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

Fabrice Prunier, Delphine Mirebeau-Prunier

Institut MITOVASC, UMR INSERM U1083 and CNRS 6015, CHU Angers, University of Angers, Angers, France

Correspondence to: Prof. Fabrice Prunier, MD, PhD. Institut MITOVASC, UMR INSERM U1083 and CNRS 6015, University of Angers, 3 rue Amsler, Angers 49100, France. Email: faprunier@chu-angers.fr.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Wankun Chen (Department of Anesthesiology, Fudan University Shanghai Cancer Center, Shanghai, China).


doi: 10.21037/jtd.2017.12.16

View this article at: http://dx.doi.org/10.21037/jtd.2017.12.16

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 bloodborne 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 humoral factors, provoking multiple endogenous 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.

Acknowledgements

None.

Footnote

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

References

Journal of Thoracic Disease, Vol 10, No 1 January 2018
