



RESEARCH PROGRESS OF SEVOFLURANE ON LUNG FUNCTION PROTECTION MECHANISM IN SINGLE LUNG VENTILATION

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ABSTRACT

Objective: To investigate the Effects of sevoflurane preconditioning on pulmonary function in patients undergoing pulmonary lobectomy during one lung ventilation (OLV).

Key words: sevoflurane; one lung ventilation (OLV); lung injury; dynamic pulmonary compliance (Cdyn);
KL-6

INTRODUCTION

Single lung ventilation is a common method of performing lung isolation technique in modern thoracic surgery. The application of this technique has greatly improved the surgical conditions, expand the indications for thoracic surgery. But with the prolongation of single lung ventilation can cause patients with varying degrees of pulmonary dysfunction. The main factors related to ischemia- reperfusion injury of lung injury, mechanical ventilation-related lung injury and alveolar and systemic inflammatory response and other factors. Lung injury caused by a single lung ventilation can lead to delayed postoperative pulmonary function recovery, extended hospitalization stay, and even lead to death. Therefore, the prevention and treatment of lung injury in thoracic surgery has been the focus of clinical anesthesia practice. Sevoflurane is currently one of the most widely used inhalation anesthetics in clinical practice. With the popularity of its application, in recent years, its research on the protection of lung injury has been emerging. The related research in recent years is summarized as follows:

Lung injury during single lung ventilation mechanism:

Ischemia reperfusion lung injury:

Experimental studies have shown that more than 2 hours of single lung ventilation can cause acute lung injury, because in the single lung ventilation process, there is the potential risk of intraoperative hypoxemia. Single lung ventilation this non-physiological ventilation can make the ventilation / blood flow ratio imbalance, the occurrence of hypoxemia, the incidence rate of 9% -27%. The main reason for hypoxemia is that non-ventilated lungs still have blood flow, resulting in ventilation / blood flow imbalance [1].

The most important mechanism to reduce hypoxemia during pulmonary ventilation is to reduce pulmonary vasoconstriction in the hypoxic region due to reduced oxygen concentration in the non-ventilated side of the hypoxic alveoli, and to increase the pulmonary vascular resistance, so that the distribution to the hypoxia of the pulmonary blood flow reduction, that is hypoxic pulmonary vasoconstriction (HPV). Hypoxic pulmonary vasoconstriction is a protective mechanism of the body through which the flow of blood can be transferred from the lower concentration of alveolar tissue to a better ventilation area to reduce pulmonary shunt and hypoxemia. Single pulmonary ventilation when the main pathological changes in alveolar arterial oxygen partial pressure increase, arterial oxygen pressure decreased, or even hypoxemia [2]. If the body appears hypoxemia, it will affect the outcome of its disease, severe cases of cerebral hypoxia, myocardial ischemia and other important organs of ischemia-reperfusion injury [3,4]. Lung ischemia-reperfusion can lead to up-regulation of surface adhesion molecules in pulmonary vascular endothelial cells, promote neutrophil-endothelial cell adhesion and neutrophil isolation in lungs, causing more severe structural and functional abnormalities of pulmonary vascular endothelial cells.

Mechanical ventilation-related lung injury:

Mechanical ventilation would itself cause mechanical damage to the lung:

- (1) lung pressure injury is the lung injury during mechanical ventilation, the pressure gradient between the alveolar and peripheral blood vessels significantly increased, resulting in ruptured alveolar pulmonary interstitial emphysema, bronchial vascular sheath into the mediastinum, and along its peripheral clearance into subcutaneous tissue, pericardium, retroperitoneal and abdominal cavity. If the visceral pleural rupture, the gas can enter the thoracic cavity, eventually forming interstitial lung, mediastinal and subcutaneous emphysema [5].
- (2) The high volume airway ventilation of lung volume not only causes air pressure injury, but also induces diffuse damage to the alveoli and the pulmonary capillaries. High tidal volume leads to excessive stretch-out of lung tissue, or extensive mechanical injury of alveolar epithelial and endothelial cells due to excessive opening and closing of small airway and alveolar with periodic opening and closing of mechanical ventilation. The high air volume also causes the pulmonary alveolar capillary membrane to increase the permeability due to excessive expansion, the alveolar surfactant is destroyed and deactivated [6].
- (3) Extensive study also found that, lung atelectasis end-expiratory lung volume is too low, some small airways and alveolar collapse and occlusion. the terminal bronchioles and alveolar tissue around it will be forced to withstand greater pressure, followed by damage [7,8].

Mechanical traction during the operation of the lungs:

Surgical operation of the lung tissue traction, extrusion, clamp, etc. can cause lung injury.

Inflammatory response:

These mechanical factors can shed endothelial cells, creating opportunities for inflammatory cell activation and adhesion to the basement membrane and thus into the lungs, thereby stimulating inflammatory responses in the lungs. TNF- α as an early inflammatory factor can induce the release of other inflammatory mediators, including IL-6, IL-8, etc., initiate the inflammatory cascade, induce neutrophil degranulation and adhesion to endothelial cells, is the strongest inflammatory mediator of pro-inflammatory cytokines and correlates with the severity and duration of tissue damage and reflects the severity of the inflammatory response caused by surgical stress. IL-8 is thought to cause inflammation in the lung Tissue injury-specific cytokines, a strong white blood cell chemotaxis [9]. Eguchi et al [10] study of the rat model found that both lung ventilation or OLV can cause increased neutrophil accumulation within the lungs, especially in the OLV lung 30 minutes after re-exposure, non-ventilated lung Neutrophil isolation more significant, through the morphological analysis of neutrophils found cytoskeletal remodeling is the cause of mesangial cell

deformability decreased the main reason that the cytoskeletal remodeling is due to neutrophils resulting in the rapid polymerization of actin in neutrophils. This shows that alveolar and systemic inflammatory response plays an important role in the occurrence and development of lung injury caused by OLV.

Sevoflurane mechanisms of lung protection:

NF-KB pathway:

NF- KB is the convergence point of multiple single transduction pathways in inflammation response, available with TNF $-\alpha$, IL-1 β and other genetic promoters and enhancers, are combined to promote transcription ,Further activation of various signaling pathways and transcription factors , Pre- inflammatory factors such as TNF $-\alpha$, IL-1 β further activate NF-kB ,thereby expanding the inflammatory response.

Most of the cases, NF-kB dimers bind to I κ B and are inactive. When the body is stimulated by the environment, NF-kB dissociation from I κ B and NF-kB is rapidly activated by nuclear translocation, Gene promoter region kB site-specific binding, start gene transcription .NF-kB activates the transcription of many genes, including immune cytokines, inflammatory cytokines and so on. Sevoflurane preconditioning can inhibit the expression of NF-kB and thus block a series of enlarged inflammatory response that it produces, protecting lung during one lung ventilation and relieving acute lung injury [11].

Toll- like receptor 4(TLR4) pathway:

Toll-like receptor 4(TLR4) is expressed in a variety of antigen presenting cells and is a key receptor for endotoxin transmembrane signaling. TLR4 plays an important role in endotoxin-induced acute lung injury. When TLR4 binds to corresponding ligand. TLR4 further activates NF-kB and activates protein kinase signaling through myeloid differentiation protein 88 dependent or non- dependent signal transduction pathway, thereby promoting a variety of inflammatory cytokine gene expression^[12]. Imai et ^[13] The study found that pathogenic micro-organisms, oxidative stress and so on can activate TLR4 pathway and lung injury. Studies have shown that sevoflurane preconditioning and post conditioning can reduce the degree of lung injury, the mechanism may be related to the inhibition of TLR4 pathway upregulation of inflammatory response to reduce ^[14,15].

gamma-amino-butyric acid type A receptor (GABA_A) pathway:

GABA_A is an inhibitory neurotransmitter that inhibits signal transduction when activated by the release of GABA_A receptor and expression of GABA_A receptor has also been found on the surface of type II alveolar cells^[16].In vitro experiments showed that sevoflurane can enhance the outflow of chloride ions by regulating the activity of GABA_A receptors on the surface of type II alveolar cells and induce cyclooxygenase

(COX-2) Expression down^[17], resulting in resistance to inflammatory response^[18]。

iNOS pathway:

Currently known nitric oxide synthase(NOS) is divided into three types:(1)neuronal nitric oxide synthase(nNOS),(2)endothelial nitric oxide synthase (eNOS) ,and (3) inducible nitric oxide(iNOS).Among them neuronal nitric oxide(nNOS) and endothelial nitric oxide(eNOS) are expressed under normal circumstances whereas inducible nitric oxide(iNOS) synthase is expressed after injury induction. The characteristic inflammatory response of acute lung injury is associated with the increase of iNOS activation and expression, and the latter cause an increase in nitric oxide (NO) production.NO rapidly degrades under the action of reactive oxygen species to produce lung injury effects ^[19] 。 In addition, NO free radicals also aggravate the inflammatory response by promoting the inflammatory and cytotoxic responses on uninjured peripheral cells ^[20] 。 Sevoflurane reduces alveolar neutrophil accumulation and cytokine release during single lung ventilation ^[21, 22] in patients. Casanova et al ^[23] found that sevoflurane preconditioning can inhibit the expression of iNOS and maintain the balance of NO in the lung, thereby reducing lung injury.

HO-1 pathway:

The main function of heme oxygenase 1 (HO-1) is to decompose heme and act as a catalyst to catalyze heme formation to carbon monoxide (CO), iron and biliverdin with highly inducible, hyperthermal, hyperoxic, endotoxins And inflammatory factors can induce its expression increased, participate in various protective physiological processes such as anti-inflammatory, inhibit cell proliferation and apoptosis, dilate blood vessels, sevoflurane can be induced by ERK1 / 2 / Nrf2 signaling pathway HO-1 gene expression, making HO-1 involved in anti-inflammatory processes of acute lung injury during one-lung ventilation^[24,25]。

Degradation of polysaccharide package:

Polysaccharide coating is located in a complex layer of vascular endothelial cells. In addition to polysaccharide coating can regulate the colloid osmotic pressure, but also can prevent leukocytes and platelets in the non-activated state adhesion to the surface of vascular endothelial cells^[26].Chappell et al ^[27]studies have shown that inflammatory factors can be polysaccharides coated degradation, causing platelet and leukocyte aggregation. Studies have also found that in the event of lung injury, the polysaccharide coating on the pulmonary vascular endothelial cells is degraded, and its degradation has an important role in the inflammatory response ^[28].Annecke et al ^[29]found that preconditioning or postconditioning with sevoflurane can reduce the degradation of polysaccharide-coated lung injury and reduce the inflammatory response.

Other ways:

The protective mechanism of sevoflurane on lung during one lung ventilation is CXCL1,CXCL2/3 pathway, K ion and ATP dependent K channel and adenosine receptor pathway.in this article ,we need to take further step in further research and find that we should make full use of the protective effect of sevoflurane on one lung ventilation.

CONCLUSION

Now, due to the development of thoracic surgery, the need for bronchial anesthesia is increasing, on lung ventilation essential. Here sevoflurane may be a good balance because sevoflurane may be able to exert its effect by reducing the lung damage caused by one lung ventilation as much as possible while ventilating on a single lung. Inhibition of acute lung injury in collapsed lung tissue during one lung ventilation improves lung oxygenation and reduces pathological changes.

The protective effect of sevoflurane on the acute lung injury caused by single lung ventilation should be fully exerted, making the single lung ventilation process more safe and ideal.

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