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Opinion

Remote Ischemic Preconditioning Protects Against Post-Thoracotomy Acute Lung Injury: Chances and Challenges of Translation from Bench to Bedside

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During the last decade, despite increases in patient age and comorbid conditions in thoracic surgery, the duration of inhospital stay has become shorter with a reduction of surgery-related complications. Now, the primary causes of mortality following thoracic surgery have shifted away from cardiac and surgical complications toward pulmonary problems, such as postoperative pneumonia, empyema and sepsis, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (1). The available data suggest that incidence of post-thoracotomy ALI has not shown any significant decrease over the last two decades (2- 5%), though the case- fatality rate has decreased from almost 100% to less than 40% due to improved ICU medical management (2). In fact, post-thoracotomy ALI has become the leading cause of patient death in modern thoracic surgery (1).

The pathogenesis of post-thoracotomy ALI has not been fully elucidated, but various triggering factors including preoperative comorbid conditions, genetic predisposition, surgery-induced inflammation, ventilator-induced injury, fluid overload, and transfusion are involved (1). Also, ischemia/reperfusion (I/R) injury of the operated lung has been demonstrated as one of the most vital factors causing and aggravating post-thoracotomy ALI and ARDS (3, 4). By multivariate regression analysis, a large cohort clinical study of thoracic surgical patients has identified several risk factors for post-thoracotomy ALI, e.g., severe pulmonary dysfunction, chronic alcohol consumption, extended lung resection, injurious ventilation and excessive fluid load, etc (5). Moreover, it is reported that the occurrence of post- thoracotomy ALI is more common after right pneumonectomy in elderly patients with colonized airways or in those requiring multiple transfusions or received preoperative chemoradiotherapy (6-8). To attenuate post-thoracotomy ALI and improve clinical outcomes, several changes in the perioperative management of thoracic surgical patients have recently been implemented, particularly in high- risk patients: an 'open- lung' protective ventilation strategy (low tidal volume, positive endexpiratory pressure and recruitment), titrated fluid regimen, assessment of pulmonary fluid compartment and early treatment of lung edema with noninvasive ventilation, aerosolized β_2-adrenergic agonists or both (2). Despite so, there remains no significant change trend in post-thoracotomy ALI and endeavors to seek the new schemes of prevention and treatment still continue.

Remote ischemic preconditioning, which was found by Przyklenk and colleagues (9) in 1993, is a phenomenon whereby transient non-injurious ischemia followed by reperfusion of one tissue or organ leads to the protection of another visceral organ against an injurious ischemic insult. The discovery of remote ischemic preconditioning has provided an innovational therapeutic strategy for the prevention of acute I/R injury in susceptible organs and tissues. Specially, the ability to induce remote ischemic preconditioning by a standard blood pressure cuff placed on the upper or lower limb has facilitated its translation into the clinical setting (10, 11). During the past three decades, experimental cardiology studies have shown that remote ischemic preconditioning can protect against myocardial I/R injury (10). More valuably, remote ischemic preconditioning can prevent I/R injury of both the heart and extra-cardiac organs (such as lung and kidney) at the same time as patients are subjected to the open heart surgery (12, 13). Furthermore, a recent meta-analysis indicates that remote ischemic preconditioning reduces troponin release in patients undergoing coronary artery bypass grafting (14). In spite of

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these beneficial results, there is continued skepticism regarding the clinical efficacy of remote ischemic preconditioning against perioperative myocardial I/R injury (15).

Similarly, regarding the lung protection of remote ischemic preconditioning, available literatures including basic and clinical trials provide conflicting results. In a rat model, the remote ischemic preconditioning by unilateral lower limb I/R significantly attenuates pulmonary neutrophil infiltration, lung edema, myeloperoxidase and oxidative stress (16, 17). Furthermore, limb remote ischemic preconditioning can attenuate hemorrhagic-shock induced lung injury, and improve lung function by inhibiting inflammation and lipid peroxidation (18, 19). In patients undergoing lower limb orthopedic surgery, limb remote ischemic preconditioning induced by unilateral thigh tourniquet improves arterial-alveolar oxygen tension ratio, reduces respiratory index and attenuates cytokine and free radical release (20). In a randomized clinical trial with 60 infants undergoing congenital heart defect corrective surgery, Zhou and colleagues (13) show that limb remote ischemic preconditioning induced by unilateral arm tourniquet before surgery reduces inflammatory cytokine release, preserves lung compliance and attenuates lung I/R injury. In adult patients undergoing elective open infrarenal abdominal aortic aneurysm repair, moreover, limb remote ischemic preconditioning improves lung oxygenation (21). However, Cheung and colleagues (22) show that limb remote ischemic preconditioning does not improve postoperative oxygenation in children undergoing cardiac surgery. Another recent study also suggests that limb remote ischemic preconditioning does not provide significant pulmonary benefit after complex valvular cardiac surgery (23). The conflicting results could be attributable to different experimental protocols and research subjects.

Most interestingly, in a recent article published in *Anesthesiology*, Li and colleagues (24) demonstrate the beneficial efficacy of limb remote ischemic preconditioning against the post-thoracotomy ALI in a randomized, double blind, single-centre study with 216 patients undergoing elective thoracotomy and lung resections. In this study, three cycles blood pressure cuff inflation on the left upper arm (5 minutes each cycle), followed by reperfusion (5 minutes each cycle), significantly improved intraoperative oxygenation, decreased incidence of postoperative ALI and attenuated the rise of biomarkers reflecting inflammatory response and oxidative stress when compared with no remote ischemic preconditioning.

The present study is noteworthy because it is the first clinical trial to show that the reduction in surrogate endpoints in patients treated with remote ischemic preconditioning before thoracotomy translates into clinical benefit. Moreover, many things of this study were well done. Other than strict inclusion and exclusion criteria of patients, Li and colleagues tried to control most of known risk factors that can affect ALI following lung resection, such as age, gender, pre-existing mobidities, preoperative pulmonary function, smoking history, duration of anesthesia, durations of one-lung ventilation and surgery, ventilation model, intraoperative infusion and transfusion, postoperative pain management, etc (2, 25-29). All of these are strengths in their study designs. Before the exciting findings of Li and colleagues are adopted into routine practice, however, several important issues of this study must be noted and clarified.

Firstly, this study excluded the patients at high risks of post-thoracotomy ALI, such as elderly patients and those with the American Society of Anesthesiologists (ASA) physical status 3 to 4 category, severe impairment of cardiorespiratory function, previous chemotherapy or radiation therapy or immunotherapy, and pneumonectomy (2, 25-29). Thus, an important issue that was not addressed by this study is whether limb remote ischemic preconditioning can protect against the post-thoracotomy ALI in high-risk patients undergoing lung resections and thereby improve clinical outcomes. From an anesthesiologist's perspective, we believe that if the beneficial efficacy of limb remote ischemic preconditioning against the post-thoracotomy ALI in high-risk patients undergoing lung resections can be soundly validated by robust evidences from further large- scale randomized controlled trials, the clinical applications in the thoracic surgical setting would have a greater value.

Secondly, in this study, the authors only reported that the right- or left-side surgery and types of surgery (wedge resection and lobectomy) were not significantly different between the two groups. Actually, post-thoracotomy ALI is closely associated with the extent of lung resection. Segmental or wedge resections have the lowest risk, lobectomy the mediate, and pneumonectomy the highest (28). Therefore, in a randomized controlled trial of assessing post-thoracotomy ALI, providing the detailed extent and amount of lung tissues removed by surgery, such as segmentectomy, wedge resection, unilobectomy, bilobectomy, and pneumonectomy, is very important for ensuring group comparability. Moreover, other than standard pulmonary function examinations, preoperative evaluation is best to include the split-function tests as they can calculate the relative function of the tissue to be removed to the total function of both lungs, and thereby predict postoperative pulmonary function and risks for post-thoracotomy ALI (30). In addition, serum albumin level should be included in the patients' demographic data as it is associated independently with pulmonary complications in patients undergoing lung carcinoma resection (31).

Thirdly, this study reported a 12.0% overall incidence of ALI after lung resections. Li and colleagues stated that this result was in agreement with the findings of previous reports based on their references 5 and 6. However, in their reference 5, Alam et al. (26) reported a 3.1% incidence of ALI after lung cancer resection. Their reference 6 is a review, in which Licker et al. (2) reported a 2-5% combined incidence of ALI after thoracic surgery. According to the American- European consensus conference definitions for ALI/adult respiratory distress syndrome applied in the trial by Li and colleagues, most of previous studies show that ALI following lung resection is infrequent, occurring in just 2.5% of all lung resections combined, with a peak incidence of 7.9% after pneumonectomies (5, 26, 28, 29). That is, incidence of post-thoracotomy ALI reported by Li and colleagues is about 2-5 times higher than findings of previous studies. Unfortunately, Li and colleagues did not provide the possible causes for the high incidence of post-thoracotomy ALI, though they may be important contributors of their findings. We believe that addressing these factors would further clarify the transparency of this study.

Fourthly, Li and colleagues did not specify the surgery-related complications, such as postoperative bleeding, air leakage, chest infection, bronchopleural fistula, etc. Actually, two clinical patterns of post-thoracotomy ALI have been described, corresponding to different pathogenic triggers: primary ALI develops within 3 days triggered by surgery and a delayed form triggered by postoperative complications, such as bronchoaspiration, pneumonia, or bronchopleural fistulas, generally observed between days 3 and 10 after surgery (1). The postoperative complications not only contribute to the post-thoracotomy ALI and ARDS, but also aggravate postoperative inflammatory response and prolong duration of in-hospital stay (32). Moreover, in this study, data regarding postoperative fluid management were evidently missing, though fluid overload in the first postoperative 24 hours is an independent risk factor for post-thoracotomy ALI (32, 33).

Fifthly, Li and colleagues reported that incidence of postoperative renal complications is 0% . In the methods, we were not provided with the details of perioperative renal function assessment. The available data show that the risk of acute kidney injury within 72 hours after lung resections varies between 6 and 24% (32), and development of acute kidney injury has been associated with increased rates of tracheal reintubation and postoperative mechanical ventilation, and prolonged duration of in-hospital stay (33). Moreover, the study by Li and colleagues was not powered to show a difference in postoperative mortality and the number of adverse events occurred during the follow-up period was small. Thus, it is unclear whether favorable effect of remote ischemic preconditioning on post-thoracotomy ALI can be translated to postoperative mortality benefit. To address this issue, large-scale clinical trials are still required, and these new studies should have enough power for postoperative mortality (11). If further studies show consistent beneficial effect of remote ischemic preconditioning on ALI and mortality following lung resections, the implications for practice are immense.

In conclusion, in a prospective, randomized, and controlled clinical trial, Li and colleagues challenge the hypothesis whether limb remote ischemic preconditioning can produce a beneficial effect on post- thoracotomy ALI, and show that intermittent upper limb ischemia as a remote ischemic preconditioning stimulus improves intraoperative pulmonary function after lung resection in patients without severe pulmonary disease. Undoubtedly, this study further enriches our knowledge regarding the effect of limb remote ischemic preconditioning on perioperative organ injury. Furthermore, their findings might change the current practice of perioperative management of thoracic surgical patients. However, it must be emphasized there are some limitations in the study design and conflicting results regarding the lung protection of remote ischemic preconditioning in available literatures. Before remote ischemic preconditioning can be recommended as a routine clinical practice to attenuate post-thoracotomy ALI, we believe there is still a long way to go. Specially, it needs to address some crucial problems about use of the remote ischemic preconditioning. For example, what is the extent of lung protection by remote ischemic preconditioning? What is the best time to perform remote ischemic preconditioning before surgery? What are precise mechanisms of remote ischemic preconditioning against post- thoracotomy ALI? Can remote ischemic preconditioning be combined with other lung protective measures, for example pharmacological preconditioning or postconditioning? If combined, can a synergistic lung protection be obtained? Can favorable effect of remote ischemic preconditioning on post-thoracotomy ALI be translated to postoperative mortality benefit? Evidently, future experimental and clinical trials are needed to answer these questions.

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