

Lung preconditioning in anesthesia: Review of the literature

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Abstract

Lung injury can arise during or after anesthesia and can lead to a complicated postoperative course with great implications for the patient. Unfortunately, treatment of acute lung injury is at the moment mainly supportive and rates of recovery have not really improved in the recent years. In many cases, lung injury can be anticipated and preventive measures seem possible. This represents a unique challenge to the anesthesiologist, as some new opportunities to reduce the frequency and/or severity of lung injury seem now available. These chances may arise from the potency of preconditioning the lungs before the main injury, with smaller injurious insults. Although preconditioning began to be applied first on the myocardium, experimental studies have shown potentially beneficial results also for the lungs. This review summarizes the main methods of lung preconditioning that have been tried in experimental studies in the literature and the main mechanisms that are perhaps involved. Emphasis is given in the two main methods of preconditioning that seem readily applicable in the clinical praxis, that is ischemic preconditioning, as well as preconditioning with volatile anesthetics. The few, but interesting clinical studies are also summarized and the future research points in this evolving field of anesthesia are stressed.

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Key words: Preconditioning; Ischemic preconditioning; Lung injury; Anesthesia; Volatile anesthetics

Core tip: Currently, the efficacy of lung preconditioning is tested in various experimental studies. The first clinical studies regarding remote ischemic preconditioning have appeared, with conflicting results. This review summarizes the scientific knowledge on this arising research field.

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INTRODUCTION

Acute lung injury (ALI) is diagnosed based on simplified criteria, published in 1994, in a consensus conference: arterial hypoxemia with partial pressure of oxygen to inspired fraction of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio less than 300 mmHg and less than 200 mmHg to define ALI and acute respiratory distress syndrome (ARDS), respectively, and bilateral radiographic opacities without evidence of left atrial hypertension^[1]. Additionally, some investigators believe that the definitions should specify the level of positive end-expiratory pressure and/or the fraction of inspired oxygen. A recent report - what is now called the Berlin definition - recommends use of three categories of ARDS, based on the degree of hypoxemia: mild ($200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$), moderate ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$), and severe ($\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$)^[2]. Lung injury and ARDS still carry a high mortality and recent therapeutic efforts have been proved mainly unsuccessful^[3-5].

Preconditioning (PC) was first used as ischemic PC, whereby brief periods of ischemia of myocardium exert a protection against subsequent, more prolonged periods of ischemia^[6,7]. Although PC was first used for the myo-

cardium, it was later applied also to other tissues, such as the lungs^[8]. PC has been achieved not only through ischemia, but also through hypoxemia^[9], catecholamines^[10], pharmaceutical interventions and volatile anesthetics^[7,11]. From the above it is obviously important that in order to apply PC, one should foresee the upcoming injury, as for example in types of surgery that frequently lead to lung injury. On the other hand, a sudden bleeding and ALI resulting from the hemorrhagic shock, is not a scenario appropriate for such a preparation.

LITERATURE RESEARCH

The Medline database of the National Library of Medicine was used to conduct a search of the literature. Keywords used were “lung preconditioning”, “lung preconditioning AND anesthesia” (with and without filter for human studies), “preconditioning AND volatile anesthetics” and “lung ischemic preconditioning” for the years from 1990 until today. Only articles written in the English language were included. From the literature search, a total of 25 articles referring strictly to lung preconditioning were retrieved and from those 5 were conducted on humans.

ANTICIPATED LUNG INJURY DURING ANESTHESIA

During or after anesthesia, ALI can arise under variable circumstances. Some of these may be directly linked to anesthetic interventions itself, such as aspiration of gastric contents, whereas others derive from the surgical intervention, such as aortic cross-clamping^[12,13]. Lung injury can be precipitated by embolic events during orthopaedic surgery, by inflammation and oxidative stress or due to inflammation after aortic surgery^[14-17]. Lung injury can also arise due to a pre-existing illness that has lead the patient to the surgical procedure, such as sepsis, or may arise in the postoperative period as a result of shock^[18,19].

In some instances, such as after thoracic procedures like major pulmonary resection, lung injury is relatively common and can be expected in up to 7% of cases^[20-23]. Sen *et al*^[20] reported ARDS after lung resections in 7.5% of cases with a mortality of 18.8%. In this study, alcohol abuse, fresh frozen plasma use, pneumonectomy and American Society of Anesthesiologists class of patients were significant predictors for development of ARDS postoperatively. In another study^[24], high intraoperative ventilatory pressure, excessive fluid administration, pneumonectomy and preoperative alcohol abuse were found as independent risk factors for primary ALI after lung resection surgery.

Another major entity whose prevalence and significance has received a more appropriate attention in recent years is the transfusion-related acute lung injury (TRALI)^[25]. Criteria for the diagnosis of TRALI have been also introduced, and although a “two hit” model has been proposed, suggesting the significance of the activation of neutrophils and endothelium^[26,27], the pathogenesis re-

mains unclear. Specific therapeutic measures do not exist, and preventive measures that were early introduced such as the use of plasma components of mainly male donors have been criticised, leaving great questionmarks in the prevention of TRALI^[28-30].

Lung injury after cardiac surgery is common and multifactorial and a significant risk factor is considered the transfusion of blood products. However, lung protection strategies have not been always successful^[31,32]. Specifically, remote ischemia of the lower limb was found to have a protective effect on airway resistance in children undergoing heart surgery^[33], but a subsequent larger study showed no effect of remote ischemic preconditioning on PaO₂/FiO₂ ratios or time to extubation after cardiac surgery^[34]. Interestingly, in a recent prospective study it was shown that the major determinant of lung injury after cardiac surgery is not the extracorporeal circulation (heart-lung machine), but atelectasis^[35]. Unfortunately, the study included a very limited number of patients to make any definitive conclusions. Importantly, an analysis of 4366 patients identified high risk cardiac, vascular or thoracic procedures, diabetes mellitus, chronic obstructive pulmonary disease, gastroesophageal reflux disease and alcohol abuse as important predictors for postoperative ALI^[36]. Lobectomy, multilobectomy, pneumonectomy, esophagectomy and lung decortication were considered as high-risk thoracic procedures; whereas high-risk cardiac procedures included coronary artery bypass surgery, valve replacement or multiple valve repair, pericardial resection, aortic arch repair, cardiac transplantation, congenital heart repair and cardiac reoperations. It seems that diseases associated with immunosuppression, such as diabetes mellitus and alcohol abuse, may play an important role in the development of ALI postoperatively.

Lung injury after lung transplantation represents another entity of predictable postoperative lung injury. During lung transplantation, ischemia-reperfusion (IR), one-lung ventilation and inflammation combine and create the appropriate circumstances for the development of ALI, which endangers the viability of the lung transplant^[37]. Postoperative ALI is perhaps the most significant factor for early postoperative mortality after lung transplantation^[38]. The IR injury during lung transplantation takes the form of the primary graft dysfunction, characterized by inflammation and lung fluid dysregulation^[39].

VARIETIES OF LUNG PRECONDITIONING

Ischemic preconditioning

Ischemic PC has been tried successfully in a model of lung transplantation in rats, in which 5 min of ischemia and 10 min of reperfusion were applied before the lung was transplanted^[40]. The researchers found a significant improvement in gas exchange in the transplanted lungs 12 h after transplantation, along with a reduction in thio-barbituric acid reactive species. This was one of the first findings that ischemic PC can attenuate primary graft dysfunction, which is the most significant reason of early

mortality and morbidity after lung transplantation and is caused by ischemia and reperfusion injury of the lung^[39]. Although this effect was studied in previously healthy lungs, it would be very interesting to be tested in marginal donor lungs, in prolonged ischemia duration and in significant pulmonary hypertension of the recipient, which represent cases in which primary graft dysfunction is particularly important^[41]. The beneficial effects of ischemic PC were also verified in a *ex vivo* model^[42]. These investigators found that 15 min but not 5 min of ischemia can significantly attenuate graft dysfunction after 2 h. However, the number of animals per group ($n = 4$) was rather small and unfortunately no conclusion could be drawn as to whether repetitive ischemia offers better outcomes or not. In the setting of primary graft dysfunction, the role of intercellular adhesion molecule-1 (ICAM-1) and P-selectin has been acknowledged, but their role in ischemic PC remains elusive^[43]. Nevertheless, in an earlier study, 10 min of ischemic preconditioning of the lungs resulted in reduced infiltration by neutrophils and reduced production of oxygen-free radicals, which is in accordance with such a mechanism of reduced activity of adhesion molecules^[44]. Of course, the general problem with oxygen radicals is also here an issue, since we cannot tell whether reduced oxygen free radicals is part of the protective mechanism or a consequence of the protection. Future studies should aim at distinguishing between the two before we can draw any certain conclusions.

Remote ischemic PC

Remote ischemic PC, through PC of the lower limbs (3 cycles of 10 min ischemia and 10 min reperfusion) was also tested before hemorrhagic shock (representing global ischemia) lasting 2 h^[45]. The investigators found that remote ischemic PC was protective for the lungs and that, at least partially, this protection derives from the enhancement of heme-oxygenase-1 expression in the lungs. Also in this study the role of neutrophils and the decreased oxidative stress was depicted as a benefit of ischemic preconditioning. An initial work had shown that remote ischemic PC suppresses peripheral blood leukocytes genes important for cytokine synthesis, leukocyte chemotaxis, adhesion, migration and other functions during inflammation^[46]. However, these benefits on gene expression were not translated in a benefit for patients, because remote ischemic PC (lower limb 3 cycles of 10 min ischemia) combined with postconditioning did not improve oxygenation and lung injury, except for an improvement in A-aDO₂ and dynamic lung compliance^[47]. This could be because ischemic PC does not result in changes in the corresponding proteins or because the protection is not strong enough for an injury such as that of ALI after coronary artery bypass graft surgery. The authors postulated that the lack of effect could perhaps be related to the presence of anesthesia, because intact nervous pathways were shown to be a prerequisite for the benefit of preconditioning or because inhalational anesthetics could have obscured any additional benefits of remote ischemic PC^[48]. Another recent study also did not

find any benefit of remote ischemic PC in lung compliance, alveolar-arterial oxygen gradient, oxygen index and time of mechanical ventilation in infants undergoing ventricular septal defect repair^[49]. The authors used 4 cycles of 5 min lower limb ischemia-reperfusion. Although the study was organized for myocardial injury and was not powered for lung function variables, the authors suggested that the use of inhalational anesthetics and steroids may have masked any potential benefit from the ischemic preconditioning. In a study that aimed mainly at the systemic inflammation, an index of lung catabolism was also measured, after applying remote preconditioning to the limb, before knee surgery, and the authors found no significant benefit for lung catabolism^[50]. In a recent and adequately powered study however, 3 cycles of 5 min ischemia and 5 min reperfusion of the upper extremity achieved significant better oxygenation and decreased markers of intestinal injury^[51].

PC through volatile anesthetics

Based on previous reports on the beneficial effect of volatile anesthetics on ischemia/reperfusion of the heart and liver, Liu and colleagues assessed the efficacy of isoflurane in an *ex vivo* model of lung ischemia and reperfusion^[52]. The authors concluded that pretreatment with isoflurane could improve parameters such as vascular resistance and pulmonary edema. The authors further compared sevoflurane and isoflurane in their potential to reduce IR injury and found that administration of 1 MAC (minimum alveolar concentration) for 30 min before IR of either anesthetic reduced several markers of ALI in an *ex vivo* model^[53]. The authors, taking into account studies concerning the effects of anesthetic preconditioning on other organs, mainly the heart, proposed several hypothetical mechanisms, such as a reduction of tumor necrosis factor- α (TNF- α) release, reduced adhesion and migration of neutrophils, decreased generation of oxygen free radicals, suppression of metabolism or use of adenosine triphosphate (ATP) and activation of K_{ATP} channels^[53,54]. Preconditioning with isoflurane also mitigated lung injury from aerosolized lipopolysaccharide in mice^[55]. In that model, early preconditioning (1 h before lung injury) was associated with decreased concentrations of chemotactic chemokines, although it is not clear whether this was the result or a mechanism of protection. In another study, preconditioning with either isoflurane or sevoflurane was successful in improving survival in a rat model of sepsis-induced lung injury^[56]. Although in the case of sevoflurane this was accompanied by a decrease in oxidative stress markers and soluble ICAM-1 levels in plasma, the mechanism of protection still remains elusive. The protection offered by sevoflurane preconditioning was also shown in an *in vivo* model of lung auto-transplantation in swine, in which TNF- α , interleukin-1 (IL-1), lipid peroxides and nitric oxide (NO) were reduced^[57]. Regarding the clinical variables, sevoflurane PC reduced lung edema and improved PO₂ in pulmonary vein of the re-implanted lobe. However, systemic oxygenation was improved only transiently (at

10 min after lung re-implantation, but not at 30 min). Although the duration of sevoflurane preconditioning in that study is not known, the results are encouraging. It remains however elusive whether these advantages are translated into a benefit for lung function in the everyday clinical praxis.

Other types of PC

Other types of preconditioning of the lungs have been also tried, such as whole body heating to 42 °C 16 h before hemorrhagic shock^[58]. The authors found that this kind of stress PC induced the expression of heat-shock-protein 27 (Hsp-27) and preserved alveolar-capillary membrane permeability. A decreased expression of inducible nitric oxide synthase (iNOS) was also noted and *in vitro* experiments confirmed that heat preconditioning readily decreased iNOS expression in alveolar epithelial type II cells. Exercise PC has been also shown to reduce lung edema, inflammation and injury, partially by inducing Hsp-27 expression in lung tissue^[59]. Although these types of PC do not seem easily clinically applicable, another recent study showed that oral administration of sildenafil can prevent lung ischemia-reperfusion injury when administered 2 h before lung injury^[60]. In another study, the role of Hsp-27 was emphasized by the successful induction by hypobaric hypoxia before heatstroke lung injury and the reduction of lung injury^[61]. Lastly, an interesting study showed that dopamine can play an important role in the protection by ischemia-reperfusion injury in the lungs through D1 and D2 receptors^[62].

DISCUSSION

From the above search of the literature it is evident that lung PC during anesthesia is an open research field, clearly requiring more clinical studies. The experimental studies have shown in many instances a protective effect of PC, either with ischemia or pharmacological, but the extrapolation of conclusions in the clinical situation is difficult. Until now, 5 clinical studies could be identified for lung PC during anesthesia^[34,47,49-51], from which only one was able to show a benefit from remote ischemic preconditioning for the lungs^[51]. Important is that this study used as primary endpoint the pulmonary function and included sufficient number of patients, but also the pattern of remote IR (3 cycles of 5 min ischemia and 5 min reperfusion) may have played a role in the success of PC. Nevertheless, more clinical studies specifically studying pulmonary function are urgently needed in order to confirm these findings. In addition, researchers should include more indices of pulmonary function, so that we can have a more complete view of the pulmonary function, but also clinical markers of direct significance, such as time to extubation and intensive care unit stay, in order to comprehend if this potential benefit has any significant effect for the patient. Regarding pharmacological PC, despite the first encouraging experimental results, clinical studies do not exist. Although no significant risks from the above interventions for PC seem probable,

based on these observations, lung preconditioning cannot be recommended in the clinical praxis, until more clinical studies are conducted.

Future research points

Other issues that need to be addressed is which type of PC is the most effective (this may differ between types of lung injury) and also the exact protocol of PC that is the most effective (such as the duration of ischemia or the duration of exposure to a volatile anesthetic or whether early or late preconditioning is most appropriate in each type of lung injury). It is also remarkable that the mechanisms regarding lung preconditioning are largely indirectly extrapolated from heart preconditioning studies, but this is of course not necessarily true. Future studies should focus on examining specific mechanisms for lung preconditioning. Also, not all types of lung injury may be improved by PC. For example, IR injury may be improved, but lung transplantation represents the extreme ischemia/reperfusion and it is not known whether PC really benefits in this context. Also PC for some other important types of lung injury such as TRALI has not at all been examined, although of direct clinical importance. One of the most important issues of course remains the clinical applicability, since a measure needs to be significantly beneficial, inexpensive, devoid of side effects and not extremely complicate the every day clinical practice.

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