Review Article

Molecular Mechanisms of Ventilator-Induced Lung Injury

Lin Chen[1], Hai-Fa Xia[1], You Shang[2], Shang-Long Yao[1]

[1]Department of Anesthesiology, Institute of Anesthesiology and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China

[2]Department of Critical Care Medicine, Institute of Anesthesiology and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China

Abstract

Objective: Mechanical ventilation (MV) has long been used as a life-sustaining approach for several decades. However, researchers realized that MV not only brings benefits to patients but also cause lung injury if used improperly, which is termed as ventilator-induced lung injury (VILI). This review aimed to discuss the pathogenesis of VILI and the underlying molecular mechanisms.

Data Sources: This review was based on articles in the PubMed database up to December 2017 using the following keywords: "ventilator-induced lung injury", "pathogenesis", "mechanism", and "biotrauma".

Study Selection: Original articles and reviews pertaining to mechanisms of VILI were included and reviewed.

Results: The pathogenesis of VILI was defined gradually, from traditional pathological mechanisms (barotrauma, volutrauma, and atelectrauma) to biotrauma. High airway pressure and transpulmonary pressure or cyclic opening and collapse of alveoli were thought to be the mechanisms of barotraumas, volutrauma, and atelectrauma. In the past two decades, accumulating evidence have addressed the importance of biotrauma during VILI, the molecular mechanism underlying biotrauma included but not limited to proinflammatory cytokines release, reactive oxygen species production, complement activation as well as mechanotransduction.

Conclusions: Barotrauma, volutrauma, atelectrauma, and biotrauma contribute to VILI, and the molecular mechanisms are being clarified gradually. More studies are warranted to figure out how to minimize lung injury induced by MV.

Key words: Biotrauma; Mechanism; Pathogenesis; Ventilator-Induced Lung Injury

Introduction

Mechanical ventilation (MV) is essential life support for patients with acute respiratory distress syndrome (ARDS); however, it can also lead to ventilator-induced lung injury (VILI) due to regional alveolar overstretch and/or repetitive alveolar collapse, which were termed as barotrauma, volutrauma, and atelectrauma. Gradually, clinicians realized that MV also mediated pulmonary injury without causing volutrauma or atelectrauma, even multi-organ dysfunction syndrome, and systemic inflammatory response. Indeed, the concept of VILI has been shifted from conventional barotraumas/volutrauma/atelectrauma to modernized biotrauma,[1-3] in which the inflammatory mediators were found to be responsible for the onset of VILI.

To understand the mechanisms of VILI are one thing, to apply MV and avoid VILI are another. Ideally, MV should maintain lung units open throughout the ventilator cycle, which minimizes lung injury due to repetitive alveolar collapse and/or overdistention. Guidelines for clinical practices are needed when it comes to how to ventilate the critical illness with or without ARDS, such as whether or not to apply low tidal volume (V_T) ventilation. An integrated understanding of the molecular pathways regarding VILI is the foundation of choosing the right strategy of MV, which certainly will help clinicians to make decisions in their daily work. This review addressed several core mechanisms underlying VILI.

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Address for correspondence: Dr. Shang-Long Yao, Department of Anesthesiology, Institute of Anesthesiology and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, China
E-Mail: ysltian@163.com

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Barotrauma

MV is an important way to provide sufficient oxygen to peripheral organs and therefore maintain their normal function. At the first beginning, it was recognized that lungs ventilated with high ventilatory pressures are prone to air leaks, which was the origin of barotrauma.[4] Actually, VILI was synonymous with barotrauma for many years. Disruption of the normal airspace wall causes the accumulation of air beyond alveoli and leads to tension pneumothorax. This particular adverse consequence is obvious and can be observed by physicians easily.

Volutrauma

Apart from the physical alveolar disruption induced by MV, researchers realized that it was excessive lung volume which leads to overdistention of the lung, i.e., volutrauma, characterized by hyperpermeability of the alveolar-capillary barrier.[5] A classical experiment found that pulmonary edema and cellular ultrastructural abnormalities were encountered only in rats subjected to high V_T but not in those in which lung distention was limited by thoracoabdominal strapping, which highlighted the effect of transpulmonary pressure instead of airway pressure during VILI. The importance of transpulmonary pressure and how it can predict the risk of VILI has been discussed elsewhere.[6] Meanwhile, the direct effect of volutrauma results in a persistent cyclic stretch during MV, which stimulates alveolar epithelial and vascular endothelial cells through mechanosensitive membrane-associated protein and ion channels, finally leads to pulmonary edema.[7]

Atelectrauma

Later on, studies had shown that the repetitive opening and collapse of alveolar plays a pivotal role in VILI, which was known as atelectrauma. Atelectrauma is defined as lung injury caused by high shear forces from cyclic opening and collapse of atelectatic but recruitable lung units. As for atelectatic alveoli, local stress and strain of epithelial cells is generated during recruitment at the interface between the air bolus and collapsed airway, which causes mechanical injury. In the other scenario, such as in the alveoli filled with water, the formation and destruction of bubbles at the gas-liquid interface contributes additional local stress and causes membrane-cytoskeletal adhesions disruption and worsens lung injury.[8] One study reported that surfactant-deactivated lungs developed significant histopathology only in lung areas with unstable alveoli, which confirmed that alveolar instability is an independent cause of VILI.[9]

Biotrauma

The role of biotrauma in the pathogenesis of VILI was not clarified until 1998.[10] In certain circumstances, MV is able to initiate inflammation and lung injury while maintain gas exchange. The study of Slutsky and Tremblay[11] first suggested that the MV-induced inflammatory response may contribute to the development of multiple system organ dysfunction including respiratory failure in mechanically ventilated patients with ARDS. Since then, more attention has been paid to how MV triggers biotrauma within the lung. Accumulating evidence showed that biotrauma induced by MV is far more complicated than barotrauma, volutrauma, or atelectrauma and the underlying mechanisms can be categorized in the following four parts.

Proinflammatory mediators release

MV is able to trigger the release of numerous proinflammatory mediators that may induce lung injury and impair pulmonary function. High V_T ventilation increases interleukin (IL)-1β, IL-6, IL-8, tumor-necrosis factor (TNF)-α, C-X-C motif ligand 1 (CXCL1) and CXCL10, macrophage inflammatory protein (MIP)-2, and intercellular cell adhesion molecule levels in the bronchoalveolar lavage fluid (BALF) in mice with a significant increase in pulmonary vascular permeability.[12-16] Among these, the levels of IL-6 and IL-1β in the lung and BALF of $IKK\beta^{\Delta mye}$ mice were also found to cause nuclear factor-κB (NF-κB) activation in ventilator-induced IL-6 and IL-1β production. A significant decrease in ventilation-induced IL-6 levels in the lung and BALF was observed in $IKK\beta^{\Delta mye}$ mice compared to WT mice while left IL-1β unaffected. The decreased IL-6 levels and reduced VILI in $IKK\beta^{\Delta mye}$ mice suggested that NF-κB activation-induced IL-6 expression may contribute to VILI.[12] Intratracheal administration of IL-6 itself increased cell count and protein concentration in the BALF, while high V_T MV further increased lung permeability following IL-6 administration in mice. *In vitro* study also showed that IL-6 increased the permeability of pulmonary endothelial cells in a Rho-independent manner.[17] One research reported that MV increased the expression of IL-8 and monocyte chemoattractant protein-1 modestly when compared with the control group; however, the increase was more evident in mice treated with both MV and lipopolysaccharide,[18] which suggested that MV is capable of augmenting the preexisting inflammatory response.

Another research showed that rats with VILI were associated with high expression of IL-33 in lung tissue; it also indicated that the membrane form of IL-33 receptor translocation from cytosol to the cell membranes of lung tissue can be seen as a new biomarker of VILI.[19] Hoegl *et al*.[20] demonstrated that high-pressure ventilation increased the concentrations of MIP-2 and IL-1β in BALF and plasma and this increase can be reduced by inhalation of IL-10 in mice. In addition, IL-10 inhibited nitrogen oxide (NO)-release from alveolar macrophages, reduced heat shock protein-70 expression, and even reduced the activation of matrix metalloproteinase (MMP)-9 in BALF in a dose-dependent manner. In contrast to the detrimental role of TNF-α in lung injury, TNF-α derived TIP peptide is able to protect the lung against injurious ventilation. Studies had proved that TNF-α derived TIP peptide inhalation could reduce the extravascular lung water index as well as increase the PaO(2)/FiO(2) ratio.[21,22] The protective role

of TNF-derived TIP peptide lies in that through binding to epithelial sodium channel-α, it is able to strengthen the barrier function and maintain permeability of the alveolar-capillary barrier.[23]

MMPs also participate in the pathogenesis of VILI. In a lung injury model of mice induced by sepsis followed by high V_T ventilation, WNT/β-catenin signaling pathway was activated as the protein levels of WNT5A and β-catenin increases, more MMP-7 was released in this process. Which then causes significant lung inflammation and perivascular edema.[24] The activity of MMP-9 is highly related to neutrophil transmigration during VILI and its detrimental role is evident. High V_T ventilation increases acute lung injury score, neutrophil infiltration, and myeloperoxidase (MPO) activity, along with higher MMP-9 activity. However, pretreatment with MMP inhibitor mitigates VILI, as well as neutrophil infiltration and MPO activity, which suggests that inhibition of MMP-9 exert protective effect against VILI through downregulation of neutrophil-mediated inflammation.[25] Meanwhile, MMP-8 is also involved in the initiation of lung inflammation. In comparison with control group, MMP-8 deficient mice ventilated with high pressure resulted in improved gas exchange, decreased pulmonary edema, and less histopathological changes in lung tissues. Interestingly, MMP-8 deficient mice showed different immune reaction against injurious ventilation, characterized by lower levels of interferon-γ and MIP-2, and increased levels of anti-inflammatory mediators (IL-4 and IL-10) as well as inhibited neutrophil infiltration. An inhibitor of MMP-8 was also shown to confer protective effect in limiting VILI.[26]

However, a study conducted by González-López *et al*.[27] showed different results. To a better understanding of mechanisms of repair after VILI, they set up control groups with other two different groups: (1) injury group (90 min of high-pressure ventilation without positive end-expiratory pressure [PEEP]) and (2) repair group (injury followed by 4 h of low-pressure ventilation with PEEP). Research data showed that histopathological injury and pulmonary permeability accompanied by a robust proinflammatory response during lung injury, which were reverted partially in the repair group. However, the expression of MMP-2 and MMP-9 both increased following injury and remained elevated during repair. Furthermore, MMP inhibitor doxycycline blunted lung repair after VILI and specific MMP-2 inhibition delayed lung epithelial repair *in vitro*. It has also been shown that administration with exogenous MMP-9 was capable of reducing lung damage and promote repair in neutropenic mice with VILI.[28] These data highlighted that MMP-2 and MMP-9 potentially promote lung epithelial repair after VILI, yet its mechanisms remain to be investigated.

Reactive oxygen species generation

Apart from proinflammatory mediators, the other potential initiating signal for biotrauma during VILI may be increased production of reactive oxygen species (ROS) in the lung triggered by cyclic stretch. Increased ROS production in response to mechanical stress has been described in various cell types. Endothelial cell production of ROS has been shown to be increased in response to shear stress as well as to cyclic mechanical stretch.[29,30] It was reported that A549 cells subjected to cyclic stretch significantly increased levels of isoprostane (a marker of oxidant injury) with obvious decreased glutathione (GSH, an endogenous antioxidant) 60 min after cyclic stretch. Pretreatment with antioxidants prevented the elevated level of isoprostane.[31] Chapman *et al*.[32] showed that strain level of 10% did not increase O_2^- concentration in 16HBE (an immortalized human airway epithelial cell line) cells after 2 h, whereas 15%, 20%, or 30% significantly increased the generation of O_2^-. NADPH oxidase activity was upregulated after 2 h of cyclic mechanical stretch, which contributed to the production of O_2^-. Using a mitochondrial complex I inhibitor, they proved that rotenone could partially abrogate the generation of O_2^- induced by 2 h cyclic mechanical stretch, suggesting that increased ROS production in lung epithelia in response to elevated stretch may contribute to VILI. Recently, Tanaka *et al*.[33] reported that 24 h of cyclic mechanical stretch mediated a significant release of 8-isoprostane and 3-nitrotyrosine (oxidative stress markers) in A549 cells; it also increased the expression of nicotine adenine dinucleotide phosphate oxidases (NOXs). In addition, cyclic mechanical stretch-induced NOX activation was associated with late phase apoptosis/necrosis in alveolar epithelial cells.

However, the link between ROS generation induced by cyclic stretch and the loss of function of alveolar epithelial cells is still missing. To figure out the possible relationship mentioned above, Davidovich *et al*.[34] performed the following experiment. First, they detected the production of ROS induced by cyclic stretch in Type I-like rat alveolar epithelial cells using cell-permeant fluorogenic probe. The level of ROS and release of NO were increased after 10 min and 60 min of cyclic stretch at 37% change in surface area compared with the unstretched cells. Next, the permeability of Type I-like rat alveolar epithelial cells monolayer stimulated by ROS was assessed. In comparison to control group, cells treated with NO donor and superoxide donor showed a significant increase in the monolayer permeability. Hyperpermeability of rat alveolar epithelial cells monolayer was accompanied by NF-κB and ERK signaling pathway activation. Tight junctions (TJs) located between adjacent Type I epithelial cells are the primary barrier to paracellular transport. Song *et al*.[35] investigated whether ROS is able to rearrange TJs in alveolar epithelial cells and mediate barrier malfunction during cyclic stretch or not. This time, they used a precision cut lung slices model as well as rat alveolar epithelial cells under identical mechanical loads. Results indicated that in similar to rat alveolar epithelial cells under cyclic stretch, the novel model showed ROS generation under uniform and cyclic stretch. Furthermore, their permeability increased after stretch as TJs protein (occludin, claudin-4) dissociated from zona occludins-1.

Given the important role of ROS generation in the pathogenesis of VILI, researchers have been working hard to find ways to reduce ROS biosynthesis to prevent it. Recently, one study reported that apocynin (a naturally occurring methoxy-substituted catechol which inhibits NADPH oxidase in activated leukocytes) prevented VILI.[36] In detail, VILI was induced by MV with high V_T utilizing isolated and perfused rat lung, an increase in lung permeability and lung weight gain can be observed in this model. The level of proinflammatory cytokines increased in BALF, concentrations of carbonyl and H_2O_2 were higher in BALF, mitogen-activated protein kinase signaling was also activated in high V_T group. However, administration of apocynin at the onset of MV alleviated these inflammatory responses and maintained pulmonary permeability, along with decreased activation of NF-κB. In addition, researches have demonstrated that administration of N-acetylcysteine or resveratrol attenuated the inflammatory responses and oxidative damage in the same model.[37,38]

Complement activation

The complement system is a major component of our innate immune system and is highly related with coagulation. Alveolar coagulopathy is associated with ALI/ARDS and VILI. Accumulating evidence had shown that activation of the complement system was involved in VILI.

Takahashi *et al*.[39] were the first to validate the link between complement C3 activation and VILI. They demonstrated that high V_T induced lung injury and resulted in elevation of activities of thrombin, gelatin/collagenase, and MMPs in BALF in mice, suggesting C3 was activated following MV. Next, they applied MV to C3 deficiency mice and proved the activity of thrombin and MMPs were lowered compared with that in wild-type mice. Finally, they used humanized cobra venom factor (HCVF) to inactivate C3 in the lung during MV and data showed that pretreatment with HCVF significantly reduced C3 deposition within lung tissue, lung injury was also mitigated. There was another research showed a similar result. MV caused a tremendous increase of complement component C3a compared with the control group (1017 ± 283 ng/ml vs. 258 ± 82 ng/ml, $P < 0.05$) and lowered the arterial oxygen tension (193 ± 167 mmHg vs. 569 ± 26 mmHg, $P < 0.05$). Interestingly, it was shown that plasma level of C3a in mice following MV was inversely correlated with arterial oxygen tension ($R = -0.734$; $P < 0.001$).[40]

Once C3 was activated, the complement cascade would be activated and finally form the terminal complement complex C5b-9. Liu *et al*.[41] reported that the activity of serum complement was higher along with aggravated pulmonary edema in a rat model of VILI compared with the control group. At the same time, they found the permeability of pulmonary endothelial monolayer was increased after soluble C5b-9 stimulation. Further research revealed that soluble C5b-9 caused a significant increase in rat pulmonary microvascular permeability by activating RhoA and led to higher expression of phosphorylated myosin light chain, finally resulted in stress fiber and gap formation.[41] Therefore, pulmonary endothelial barrier dysfunction mediated by complement activation may be involved in the pathogenesis of VILI.

Mechanotransduction and ion channel

Although the effects of MV *in vivo* and mechanical stretch *in vitro* are identified, the mechanisms of how cells transfer mechanical signals to biological signals remain elusive. After decades of research, it has been proved that the activity of ion channel changed quickly in response to mechanical stress and contributed to vascular hyperpermeability.[42]

Recent studies suggested the detrimental role of transient receptor potential vanilloid (TRPV) in the development of lung injury induced by MV or other insults. In particular, TRPV4 is a calcium permeable cation channel gated by various stimuli, including heat, osmotic stimuli as well as mechanical stimuli. It is expressed in a diverse range of tissues and cells, such as lung, kidney, brain, liver, and vascular endothelium.[43] In 1998, Parker *et al*.[44] reported that gadolinium (which is able to block stretch-activated nonselective cation channels) inhibited the increase in vascular permeability induced by high airway pressure ventilation in isolated rat lung, demonstrating that stretch-activated cation channels could trigger acute vascular hyperpermeability after MV. Moreover, Hamanaka *et al*.[45] clarified the specific role of TRPV4 during VILI in 2007. First, they applied high peak inflation pressure (PIP) to isolated perfused lungs and evaluated the permeability as indexed by filtration coefficient (K_f). Research showed high PIP ventilation increased pulmonary permeability compared with baseline but pretreatment with TRPV4 inhibitor abolished this effect. In isolated perfused lungs from TRPV4 knockout mice, the same ventilation setting failed to increase K_f. Next, they demonstrated lung distention mediated by ventilation caused Ca^{2+} entry in the control group, alveolar and perivascular edema were also induced. However, high PIP ventilation-induced Ca^{2+} entry and perivascular edema were abrogated in TRPV4$^{-/-}$ lungs.[46] Interestingly, they conducted another research and proved that high PIP ventilation induced calcium entry, NO and O_2^- production through activating TRPV4 macrophages, which was the reason why vascular permeability in lung increased rapidly following high pressure ventilation.[46]

It was reported that TRPV4 and its upstream kinase-mediated lung injury after high V_T MV.[47] By utilizing real-time imaging of endothelial Ca^{2+} in intact lungs, Michalick *et al*.[47] were able to show that acute airway pressure elevation in normal mice caused an evident increase in endothelial Ca^{2+} and lasted for more than 15 min, whereas TRPV4 inhibitor abolished the increase. TRPV4 has also been found to be a key mediator during inflammatory cell infiltration, inflammatory cytokines, and chemokines release as well as edema formation in mice ventilated with high V_T. In addition, as serum glucocorticoid regulated kinase 1 (SGK1) inhibition mitigated TRPV4-mediated endothelial Ca^{2+} entry, proinflammatory cytokines release,

and prevented Ser824 phosphorylation of TRPV4 induced by mechanical stretch, the authors revealed that both SGK1 (an upstream regulator of TRPV4) and TRPV4 were critical molecules in VILI. Given the role of TRPV4 in VILI, numerous researches had demonstrated that inhibition of TRPV4 by knockout or its pharmacological inhibitor confer lung protection, including attenuated inflammation and improved pulmonary function, against VILI or ALI induced by chemical reagents.[47,48]

As stretch-activated two-pore domain K^+ channel (K2P) TREK-1 participated in the regulation of inflammation response and repair, whether it can regulate the mechanobiology of alveolar epithelial cells or not has been investigated. TREK-1 deficient A549 cells showed less F-actin formation while its deformability increased, which also induced higher expression of phosphorylated FAK. Thus, alveolar epithelial cells expressed TREK-1 were more sensitive to stretch-induced lung injury.[49,50]

Different from the effect of TREK-1, Na^+ transport by Na^+-K^+-ATPase facilitated the clearance of pulmonary edema.[51-56] One study demonstrated that 30 min or 60 min of cyclic stretch-induced an increase of Na^+-K^+-ATPase in murine lung epithelial cells.[51] Fisher and Margulies[52] reported that in Type II alveolar epithelial cells, the activity of Na^+-K^+-ATPase was increased in response to cyclic stretch in a dose-dependent manner while lasting tonic stretch showed no effect on Na^+ pump. Furthermore, Fisher and Margulies[53] set up a new model which could evaluate the relationship between plasma membrane tension and Na^+-K^+-ATPase stimulation. They proved that MV with PEEP (with constant amplitude and relatively high volume) was associated with highest Na^+-K^+-ATPase stimulation. Interestingly, a recent study revealed that β1 subunit of Na^+-K^+-ATPase played a vital role in alveolar fluid clearance during VILI.[54]

Conclusions

In summary, inappropriate use of MV will lead to VILI and a better understanding of biotrauma is required. Biotrauma is characterized partially by proinflammatory responses within the lung or in the circulatory system, which can explain the lung-organ crosstalk and interactions (including MODS). From traditional concept "barotraumas, volutrauma, and atelectrauma" to a relatively newly recognized biotrauma, the mechanisms underlying VILI is still developing. There is an intrinsic relationship between the traditional mechanisms and biotrauma. Traditional ones are established on the basis of lung structure and function, which can be observed easily. However, biotrauma emphasis on signal transduction and direct effect of mechanical stress within cells. For example, high V_T ventilation is able to cause lung injury, this can be seen as volutrauma; it also can be explained by biotrauma, alveolar epithelium sense, and transform mechanical stress to biological signal, which then increase the activity of TRPV4 and result in hyperpermeability and edema. Based on these, many factors should be considered when providing MV to a critically ill patient. Lung protective strategies should be applied depend on individualized situation to improve the outcomes of ARDS patients.

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Conflicts of interest

There are no conflicts of interest.

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机械通气肺损伤的分子机制

摘要

目的：机械通气作为生命支持的重要治疗方法，数十年来其已经在临床上被广泛应用。但是研究人员发现机械通气不仅是维持生命的方法之一，而且其在不恰当使用的情况下会引发肺组织损伤，即机械通气肺损伤。本综述拟探讨机械通气肺损伤的发生发展及有关分子机制。

数据来源：本综述所选取的文献均来自PubMed的数据库，截止时间为2017年12月。采用以下关键词进行搜索：呼吸机相关性肺损伤、发生发展、机制、生物伤。

研究选择：主要选择与呼吸机相关性肺损伤机制有关的论著以及综述，并对选取的文献加以分析总结。

结果：从传统的病理机制（气压伤、容积伤以及萎陷伤）到生物伤，研究人员对机械通气肺损伤发生发展的认识是逐渐加深的。较高的气道压、跨肺压以及肺泡的反复开放/闭合是导致气压伤、容积伤以及萎陷伤的主要原因。在过去的二十年中，越来越多的研究证实了生物伤在机械通气肺损伤中的重要作用，其潜在的分子机制包括但不限于以下几个方面：促炎性细胞因子的释放、活性氧簇的合成、补体激活以及机械转导。

结论：气压伤、容积伤、萎陷伤以及生物伤均可以引起机械通气肺损伤，相关的分子机制正逐渐被阐明。在此基础上，需要进一步研究如何减轻机械通气过程中的肺损伤。