

Protection of lung oxidative injury by remote ischemic preconditioning: a study of exhaled water during pulmonary lobectomy

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We thank the editor for inviting editorial on our recent publication. We have read with great interest the editorial of Prunier and Mirebeau-Prunier about our recently published study on remote ischemic preconditioning (RIPC) in patients undergoing pulmonary lobectomy for lung cancer (1). We agree with all the aspects treated, but I would like to add some comments that can provide some information on this matter.

Twenty-five years ago, the phenomenon of remote conditioning by ischemia-reperfusion (I-R) was described for the first time. In all this time numerous studies with animal models have shown that RIPC might be capable of reducing acute lung I-R injury. However, until now the vast majority of studies on remote conditioning (pre, per or post) have been on the heart. The protection of the lungs by RIPC has been studied only in very few randomized clinical trials. In addition, many of these studies have not aimed on the protection of the lungs as a primary objective. Specifically, the only studies that have focused particularly on the lungs protection by RIPC in patients undergoing major surgery have been only three (1-3). However, only two of these studies were performed selectively in patients with lung cancer undergoing pulmonary lobectomy (1,3). In a study, the primary objective was to demonstrate whether RIPC attenuated lung injury, based on values of arterial blood gases after pulmonary lobectomy (3). While

in the other study, the primary objective was to check whether the RIPC improved oxidative stress markers levels (8-isoprostane, $\text{NO}_2^- + \text{NO}_3^-$ and H_2O_2) in pulmonary exhaled water, as a direct proof of the oxidative lung injury that occurs during the pulmonary collapse, but especially after the pulmonary expansion (1).

The lungs acquire oxygen directly from the air by alveolar gas exchange, as well as by the blood of a dual circulatory system by the bronchial arteries and by pulmonary arteries. Therefore, pulmonary I-R is also quite different to that which occurs in other organs (4). Ischemia is as harmful as the reintroduction of oxygen during pulmonary reperfusion after lobectomy, which exacerbates the damage by the formation of reactive oxygen species. The mitochondrial electron transport chain generates superoxide at complexes I, II and III resulting in the release of superoxide into either the intermembrane space or the matrix (5). Therapeutic strategies to treat I-R injury are urgently needed. RIPC seems to exert beneficial effects for patients undergoing thoracic surgery, particularly in those surgeries where the lung collapses and is deprived of ventilation. The protection mechanisms that RIPC potentially generates are very abundant and varied. However, the underlying signaling remains incompletely understood. This is particularly related to the mechanism by which the protection signal is transferred from the

remote site to the target organ. Therefore there is a lot of work to be done.

Nitrites (NO_2^-) are the stable form of oxidation of nitric oxide (NO). The nitrites present in the blood act as a reserve of NO, particularly in situations of hypoxia, when NO production is compromised (6,7). Nitrites can be reduced to NO via myoglobin reduction in the heart or hemoglobin reduction in the systemic circulation (8). Remember that a part of the nitrites in the blood come from pyroxenite anions (ONOO^-) formed by reacting the NO with the superoxide radical generated in the mitochondria. Therefore, high levels of nitrites also indicate a greater formation of superoxide generated in complexes I, II and III of the mitochondria during the I-R in a very important way (9). In addition, as Prunier *et al.* comments in its editorial, the nitrites can mediate beneficial effects and acute protection after I-R in preclinical models by attenuation of reactive oxygen species generation by inhibition of complex I (NADH dehydrogenase) which is a point of entry of electrons in the mitochondrial respiratory chain. This inhibition is due to the post-translational S-nitrosation of a critical cysteine residue in complex I (7,10).

Regarding remote ischemic conditioning, I believe that we are facing a physiological phenomenon of enormous complexity that involves the most basic mechanisms in the protection of cellular life. Whose ultimate goal is to preserve the proper functioning of the mitochondria, so that they continue to produce ATP and the cells do not end in apoptosis. Taking into account that eukaryotic cells contain mitochondria, which are remnants of an ancestral endosymbiotic event that occurred 2 billion years ago, when the atmosphere increased its oxygen content. But translating these biological facts to the field of clinical prevention, where there are numerous individual, pharmacological and assistance factors, is very difficult. Therefore, larger clinical trials and much more selective populations will be necessary.

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Footnote

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

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