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Current Concepts in Critical Care 2022

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CHAPTER

Ventilation-induced Lung Injury: Ergotrauma

Suresh Ramasubban

INTRODUCTION

Even before the advent of mechanical ventilation, the deleterious effects of positive pressure ventilation were well known in medical science. With the advent of positive pressure ventilation after the Scandinavian polio epidemic, ventilation has become the cornerstone of intensive care unit (ICU) care. Associated with the increase in usage of ventilation what has been prominent, is the negative consequence of ventilation. Initially the negative consequences focused on barotrauma, manifesting with air leaks, over the last three decades, focus has shifted to the injury to the alveoli, manifesting as pulmonary edema and diffuse alveolar damage. Along with increasing awareness of the concept of ventilator-induced lung injury (VILI), theoretical and experimental data have shed light on etiology of VILI. The evolution of the etiological cause has progressed from focusing on pressure, subsequently on volume, then onto atelectasis and then dynamic factors such as flow and rate and now a unifying theory that incorporates all these concepts as a single entity called as ergotrauma. The energy expended and the power applied to the lung during mechanical ventilation can be calculated from analysis of the dynamic pressure volume loop and can be applied to clinical practice at the bedside. Validation of the lung damage contributed by ergotrauma has been done in small studies and large clinical studies are lacking.

HISTORY

"The lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined". Almost 250 years ago, while rescuing asphyxiated miners, Fothergill made this observation, which now stands as a testimonial to the damaging effect of the modern bellow, i.e., the ventilator. The barotrauma related to mechanical ventilation was also well known to the physicians practicing in the era of ventilation provided for normalization of respiratory parameters. Prophylactic bilateral chest tubes were routinely considered in patients on mechanical ventilation. However, the less obvious damage to the alveoli, i.e., damage that does not cause rupture of the alveoli was also being noted.

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It was as far back in 1967 that the term "Respirator Lung" was coined to describe the pathological findings of diffuse alveolar infiltrates and hyaline membranes on a postmortem examination of patients who had been on mechanical ventilation. Ever since the seminal publication by Webb and Tierney[1] in 1974, it is a well-known fact that ventilation could result in lung lesions. They ventilated rats with peak inspiratory pressures of 45 cm and they noted that the rats developed pulmonary edema in about 20 minutes. Electron microscopic studies of these lungs demonstrated diffuse alveolar damage. The nature of this pulmonary edema was extensively investigated. Experiments measuring the extravascular lung water along with dry lung weight by Dreyfus et al.,[2] in the late eighties demonstrated the presence of a permeability pulmonary edema leading to VILI. Their seminal experiments with iron lung as well as strapped chest wall rats clarified the role of volume as the main mediator of VILI, and the term volutrauma was coined to signify the injury produced due to alveolar distention. Slutsky et al., observed a sharp increase in inflammatory cytokines in rats when their lungs were allowed to cyclically collapse and open. Their concept of atelectrauma and biotransduction of inflammatory mediators[3] is now well entrenched as the causative factor for VILI. Over the last decade, the concept of stress and strain to the lungs during mechanical ventilation has been well studied and the resultant energy and power applied to the lungs as a causative agent of VILI is the subject of this review.

DEFINITION

The pathological damage due to mechanical ventilation is characterized by inflammatory cell infiltrates, hyaline membranes, increased vascular permeability, and pulmonary edema. This constellation of pulmonary consequences of mechanical ventilation has been termed VILI.[4]

CAUSES OF VILI

Over the years, many factors have been implicated in the causality of VILI. A mechanical ventilator, based on modes and respiratory mechanics, is based on a combination of tidal volume, airway pressures, flows, and respiratory rate. All these factors have been implicated and we will look at all of them one by one.

Pressure

Since the beginning of the understanding of VILI, excess pressures have always been implicated in the development of VILI. Excessive pressures leading to alveolar rupture and escape of air into the pleura (pneumothorax), mediastinum (pneumomediastinum), subcutaneous tissue (subcutaneous emphysema), and even into the circulation (air embolism) have been

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well described as the entity barotrauma, a part of VILI. Pulmonary edema developing as a result of high pressures used during ventilation was well described in experimental animals by Webb and Tierney. At 45 cm H_2O pressures, 20 minutes is all that is required to develop the constellation of signs known as VILI. The level of pressure considered to be harmful was not clear for a long time, till the acute respiratory distress syndrome (ARDS) net ARMA trial[5] established an arbitrary value of 30 cm H_2O of plateau pressure as the upper safe limit of pressures in the airways. However, this must be tempered by the fact that trumpet players who develop peak pressures as high as 150 cm H_2O do not develop any lung injury. So, the pressure, which may better represent injurious stress, is transpulmonary pressure.

Transpulmonary pressure, which is the difference in pressures across the lungs, difference between alveolar and pleural pressures ($P_L = P_{alv} - P_{pl}$), may reflect the harmful pressures better. This is exemplified in a trumpet player whose alveolar pressures reach 150 cm H_2O, along with a similar increase in pleural pressures, resulting in no change in transpulmonary pressures.

In normal circumstances, the relationship between alveolar pressure and transpulmonary pressures is linear. The linear relationship holds true but the slope of the curve showing the relationship may vary. The slope of these two pressures is the ratio of elastance of the lung (E_L) to the elastance of the respiratory system (E_{RS}). Normally, the ratio is 0.7 with a range of 0.2–0.8. As the respiratory system becomes stiff, the relationship between alveolar pressures and transpulmonary pressures changes and the alveolar pressure may not reflect the transpulmonary pressures. This can be illustrated by the calculation of the alveolar pressure and transpulmonary pressures. So, if E_L/E_{RS} is 0.7, a plateau pressure of 30 cm H_2O would correspond to a transpulmonary pressure of 21 cm H_2O. However, if the E_L/E_{RS} ratio is 0.2, a plateau pressure of 30 cm H_2O, would correspond to a transpulmonary pressure of only 6 cm H_2O.

So, a threshold value of transpulmonary pressure at which the collagen fibers of the lung extracellular matrix are fully stretched would be about 21 cm H_2O.

Volume

In the early 80s, Dreyfuss et al., in a series of experiments found that VILI developed due to administered tidal volumes rather than pressures. They used a model in which the lungs were strapped resulting in high-peak pressures but delivering less tidal volume by reducing the elastance of the respiratory system, they compared VILI in animals given high volume and high pressures as well as animals in iron lung, wherein the lung pressures were very low. Among these three groups, the model with high pressure and low volume had least extravascular lung water and permeability as compared to a high-pressure, high-volume model and even as compared to

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a low-pressure high-volume iron lung model. This clearly paved the way for the concept of volutrauma.

However, the debate between volume or pressure as the cause of lung injury can be put to rest if one were to interpret the findings in terms of stress and strain.

Stress and Strain

In biomechanical terms, stress refers to "the internal redistribution of the counterforce per unit of area that balances and reacts to an external load" and "the associated deformation of structure" is called strain. In terms of the human lung on a mechanical ventilator, the pressure that acts on the lungs is the stress and the change in volume over and above the resting volume of the lungs at end of a normal expiration is the strain. The transpulmonary pressure is a better marker of stress rather than airway pressures and the debate between the proponents of pressure and volume comes to an end if we use transpulmonary pressures to define stress.

The relation between pressure and volume causing VILI can therefore be put as:

$$P_L = K \times TV/FRC$$

$$\text{Stress} = \text{Specific elastance} \times \text{Strain}$$

where P_L is the transpulmonary pressure, K is the specific elastance of the lung and TV is the tidal volume and FRC is the functional residual capacity, i.e., lung volume at atmospheric pressure.[6]

Thus, volutrauma due to high strain is related to the barotrauma due to excessive stress by a proportionality constant, the specific lung elastance, which is about 12 cm H_2O.

Tidal Atelectasis

Atelectrauma refers to the lung injury produced as a result of the repetitive opening and closing of alveolar units. This injury is exaggerated with depletion of surfactant leading to collapse of alveoli during expiration and regional hypoxia. Lungs with inhomogeneity have a significantly higher damage due to atelectrauma. Mead et al., way back in the 70s, had done theoretical calculations demonstrating the stress at the interface of collapsed and aerated regions could be four to five times higher and thus the stress levels of these atelectatic units are much higher leading to VILI. The tidal swing in volume also leads to transduction of inflammatory mediators, which is known as biotrauma.

Flow

For many years, the research for the causative factors leading to VILI has focused on the static parameters and ignored the dynamic component

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of flow. The rate of strain that the lung undergoes during ventilation is determined by the flow rate. Since the lung is a viscoelastic structure, the higher the rate of strain greater is the resistance developing within the lung scaffolding. The process of developing resistance in the extracellular matrix requires energy and this energy is distributed to the lung parenchyma. The amount of energy dissipated into the lung parenchyma from the extracellular matrix can be measured as the change in pressure after a sudden interruption of the inspiratory flow. This process is called as stress relaxation. The energy dissipated into the lung parenchyma depends on the rate of strain, the respiratory rate, and lung inhomogeneity.

Respiratory Rate

Despite the near intuitive effect of respiratory rate on VILI, it has not received much attention. Recent experiments by Cressoni et al., have shown that tidal volumes, which are lethal at a rate of 15/min, are not fatal at rates of 3/min, 6/min, and 9/min, pointing to the role of rate in the development of VILI. The principle of lung rest has been well established clinically in the context of ventilation settings during extracorporeal membrane oxygenation (ECMO), where respiratory rate is set at not >10/min. From a material engineering perspective, the respiratory rate is a measure of the number of cycles of stress and strain that the lung is exposed to and it may be possible that damage to the lung parenchyma happens only after a given number of such cycles have been delivered.

Driving Pressure

The driving pressure [plateau pressure minus positive end-expiratory pressure (PEEP)] is considered the best predictor of VILI in patients with ARDS. However, the driving pressure is not another static parameter that causes VILI but an amalgamation of elastance and strain. *Driving pressure is coupled to elastance and tidal volume*:

$$DP = VT \times E_{RS}$$

The effect of driving pressure on outcomes is a result of the severity of disease (elastance—E) or tidal volume (VT) (strain). The major drawback of using driving pressure as the sole measure of VILI is the ignorance of PEEP.

Combination of Factors

While delivering mechanical ventilation with an intent to prevent VILI, we need to focus on all the components just described. These include tidal volume, respiratory rate, PEEP, driving pressure, resistances, and flow. Vasques et al., describe these six components as part of an irregular solid with each component having a different area, contributing differently to the development of VILI. Each component by itself is important, but it is

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the composite effect that is important and contributes to the development of VILI. This composite factor may be mechanical power and the resultant injury to the lungs is referred to as ergotrauma.

ERGOTRAUMA

The contribution of the energy and power applied to the lung during ventilation leading to VILI is defined as ergotrauma.

Physics for the Intensivists

Work is said to be done when a force applied to an object produces movement of the object.

$$\text{Work} = \text{Force} \times \text{Distance}$$

In case of lungs where pressure is applied to produce a volume change, pressure is force/area and volume is length × area, the product of pressure and volume is force × length, which is the work done during inflation of the lungs.

Energy is defined as the capacity to do work and power is the rate of energy expenditure and work performance. Work and energy have the same unit, i.e., Joules while work/unit time is power and has the unit of Joules/s (watt). In case of lungs, power is pressure × volume/unit time or rate.

The equation of motion describes the opposing forces to lung inflation. Work is done to overcome the resistive and elastic opposing forces. The equation of motion is mathematically represented by the equation.

$$P = F \times R_{aw} + TV \times E_{rs} + PEEP$$

In this equation, P is the pressure in the respiratory system, E_{rs} is the elastance of the respiratory system, TV is the tidal volume, R_{aw} is the airway resistance, F is the flow, and PEEP is the positive end-expiratory pressure.

All the components of the equation of motion[7] are contributing to VILI.

- The product of tidal volume and elastance is the pressure required to overcome the elastic forces of the entire respiratory system and this is the same as driving pressure.
- The product of $F \times R_{aw}$ is the pressure needed to overcome the resistance of the respiratory system.
- PEEP is the pressure generating the baseline static stretch of the lung fibers.

If we now multiply the total pressures present in the respiratory system by the changes in lung volume and rate, we can obtain a power equation as described by Gattinoni et al.[8]

$$\text{Power}_{rs} = 0.098 \times RR \times \left\{ \Delta V^2 \times \left[\frac{1}{2} \times E_{rs} + RR \times \frac{(1+I:E)}{60 \times I:E} \times R_{aw} \right] + \Delta V \times PEEP \right\}$$

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In this power equation 0.098 is the conversion factor for units, RR is the ventilatory rate, E_{rs} is the elastance of the respiratory system, I:E is the ratio between inspiratory and expiratory time, R_{aw} is the airway resistance, and ΔV is the tidal volume. Thus, for a normal patient on a ventilator, breathing at 15/min, with a tidal volume of 500 mL with an I:E ratio of 1:1, a normal respiratory system elastance of 10 cm H_2O/L and raw of 10 cm H_2O/L/S and at 0 PEEP, the mechanical power in J/min equals 3.675.

Physical and Biological Basis of Ergotrauma

If the power generated during ventilation is excessive, then the chemical bonds of the polymers, which make up the extracellular matrix, will be disrupted. There can be a range of insults to the extracellular matrix ranging from an excessive deformation to microfractures to frank stress fractures. The quantum of energy required to cause this is unclear at present; however, a few molecules may lose their covalent bonds during each respiratory cycle. However, the rate of repair is usually greater than the rate of injury due to power applied during ventilation. VILI manifests when the rate of repair lags the rate of fractures.

The physical distortion of the extracellular matrix, the microfractures, and stress fractures also lead to an inflammatory reaction. Cytokine production originating from the distorted epithelial cells leads to a cascade of reaction, leading to the typical consequences of increased vascular permeability, activation of coagulation, and recruitment of inflammatory cells.

The main advantages of the theory of ergotrauma and the power equation as described by Gattinoni et al., are that it accounts for all the key variables involved in VILI, including both static and dynamic variables. The power hypothesis gives plausibility to the fact that driving pressure is more contributory than plateau pressures toward VILI.

Despite its ability to explain VILI in a new light, ergotrauma has a few shortcomings. The issue of lung heterogeneity is not readily quantified is one issue. Second is the inclusion of flow, which acts at the airway and how it dissipates to the alveoli is not clear. The third issue is whether PEEP should be used in this calculation of power. The role of PEEP in tissue injury is controversial.

CONCLUSION

Ergotrauma/mechanical power is a composite concept that can explain the concept of VILI. It includes all the static and dynamic parameters which may be involved in the genesis of VILI. It is not very far in the future that ventilator software would incorporate power measurement and we would be tailoring the ventilator support to adjust power to prevent VILI.

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Current Concepts in Critical Care 2022

This book has been brought to you by the ISCCM Hyderabad branch. This first edition, launched during our signature event—CRITIC 2022, provides a comprehensive overview of the latest developments and advancements in critical care medicine. From the latest research and guidelines in sepsis management to the newest technologies in mechanical ventilation, this book has covered a wide range of topics that are essential for critical care practitioners. The book has been laid out in a lucid form, and the chapters have been contributed by critical care fraternity across the country.

We hope that the book serves as a valuable resource for critical care professionals and helps to improve the quality of care for critically ill patients. We also hope that it inspires further research and innovation in the field of critical care medicine. As the field of critical care medicine continues to evolve, we look forward to updating this book with new information and developments. We also look forward to continuing to serve as a trusted resource for the critical care community.

ISCCM Hyderabad is well known for its academic activities and been awarded the best branch of ISCCM across the country thrice in a row. It also has a presence on various social media platforms such as Facebook and YouTube, where members can find information about the chapter's activities, videos of lectures, presentations and upcoming events, updates and news related to critical care medicine and provide resources and educational materials for members.

Thank you for reading the ISCCM Hyderabad Current Concepts in Critical Care 2022.

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