RenalRIP protocol only used three times 5 min of ischemia with identical reperfusion intervals. It may very well be that the devil is in the detail and the optimal protocol for effective RIPC in humans has not yet been discovered. Systematic evaluation of RIPC protocols in humans is needed to find the optimal one for postoperative organ protection. Such studies could initially be done in volunteers to examine optimal release of soluble mediators, such as interleukin-10,[11] before examining organ protection in patients. As the RIPC protocol of the current study by Zarbock *et al*.[4] provided robust protection, it will also be critical to repeat their findings in larger patient populations and different surgical and patient settings.

In summary, the exciting finding of Zarbock *et al*.[4] demonstrate for the first time that RIPC also has long-term renoprotective effects in high-risk surgical patients. These impressive data are the first step toward clinical implementation of RIPC for kidney protection. However, since this was a relatively small study presenting a large effect size, the findings need to be confirmed in large-scale multicenter trials. It will be exciting to see this field further evolve with the hope that in the near future, RIPC may become a routine clinical strategy to provide kidney protection for surgical patients.

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Competing Interests

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References

1. Goren O, Matot I: Perioperative acute kidney injury. Br J Anaesth 2015; 115(suppl 2):ii3–14
2. Kork F, Balzer F, Spies CD, Wernecke KD, Ginde AA, Jankowski J, Eltzschig HK: Minor postoperative increases of creatinine are associated with higher mortality and longer hospital length of stay in surgical patients. Anesthesiology 2015; 123:1301–11
3. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, Schmidlin D: Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: Do we have to revise current definitions of acute renal failure? Crit Care Med 2008; 36:1129–37
4. Zarbock A, Kellum JA, Van Aken H, Schmidt C, Küllmar M, Rosenberger P, Martens S, Görlich D, Meersch M: Long-term effects of remote ischemic preconditioning on kidney function in high-risk cardiac surgery patients: Follow-up results from the RenalRIP trial. Anesthesiology 2017; 126:787–98
5. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, Wolf B, Goebel U, Schwer CI, Rosenberger P, Haeberle H, Görlich D, Kellum JA, Meersch M; RenalRIPC Investigators: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: A randomized clinical trial. JAMA 2015; 313:2133–41
6. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D: Remote ischemic conditioning. J Am Coll Cardiol 2015; 65:177–95
7. Kharbanda RK, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschtitzky JA, Vogel M, Sorensen K, Redington AN, MacAllister R: Transient limb ischemia induces remote ischemic preconditioning *in vivo*. Circulation 2002; 106:2881–3
8. Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, Li J, Holtby HM, Cox PN, Smallhorn JF, Van Arsdell GS, Redington AN: Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: First clinical application in humans. J Am Coll Cardiol 2006; 47:2277–82
9. Eckle T, Köhler D, Lehmann R, El Kasmi K, Eltzschig HK: Hypoxia-inducible factor-1 is central to cardioprotection: A new paradigm for ischemic preconditioning. Circulation 2008; 118:166–75
10. Eltzschig HK, Eckle T: Ischemia and reperfusion–From mechanism to translation. Nat Med 2011; 17:1391–401
11. Cai Z, Luo W, Zhan H, Semenza GL: Hypoxia-inducible factor 1 is required for remote ischemic preconditioning of the heart. Proc Natl Acad Sci USA 2013; 110:17462–7
12. Neudecker V, Brodsky KS, Kreth S, Ginde AA, Eltzschig HK: Emerging roles for microRNAs in perioperative medicine. Anesthesiology 2016; 124:489–506
13. Randhawa PK, Jaggi AS: Unraveling the role of adenosine in remote ischemic preconditioning-induced cardioprotection. Life Sci 2016; 155:140–6
14. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Böning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schön J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K; RIPHeart Study Collaborators: A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015; 373:1397–407
15. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators: Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med 2015; 373:1408–17
16. Eckle T, Grenz A, Köhler D, Redel A, Falk M, Rolauffs B, Osswald H, Kehl F, Eltzschig HK: Systematic evaluation of a novel model for cardiac ischemic preconditioning in mice. Am J Physiol Heart Circ Physiol 2006; 291:H2533–40