Lung isolation techniques are widely used in modern thoracic surgery. Specifically, a special anesthesia technique is used to make the surgical side lung collapse, while the non-operated side undergoes one-lung ventilation (OLV) (1). Similar to other clinical technology, OLV is also a double-edged sword. If patients experienced OLV with long time, or combined with other disorders, they are prone to concurrent lung injury (2). OLV is now recognized to be a risk factor for acute lung injury (ALI), and is associated with postoperative pulmonary complications in 20% of lung resections (3). ALI and acute respiratory distress syndrome (ARDS) are the leading causes of death after thoracic surgery. Therefore, it is still important to clarify the specific mechanisms of OLV-induced lung injury for the prevention and treatment of perioperative pulmonary complications. OLV-induced lung injury involves the entire alveolar–capillary unit, with trauma to both the alveolar epithelium and the vascular endothelium (4). Destruction of alveolar-capillary membrane integrity always triggers a subsequent series of pathophysiological processes of lung injury. Endothelial glycoproteins (EG), a complex layer of membrane-bound proteins on the luminal surface of the vascular endothelium, appears to play a central role in lung injury (5). There are some evidence from clinical studies and laboratory researches with specific regard to EG integrity and damage and lung injury (6). Specific pathophysiological triggers that lead to damage of the glycocalyx are being actively investigated (7). Protection of the glycocalyx seems to be a promising target in OLV-induced lung injury.

Structure and Function of EG

The EG consists of a variety of endothelial membrane-bound molecules, including glycoproteins and proteoglycans, that provide the basis for plasma-endothelial cell interaction. Its major constituents are hyaluronic acid and the negatively charged heparan sulfate proteoglycans (Figure 1) (8). Usually glycocalyx is distributed between endothelial cells and the blood flow, which plays an important role in the maintenance of vascular permeability. Meanwhile, the glycocalyx is also able to perceive shear stress and chemical stimulation from blood flow, followed by adjustment to influence the production of nitric oxide (NO) and cytoskeleton, and finally may change the endothelial cell permeability and systolic and diastolic function. Under physiological conditions, endothelial glycocalyx plays an important vascular protective effect in determining the permeability of blood vessels, reducing blood cell interactions and vascular wall cells, conducting shear stress, and balancing signal transduction (9). Previous studies have found that direct damaged glycocalyx will result in the loss of these functions. First, endothelial cells are directly exposed to the circulating blood. Then, a number of adhesion molecules circulating leukocytes and the endothelial surface combine to promote leukocyte adhesion, migration, and exudation. After several cytokines and chemical mediators of blood integrated with endothelial cells, coagulation and inflammation cascade were activated by injured endothelial cells. Subsequently increased endothelial permeability and large amount of liquid exudation bioactive molecules, lead to destruction of the endothelial barrier function (10).

The main factors leading to vascular endothelial glycocalyx damage include inflammatory cytokines (11) and oxidative stress (12). Destruction of glycocalyx structure due to inflammatory injury is one of the early features of endothelial activation. It is now known TNF-α, oxidized lipoproteins, lipopolysaccharide (LPS), thrombin, ischemia/reperfusion and high blood sugar can damage glycocalyx structure by proteases. Less damage can release glyco-
Figure 1. Structure of the Endothelial Surface Layer.
The endothelial surface layer (ESL, the in vivo manifestation of the endothelial glycocalyx) is comprised of a layer of proteoglycans and associated glycosaminoglycans (heparan sulfate, hyaluronic acid) lining the intimal surface. Sialic acid-containing glycoproteins (not pictured) and adherent plasma proteins additionally contribute to glycocalyx/ESL structure. Image not to scale.

aminoglycan side chains; serious injury can result in the shedding of the core protein. Sepsis-induced pulmonary endothelial surface layer (ESL) loss would mediate the onset of pulmonary neutrophil adhesion and consequently inflammatory lung injury (Figure 2). Studies have also shown that the endothelial glyocalyx degradation may be triggered by TNF-α. Coronary endothelial glyocalyx got significantly thinner and vascular permeability was increased and macrophage cell was granulated in TNF-α-treated guinea pig. Meanwhile, reactive oxygen species can mediate modification of glyocalyx during ischemia-reperfusion injury. The EG has long been recognized as a site of damage following a period of ischemia (ischemia-reperfusion injury), and endothelial cells of the microvasculature are especially vulnerable perhaps as a result of production of reactive oxygen species (ROS). The pulmonary microvasculature is sensitive to a variety of injurious stimuli including excessive mechanical forces during ventilation and increased pulmonary vascular pressures, ischemia-reperfusion injury, and inflammatory mediators. During OLV, the ventilated lung is primarily affected by hyperperfusion and ventilator-induced lung injury, whereas the collapsed lung is exposed to ischemia-reperfusion injury and shear stress on reventilation (4). Therefore, pulmonary capillary EG and vascular endothelial cell barrier function are very important for exploring the pathogenesis of OLV-induced lung injury.

EG and One-Lung Ventilation Induced Lung Injury
Pathogenesis of OLV-induced lung injury is more complex, including ischemia-reperfusion injury, mechanical ventilation-induced lung injury, oxidative stress and inflammation. OLV-induced lung injury can occur in bilateral lung. Ventilated side lung damage may be closely related to mechanical ventilation induced lung injury (13). Non-ventilated side lung injury may be associated with atelectasis/recruitment (14), ischemia-reperfusion injury (15), oxidative stress (16) and surgical trauma (17), et al. In addition, pulmonary vascular endothelial cell damage is involved in the occurrence and development of OLV-induced lung injury. As endothelial glyocalyx is an important component of the vascular endothelial cells, therefore, the endothelial glyocalyx may play an important role in the OLV-induced lung injury.

EG and High Alveolar Pressures
The impact on the ventilated lung mainly refers to mechanical stretch induced lung injury, during OLV. Results of ventilator-induced lung injury showed that patients are prone to serious lung damage in plateau airway pressure exceed 30 cm H₂O (13). Patients with ARDS may have a lower mortality by the lung protective ventilation strategy with low tidal volume (18). There have been many animal and clinical studies confirmed that high-capacity ventilation is the main determining factor of lung injury (19, 20). Studies have also shown that ventilation-induced lung damage includes not only injury of pure alveolar structure, the gas gap alveolar edema, but also inflammatory cells and inflammatory factors involved in the process leading to biological damage (13). During standard tidal volume there is a large increase in tissue NOx in response to elevated vascular pressure. Thus combined effects of alveolar stretch and endothelial mechanotransduction result in more severe edema development. Cytokine increases are greater after high Vt OLV (10 ml/kg) than protective OLV (5 ml/kg) (15). Therefore, the high alveolar pressures and high tidal volume maybe cause lung endothelial glyocalyx damage and induce lung injury.

EG and Hyperperfusion/Capillary Shear Stress
The combination of high pulmonary perfusion pressures and high alveolar pressures is more damag-
ing to the endothelium and epithelium than either in isolation. Lungs exposed to high pulmonary flow displayed more pulmonary edema and hemorrhage and experienced larger decreases in compliance plus larger increases in vascular resistance. At Low tidal volume, lung filtration coefficient increased 5-fold whereas at standard tidal volume and, lung filtration coefficient increased 15-fold. Thus inflation pressure had a significant effect on the permeability response to increased vascular pressure. Capillary stress failure is described as the disruption of the capillary endothelium, alveolar epithelium, or sometimes all layers (17). Capillary stress failure is a recognized mechanism involved in ventilator-induced lung injury and may occur because of increased vascular shear stress or lung overinflation. Histopathologic evidence of increased interstitial edema and microhemorrhage in the ventilated lung after OLV support the fact that hyperperfusion is damaging to the capillaries. One of the mechanisms may be transcription-dependent changes in the glycocalyx (mechanotransduction) (20), which have been shown to occur in response to high capillary vascular pressures and result in increased vascular permeability. Studies also have revealed a space- and time-dependent reorganization of the glycocalyx that may underlie alterations in mechanotransduction mechanisms over the time course of shear exposure (21).

**EG and Hypoperfusion/Ischemia-Reperfusion Injury**

During OLV, non-ventilated lung experienced the process from collapse to recruitment. At the same time, lung tissue also experienced the process from hypoxia to re-oxygenation and from less blood flow to reperfusion, similar to ischemia-reperfusion injury. Currently findings in hepatic ischemia-reperfusion injury and cardiac ischemia-reperfusion injury, have confirmed ischemia-reperfusion injury may cause significant shedding of endothelial glycocalyx (22, 23). Organ ischemia induces capillary leak because of near-complete loss of the glycocalyx in guinea pig hearts. ROS/RNS-mediated degradation of the EG may exacerbate I/R injury by, for example, inducing vasoconstriction, facilitating leukocyte adherence, and directly activating innate immune cells (24). Similarly, the addition of ischemia to the lung collapse model results in marked worsening of the lung injury based on increased levels of tumor necrosis factor-α, decreases in nitric oxide metabolites (25). Meanwhile, non-ventilated lung has undergone tremendous changes in shear stress. Thus, Ischemia-reperfusion injury and exposure to inflammatory mediators induce further deterioration of the glycocalyx.

**EG and Inflammatory Cytokines & Oxidative Injury**

Inflammatory injury leading to changes in glycocalyx structure is one of the early features of endothelial cell activation. Systemic inflammation leads to changes in structure and physiology of glycocalyx, inducing endothelial dysfunction. In an experimental model of sepsis, high levels of TNF-α were associated with shedding of the glycocalyx (26). Alleviate LPS-induced ARDS, which potentially contributed to the suppression of MAPK pathway activation and the degradation of endothelial glycocalyx (27). There are data on the role of TLR2 and TLR4 in regulating human macrovascular aortic endothelial cells (HMAECs) inflammation and glycocalyx dysfunction under hyperglycemia. Meanwhile, after ischemia-reperfusion, a large number of oxygen free radicals generated in local sugar can lead to rapid destruction of EG, while superoxide dismutase (SOD) can significantly improve glycocalyx damage (28). NO and its reactive metabolites such as peroxynitrite can directly nitrosylate tyrosine residues on endothelial proteins, resulting in barrier dysfunction (12). Thus, both inflammatory cy-
tokines and oxidative stress, all are important risk factors leading to vascular endothelial glycocalyx injury. During one-lung ventilation, lung tissue has undergone high alveolar pressures, hyperperfusion/capillary shear stress, ischemia-reperfusion lung injury, surgical trauma/manipulation, et al. (Figure 3). These are likely to trigger upregulation of inflammatory cytokines and oxidative stress injuries, increase endothelial glycocalyx damage, and eventually lead to lung injury.

**EG and Overhydration**

Correcting low blood volume, increasing the effective circulating blood volume in order to ensure effective cardiac output blood flow and organ perfusion are fundamental objective of perioperative fluid therapy (29). Excessive fluid overload is a key factor leading to pulmonary edema and lung injury (30). Shedding of the endothelial glycocalyx in response to atrial natriuretic peptide release brought on by hypervolemia and mechanotransduction of the glycocalyx in response to capillary shear stress may be some of the underlying mechanisms to explain the harmful effects of overhydration (31).

**Research Directions in the Future**

Currently, one-lung ventilation-induced lung injury is increasingly concerned. Low tidal volume ventilation and PEEP are recommended as important lung protective measures (32, 33). In addition, avoid inhalation of high concentrations of oxygen and limit the amount of liquid can prevent the occurrence of lung injury (34, 35). Whether these measures can reduce the shedding and destruction of pulmonary vascular endothelial glycocalyx? Currently, it is still no definitive answer. Future researches will provide more clear evidence of OLV-induced injury and EG, confirm the effect of different lung protection measures on endothelial glycocalyx, and find out more effective lung protection measures.

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