Editorial

Remote ischaemic preconditioning of the lung: from bench to bedside—are we there yet?

Nina C. Weber, Coert J. Zuurbier, Markus W. Hollmann

Department of Anaesthesiology, Laboratory of Experimental Intensive Care and Anaesthesiology (L.E.I.C.A) Academic Medical Centre (AMC), Amsterdam, the Netherlands

Correspondence to: Nina C. Weber, PhD. Academic Medical Centre (AMC), Department of Anaesthesiology University of Amsterdam, Laboratory of Experimental and Clinical Experimental Anaesthesiology (L.E.I.C.A.), Academic Medical Centre (AMC), Meibergdreef 9, 1100 DD Amsterdam, the Netherlands. Email: N.C.Hauck@amc.uva.nl.

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Introduction

Despite several decades of research on varying forms of "conditioning" different organs (heart, brain, kidney and lung), we have yet not discovered the therapeutic realisation of these potential powerful protective interventions. However, several experimental and also clinical studies have shown that conditioning an organ ultimately prevents ischaemic and reperfusion damage of that organ during clinical interventions. The probably most clinically applicable form of 'conditioning' organs, remote ischaemic preconditioning (RIPC) is defined as short-lasting periods of ischaemia applied to a distant organ (an upper arm or limb) from the target organ, which eventually lead to protection of the target organ itself against ischaemia reperfusion injury (1-4).

Lung protection by RIPC: experimental evidence

When reviewing the tremendous amount of literature on RIPC over the past 15 years it becomes obvious that one organ has yet not been much in the focus for a potential protection by remote conditioning: the lung. However, acute lung injury (ALI) is a major cause of morbidity and mortality in several clinical scenarios including cardiac surgery, orthopaedic surgery and lung surgery. ALI and also adult respiratory distress syndrome (ARDS) are a major cause of death in lung resection surgery like lobectomy and lung transplantation (5).

In early experimental studies favouring RIPC for ALI, Peralta and colleagues (6) demonstrated that applying a RIPC stimulus to the liver reduces systemic inflammation and attenuates neutrophil accumulation in the lung (6). Hereafter, other studies followed supporting that RIPC might be capable of reducing acute lung ischaemia reperfusion injury in animal models (7,8).

Lung protection by RIPC: clinical evidence

Lung protection has yet only been investigated in a few randomised clinical trials. Notably, most of those did not focus directly on lung protection but on cardiac protection influencing lung function secondarily (9-15). Li and colleagues investigated whether upper arm RIPC reduces intestinal and pulmonary injury (16). The authors showed in 62 patients undergoing infrarenal abdominal aortic aneurysm repair that upper arm RIPC attenuated pulmonary injury as well as intestinal injury (16).

The most recent randomised, single-center, double-blind study by García-de-la-Asunción and colleagues used a very interesting approach to elaborate on the possible direct lung protective effect induced by limb ischaemic preconditioning (17). The authors hypothesised that

RIPC would decrease oxidative lung damage in patients undergoing lung lobectomy and improve oxygenation parameters in the postoperative period. In line with the description of the study details in the clinical trial register (NCT02734654) García-de-la-Asunción exclusively included patients elected for pulmonary lobectomy who suffered from non-small cell lung carcinoma (NSCLC) stage I–II. Lung lobectomy is a surgical procedure whereby a lobe of the lung is surgically removed. In this clinical setting the operated lung suffers from ischaemia reperfusion injury due to a hypo-perfused state which is caused by hypoxic pulmonary vasoconstriction. It is likely that ALI and also ARDS can be worsened by this condition and therefore a protective strategy for the lung in question could have great clinical implications. García-de-la-Asunción *et al.* choose the oxidative stress marker 8-isoprostane in exhaled breath condensate (EBC) as primary outcome parameter. Measuring oxidative stress parameters directly in the EBC and blood is of special interest as it has been shown that the duration of the lung collapse in lobectomy is directly related to an increase of those markers (18). The collection of EBC is non-invasive and EBC samples from the lower respiratory tract can easily be isolated. These EBC samples contain isoprostanes, nitrogen oxides and H_2O_2. Increased levels of the biomarkers like 8-isoprostane have been identified as clear *in vivo* indication of lipid peroxidation (18).

Secondary outcomes where: NO_2^-+ NO_3, H_2O_2 levels, and pH in EBC and 8-isoprostane, NO_2^-+ NO_3 in blood (17). All mentioned parameters where significantly improved in the group of RIPC either at all time points or at least directly after resuming two lung ventilation. Additionally, pulmonary gas exchange variables (PaO_2/FiO_2 ratio) as secondary outcome were improved in the RIPC group.

García-de-la-Asunción *et al.* based there sample size analysis on a previously published article in which also 8-isoprostane was measured in EBC (18). Based on these former results, the sample size of 28 patients per group, which was initially aimed for, seems to be reasonable. However, due to loss of patients during the enrolment they ended up with a little less patients in both groups, which however had most likely no impact on the results. Though, it is important to mention that pertinent conclusions on clinical outcomes like ALI, ARDS and ICU stay could not be drawn from this limited sized trial. This is of special interest as one has to realise that very promising results from smaller studies are often not confirmed in larger clinical trials with primary outcome parameters as mortality, time of hospital discharge or ICU length of stay (19). However, the authors clearly admit to these limitations in their discussion. Notably, not discussed in the study, the study was already started in 2007 (according to the trial register) and final data collection was finished in 2012. Seemingly, data analyses took quite a long time. Moreover, as clinical trial registration was performed after completion of the study, it is hard to tell if any bias and thus changes in the protocol have occurred during the study.

Li and colleagues investigated direct lung protection as primary outcome after RIPC of the upper arm in 216 patients with NSCLC between 2011 and 2013 (20). All patients underwent pulmonary resection but the surgical procedure was not limited to lobectomy as in the study by García-de-la-Asunción (17). RIPC increased pulmonary oxygenation during thoracic pulmonary resection under one lung ventilation and inflammatory markers like IL-6 and TNF-α were significantly reduced by RIPC. Additionally, Malondialdehyde (MDA), a marker of oxidative stress, was significantly lower in the RIPC group (20). Also clinical outcomes as postoperative hospital stay and overall incidence of ALI were both significantly reduced in the RIPC group.

Thus, both studies clearly point into a very promising direction for RIPC in lung resection surgery.

Possible limitations of translation

Most expert groups agree upon the fact that the impact of aging, co-morbidities and—most importantly—the drug regimen during the surgical procedure have to be addressed and clarified before implementation of RIPC into clinical practice is possible (2,21,22). In particular, for RIPC of the heart it has been shown that different anaesthetic regimens strongly influence effectivity of RIPC.

In animal experiments, Behmenburg and colleagues showed that RIPC was blocked in propofol-remifentanil anesthetized rats (23). In contrast, a recent study in pigs showed RIPC to be protective with propofol anaesthesia (24). This suggests that the presence of propofol is not a definitive factor negating RIPC effects in the hart.

On the other hand different clinical trials found propofol as a potential confounder for RIPC of the heart. Kottenberg *et al.* reported a cardioprotective effect of RIPC during isoflurane anaesthesia, but not during propofol anaesthesia (25). Likewise, two large multi-center clinical trials from 2015 suggested that propofol counteracts cardioprotection by RIPC in cardiac surgery. Both studies

have included more than 1,000 patients (19,26). Thus, whether RIPC is disturbed by the presence of propofol has yet not been fully confirmed.

Regarding the lung both early studies from Li and colleagues used propofol based anaesthesia and showed a protective effect of RIPC (16,20). In contrast García-de-la-Asunción and colleagues used thiopental-fentanyl for induction of anaesthesia and sevoflurane for maintenance of hypnosis. Thus, outcome of RIPC long studies seems to be independent of the anaesthetics employed.

Evidence suggests that other drugs, in particular a group that is frequently used in patients suffering from myocardial ischaemia, platelet P2Y12 receptor antagonist, might influence RIPC (27). These drugs have been shown to be strongly cardioprotective, limiting additional protection of other potential cardioprotective interventions (27). However, as García-de-la-Asunción *et al.* and Li *et al.* excluded patients with cardiac disease (16,17) interactions of platelet P2Y12 receptor antagonist with the lung protective measures employed were not present in these patients (16,17).

Concluding remarks

The complex signalling network, existing co-morbidities and most importantly the medication administered to the patient might severely hamper effectivity of RIPC.

The study of García-de-la-Asunción *et al.* set very important steps into the right direction and there is a lot work to do for real lung protection by limb ischaemic preconditioning. By focusing on one selective patient population measuring non-invasively a major oxidative stress marker García-de-la-Asunción *et al.* show very promising results.

Thus, larger clinical trials in patients undergoing lobectomy are warranted in the future as strong conclusions regarding major clinical outcomes can only be drawn from adequately powered and thoroughly designed clinical studies.

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Footnote

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

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