Editorial

Lung protection in patients undergoing pulmonary lobectomy: a new perspective for remote ischemic conditioning in surgery?

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In 1993, Przyklenk *et al.* reported the fascinating finding that administering brief periods of non-lethal ischemia and reperfusion to the circumflex coronary artery reduces myocardial infarct size following a prolonged occlusion of the left anterior descending coronary artery, indicating that the protection produced by ischemic conditioning can potentially be transferred from one area of the heart to another, a phenomenon which has been named remote ischemic conditioning (RIC) (1). Further experimental studies then established that the heart could be protected against ischemia-reperfusion injury by instigating brief bursts of non-lethal ischemia and reperfusion as a conditioning stimulus to an organ or tissue remote from the heart, thus extending the concept of RIC to inter-organ conditioning. Once it had been demonstrated that RIC can be induced simply by applying a blood pressure cuff to a limb, the technique has quickly developed applications in a wide range of clinical scenarios of potential ischemia-reperfusion damage (2,3). A large number of cardiac surgery studies, for example, have applied RIC via three or four cycles of 5-min ischemia followed by 5-min reperfusion of the upper or lower limb, the majority reporting reduced post-operative cardiac biomarker release, with even amended clinical outcomes in long-term follow-up analyses of studies that had insufficient power to conclude on outcomes (4). Nevertheless, two large clinical trials recently failed to achieve improved clinical outcomes using RIC in the cardiac surgery setting (5,6). Among the several confounding factors that likely altered the RIC response in these studies, the use of propofol anesthesia proved puzzling, given that this substance was already known to abrogate the RIC-induced protection (7). Consequently, the potential of RIC to confer protection in patients undergoing cardiac surgery remains uncertain (8). Nevertheless, it still has great potential, due to its infarct-sparing effect in other clinical situations at risk of ischemia-reperfusion damage, such as acute myocardial infarction (9,10). Furthermore, RIC still has a major therapeutic value in protecting non-cardiac organs exposed to ischemia-reperfusion damage, such as the brain in strokes, liver and kidneys in transplantation, and even lungs in pulmonary surgery (11,12).

In this issue, García-de-la-Asunción *et al.* tested the ability of RIC to alter oxidative lung damage in patients undergoing pulmonary lobectomy (12). Using three cycles of 5-min ischemia and 5-min reperfusion on the thigh immediately before lobectomy, the authors found that the increase in exhaled breath condensate 8-isoprostane was attenuated in patients receiving RIC, reflecting reduced lipid peroxidation levels. RIC also decreased nitrite and nitrate concentrations in exhaled breath condensate and the blood, while also improving pulmonary oxygenation variables in comparison with the control group.

The protective mechanism of RIC in this specific clinical scenario is unknown. In the more general context of ischemia-reperfusion damage, RIC stimulus is believed to produce protective signals that are conveyed from

the remote tissue to the target organ (13,14). Several concomitant mechanisms may be involved, including blood-borne factor release (15-17), neuronal pathway activation (18), as well as systemic response contribution (19). These protective signals can activate intracellular survival signaling pathways in the target organ (13,20). Several studies have described endogenous factors being involved in protective mechanisms, such as opioids (21), bradykinin (22), adenosine (23), endocannabinoids (24), erythropoietin (25), microvesicles (26), apolipoprotein A-I (27), microRNA (28), glycine (29,30), and kynurenine (29,31,32). One likely explanation is that RIC activates the release of several circulating humeral factors, provoking multiple endogen protective mechanisms. Mitochondria, recognized as the principal target of RIC, are the main cellular source of ATP under aerobic conditions, thus related to cell survival and major cellular functions. In contrast, mitochondrial permeability transition pore opening can activate cell death in the context of reperfusion. Interestingly, the nitrosation and nitrosylation of mitochondrial membrane proteins appear to be causally involved in cardioprotection (8). In mice, for example, myocardial nitrite was found to increase in response to shear stress and eNOS activation after RIC (33). Myocardial myoglobin then reduces nitrite to nitric oxide, which consequently inhibits mitochondrial complex I activity (34). Reacting to RIC, this nitrosation caused a reduction of complex I activity, leading to reduced myocardial reactive oxygen species formation (33). Given that most of these data were obtained from experiments in cardiomyocytes, however, further studies are required to clarify the protective mechanism associated with RIC in the lung surgery context. Nevertheless, though larger clinical trials are needed before applying RIC in pulmonary surgery, García-de-la-Asunción *et al.* are to be commended for their elegant study that introduced this new perspective of RIC.

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Footnote

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

References

1. Przyklenk K, Bauer B, Ovize M, et al. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 1993;87:893-9.
2. Heusch G. Cardioprotection: chances and challenges of its translation to the clinic. Lancet 2013;381:166-75.
3. Brevoord D, Kranke P, Kuijpers M, et al. Remote ischemic conditioning to protect against ischemia-reperfusion injury: a systematic review and meta-analysis. PLoS One 2012;7:e42179.
4. Le Page S, Bejan-Angoulvant T, Angoulvant D, et al. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. Basic Res Cardiol 2015;110:11.
5. Hausenloy DJ, Candilio L, Evans R, et al. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. N Engl J Med 2015;373:1408-17.
6. Meybohm P, Bein B, Brosteanu O, et al. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. N Engl J Med 2015;373:1397-407.
7. Kottenberg E, Musiolik J, Thielmann M, et al. Interference of propofol with signal transducer and activator of transcription 5 activation and cardioprotection by remote ischemic preconditioning during coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014;147:376-82.
8. Kleinbongard P, Skyschally A, Heusch G. Cardioprotection by remote ischemic conditioning and its signal transduction. Pflugers Arch 2017;469:159-81.
9. Bøtker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet 2010;375:727-34.
10. Prunier F, Angoulvant D, Saint Etienne C, et al. The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. Basic Res Cardiol 2014;109:400.
11. Le Page S, Prunier F. Remote ischemic conditioning: Current clinical perspectives. J Cardiol 2015;66:91-6.
12. García-de-la-Asunción J, Bruno L, Perez-Griera J, et al. Remote Ischemic Preconditioning Decreases Oxidative Lung Damage After Pulmonary Lobectomy: A Single-Center Randomized, Double-Blind, Controlled Trial. Anesth Analg 2017;125:499-506.
13. Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. Cardiovasc Res 2008;79:377-86.

14. Lim SY, Hausenloy DJ. Remote ischemic conditioning: from bench to bedside. Front Physiol 2012;3:27.
15. Dickson EW, Lorbar M, Porcaro WA, et al. Rabbit heart can be "preconditioned" via transfer of coronary effluent. Am J Physiol 1999;277:H2451-7.
16. Shimizu M, Tropak M, Diaz RJ, et al. Transient limb ischaemia remotely preconditions through a humoral mechanism acting directly on the myocardium: evidence suggesting cross-species protection. Clin Sci (Lond) 2009;117:191-200.
17. Breivik L, Helgeland E, Aarnes EK, et al. Remote postconditioning by humoral factors in effluent from ischemic preconditioned rat hearts is mediated via PI3K/Akt-dependent cell-survival signaling at reperfusion. Basic Res Cardiol 2011;106:135-45.
18. Lim SY, Yellon DM, Hausenloy DJ. The neural and humoral pathways in remote limb ischemic preconditioning. Basic Res Cardiol 2010;105:651-5.
19. Shimizu M, Saxena P, Konstantinov IE, et al. Remote ischemic preconditioning decreases adhesion and selectively modifies functional responses of human neutrophils. J Surg Res 2010;158:155-61.
20. Tamareille S, Mateus V, Ghaboura N, et al. RISK and SAFE signaling pathway interactions in remote limb ischemic perconditioning in combination with local ischemic postconditioning. Basic Res Cardiol 2011;106:1329-39.
21. Weinbrenner C, Schulze F, Sárváry L, et al. Remote preconditioning by infrarenal aortic occlusion is operative via delta1-opioid receptors and free radicals in vivo in the rat heart. Cardiovasc Res 2004;61:591-9.
22. Wolfrum S, Schneider K, Heidbreder M, et al. Remote preconditioning protects the heart by activating myocardial PKCepsilon-isoform. Cardiovasc Res 2002;55:583-9.
23. Kerendi F, Kin H, Halkos ME, et al. Remote postconditioning. Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces myocardial infarct size via endogenous activation of adenosine receptors. Basic Res Cardiol 2005;100:404-12.
24. Hajrasouliha AR, Tavakoli S, Ghasemi M, et al. Endogenous cannabinoids contribute to remote ischemic preconditioning via cannabinoid CB2 receptors in the rat heart. Eur J Pharmacol 2008;579:246-52.
25. Diwan V, Jaggi AS, Singh M, et al. Possible involvement of erythropoietin in remote renal preconditioning-induced cardioprotection in rats. J Cardiovasc Pharmacol 2008;51:126-30.
26. Giricz Z, Varga ZV, Baranyai T, et al. Cardioprotection by remote ischemic preconditioning of the rat heart is mediated by extracellular vesicles. J Mol Cell Cardiol 2014;68:75-8.
27. Hibert P, Prunier-Mirebeau D, Beseme O, et al. Apolipoprotein a-I is a potential mediator of remote ischemic preconditioning. PLoS One 2013;8:e77211.
28. Li J, Rohailla S, Gelber N, et al. MicroRNA-144 is a circulating effector of remote ischemic preconditioning. Basic Res Cardiol 2014;109:423.
29. Chao de la Barca JM, Bakhta O, Kalakech H, et al. Metabolic Signature of Remote Ischemic Preconditioning Involving a Cocktail of Amino Acids and Biogenic Amines. J Am Heart Assoc 2016;5. pii: e003891.
30. Garcia-Dorado D, Rodriguez-Sinovas A, Barba I, et al. Glycine as a key element of remote ischaemic conditioning cardioprotective signalling. Cardiovasc Res 2017;113:562-3
31. Kouassi Nzoughet J, Bocca C, Simard G, et al. A Nontargeted UHPLC-HRMS Metabolomics Pipeline for Metabolite Identification: Application to Cardiac Remote Ischemic Preconditioning. Anal Chem 2017;89:2138-46.
32. Olenchock BA, Moslehi J, Baik AH, et al. EGLN1 Inhibition and Rerouting of α-Ketoglutarate Suffice for Remote Ischemic Protection. Cell 2016;164:884-95.
33. Rassaf T, Totzeck M, Hendgen-Cotta UB, et al. Circulating nitrite contributes to cardioprotection by remote ischemic preconditioning. Circ Res 2014;114:1601-10.
34. Hendgen-Cotta UB, Merx MW, Shiva S, et al. Nitrite reductase activity of myoglobin regulates respiration and cellular viability in myocardial ischemia-reperfusion injury. Proc Natl Acad Sci U S A 2008;105:10256-61.

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