Letter to the Editor

Remote ischemic preconditioning in patients undergoing pulmonary lobectomy: we are on the right path

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We thank the editor for inviting editorial on our recent publication. We have read with great interest the editorial of Weber NC and cols regarding our study on remote ischemic preconditioning (RIPC) in patients undergoing pulmonary lobectomy (1). We agree in general with the aspects treated, but I would like to add some comments on this matter.

Certainly there are not too many experimental studies on lung injury induced by pulmonary ischemia-reperfusion (I-R), and much less on remote conditioning by ischemia which the goal is the protection of the lungs in cases of pulmonary surgery or lung transplantation (2). Tissue dysfunction by cell damage due to I-R injury is one of the main causes of disease and death in a large number of pathological processes. Remote ischemic conditioning (RIC) provides endogenous protective response to a tissue insult by I-R. In the coming years, it has been shown in experimental and clinical studies that RIC is a non-invasive way to induce protection organs remotely, as heart and others as kidneys, liver, lungs, intestine, brain, etc. In this sense, and very recently has been published that irisin protects mitochondria function and oxidative stress during pulmonary I-R in an animal model, which report that limb RIPC releases irisin, a myokine derived from the extracellular portion of fibronectin in skeletal muscle to protect against injury to the lung (3). Moreover, in rats has been shown that limb RIPC attenuates cardiopulmonary bypass-induced lung injury as evidenced by a combination of lower total bronchoalveolar lavage protein content, reduced intra-alveolar neutrophil infiltration and increased expression of anti-inflammatory cytokines such as IL-4 and IL-10 (4).

In the clinical setting, the RIC can be induced through the application of brief ischemia-reperfusion stimuli in the skeletal tissue of the upper or lower extremity, which facilitates its application in the clinical practice to protect organs and tissues have a high risk of acute I-R. Until now the vast majority of clinical studies with RIC have focused on cardiac surgery or myocardial infarction. Although in some cases and secondarily also was evaluated its effect on lung protection. The research of lung protection induced by RIPC in patients undergoing pulmonary resection surgery (selectively pulmonary lobectomies) only has been reported in two recently published studies (1,5).

We want to emphasize, that in our study (1) the primary objective was to verify if the RIPC would produces improvement of oxidative stress marker levels in pulmonary exhaled breath condensate (EBC), specifically 8-isoprostane and others markers (nitrites + nitrates and hydrogen peroxide). These oxidative stress markers in EBC are direct reflection of superoxide anion production in the lower respiratory tract. Remember that reactive oxygen species generated during pulmonary collapse and during pulmonary expansion are highly aggressive against proteins, lipids and

cellular DNA. Moreover, they can also be the origin of the inflammatory changes that can lead to ALI and ARDS. The EBC study as a work methodology is completely new in this type of patients submitted to lobectomy and possibly a good tool for future studies, because it is a more direct way to study oxidative stress markers and others.

Although in our study (1) we found differences in biomarkers of I-R injury, our sample size was insufficient to detect postoperative clinical differences after lung lobectomy such as ALI, ARDS, arrhythmias, critical care unit stays, and others. For these clinical outcomes require much larger populations. Although in some studies with relatively small populations promising results are obtained, especially in relation to some specific biological markers which allows avoiding the individual influences such as comorbidities, medications, idiosyncrasies, etc. We believe that to minimize these limitations of translation, the clinical studies where the primary aims are clinical outcomes, patient populations must be very homogenous demographically, with similar pathologies, similar surgical treatments and anaesthetic management, and defined post-surgical protocols (6). This would explain why studies with experimental animals obtain better results generally, where the populations are completely identical, genetically, age, weight, feeding, treatments, etc.

Certainly the study has been dilated because of several reasons not related to the study itself. Sampling occurred between November 2007 and January 2012 due mainly to a restrictive selection of patients to obtain a homogeneous population. Although initially it was not planned, the clinical trial registration was made in April 2016. However no bias is related to this, because all data were recorded according to the original protocol approved by the local Ethics Committee before the start of the study (it can be accessed through the Ethics Committee).

Finally, we speculate that the RIC is a powerful and innate protection system of biological systems, result of evolutionary changes over billions of years subject to the vital dependence on oxygen and its use in mitochondria to obtain ATP. The RIC is an innocuous system that reduces the damage by I-R, although it does not completely avoid it. It is true that clinical outcomes are not in many cases significant. However, in many cases RIC improve the levels of specific biomarkers, which is also desirable and beneficial, because it is indicative of less cellular and tissue damage and that is also objectively important.

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Footnote

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

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