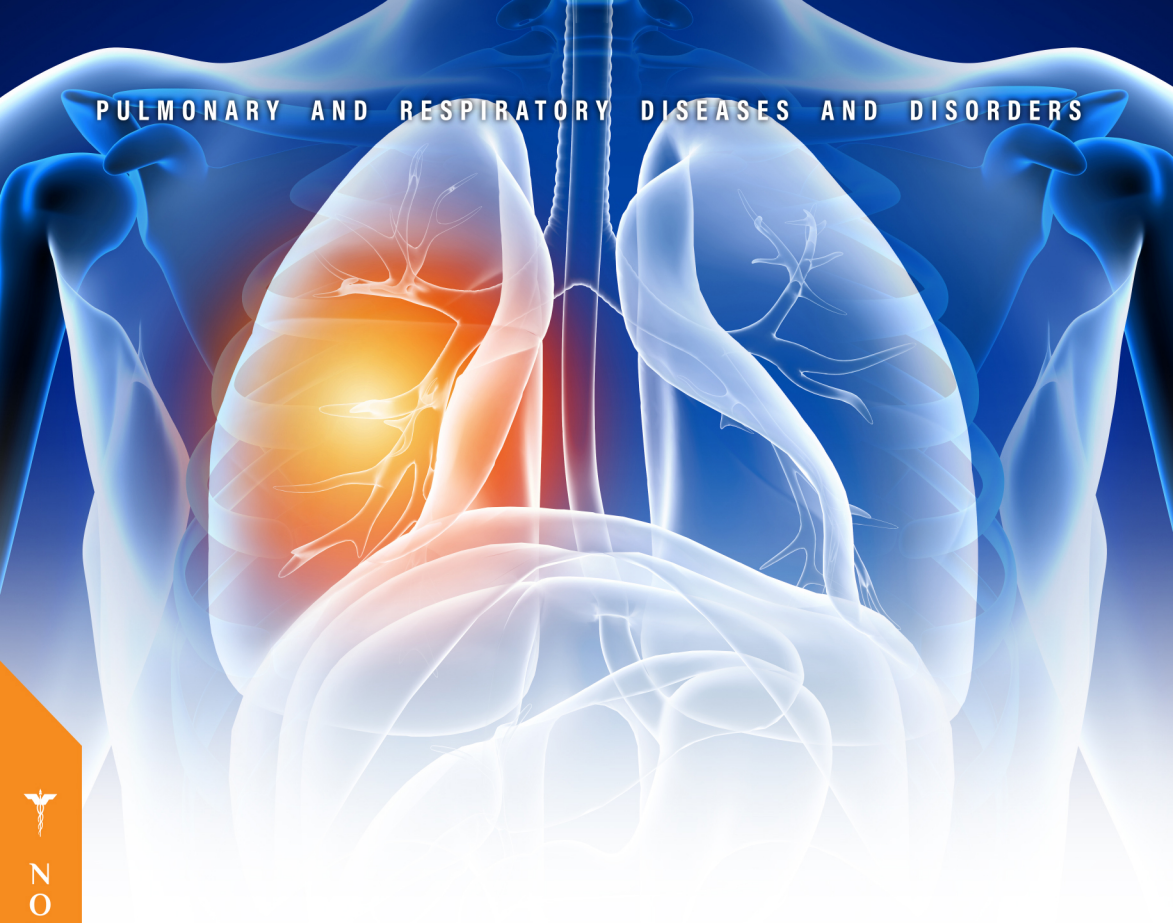

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VENTILATOR INDUCED LUNG INJURY IN NON-INVASIVE VENTILATORY SUPPORT

Pathophysiology, Treatment and Prevention

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To our patients, our major motivation.

To my wife and daughters.

Contents

Preface

Over the last two decades, it has been demonstrated that the use of non-invasive mechanical ventilation systems, in their various non-invasive, positive or negative options, as well as nasal high-flow, has proven to be very useful in various clinical indications. However, one essential aspect of all medical treatment is to determine how non-invasive ventilatory support can be a determinant of ventilatory-induced lung injury. While this concept and observation classically comes from experimental and clinical observations in patients with invasive mechanical ventilation and acute respiratory distress syndrome, there are observations and possible mechanisms that can be observed when applying non-invasive ventilatory support options. This book analyses the pathophysiology mechanisms that relate to this process commonly referred to as patient self-inflicted lung injury.

The book is structured on the description of these mechanisms (atelectrauma, barotrauma, biotrauma, volutrauma and atelectrauma, hyperoxemia, etc.), lung mechanics and inflammatory response, description of dyspnea in spontaneous acute lung injury, and pathophysiology.

An analysis of the time course of ventilator-induced lung injury in patients with non-invasive ventilation is performed, based on an analysis of summary animal studies and clinical implications. Lastly, this book provides recommendations on diagnosis and prevention based on an analysis of the monitoring of pressure/volume curves and flow waveforms.

We consider that an exhaustive knowledge of the pathophysiology is essential during all the options of non-invasive ventilatory support, interpretation of the concept of a patient self-induced lung injury in the most common scenarios of use and open to future editions the new forms of diagnosis and prevention of these situations.

One cannot consider such a commonly used technique without knowing the pathophysiology of those determinants that can limit a successful application of the technique.

"There will be no excellence in your treatment…
if we do not know the essence of its mechanism."

Antonio M. Esquinas MD, PhD,
Murcia, Spain,
November 3, 2022

Chapter 1

Epidemiology

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Abstract

Ventilator-induced lung injury is the acute lung injury inflicted or aggravated by positive-pressure ventilation during treatment, occurring both in invasive as well as non-invasive ventilation.

Four main mechanisms of VILI will be described: alveolar inspiratory and/or expiratory stress inducing overdistension (volutrauma), interfaces between collapsed or edema-filled alveoli and surrounding open alveoli, acting as stress raisers (barotrauma), alveoli that continuously open and close with tidal breathing (atelectotrauma), and systemic inflammatory response (biotrauma).

Mechanical ventilation potentially injures both normal and diseased lungs; however, the injury is much more severe in the latter. It is important to be able to recognize VILI to prevent the progression of lung damage.

Keywords: ventilator-induced lung injury, non-invasive ventilation, respiratory insufficiency

Introduction

The emergence of positive-pressure ventilation dates back to the 1950s polio outbreak [1]. The experience obtained from this epidemic became the

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foundation of critical care practice. Over more than 7 decades, positive-pressure ventilation devices have significantly evolved in both pediatric and adult patients and can now be delivered without intubation, referred to as non-invasive ventilation (NIV) [2]. There is currently robust evidence documenting its efficacy in altering outcomes in chronic obstructive pulmonary disease, cardiogenic pulmonary edema, acute respiratory failure in COVID-19 patients, and acute respiratory failure in immunocompromised patients [3]. However, despite being a beneficial intervention, positive-pressure ventilation must be carefully titrated since it may be associated with lung damage and lead to ventilator-induced lung injury (VILI) [4].

VILI is the acute lung injury inflicted or aggravated by positive-pressure ventilation during treatment [5]. It can occur during invasive as well as NIV and proven to contribute to mortality in patients with acute respiratory distress syndrome (ARDS) and might contribute significantly to the morbidity and mortality of other critically ill patients [6]. Though mechanical ventilation potentially injures both normal and diseased lungs, the injury will be much more severe in the latter due to higher microscale stresses [5]. Despite being used interchangeably, the term 'ventilator-associated lung injury' (VALI) refers to the presence of lung injury during mechanical ventilation when a causal link is not ascertained [7].

The notion of injury by mechanical ventilation was first described in the mid-18th century by John Fothergill [8, 9]. He postulated that mouth-to-mouth ventilation might be a better option than machine bellows in resuscitation since "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" [8]. During the 1952 polio epidemic, structural lung damages caused by mechanical ventilation were documented [10]. Thereafter, in 1967, the term "respirator lung" used to describe the postmortem lung injury on autopsy of patients exposed to positive-pressure ventilation and whose lungs showed extensive alveolar infiltrates and hyaline membrane formation [5]. Over the past decades, evidence on VILI mechanisms and etiology has evolved, which contributed to new lines of investigation towards personalizing lung-protective strategies [11].

Classically, four mechanisms of VILI have described, which include: alveolar inspiratory and/or expiratory stress inducing overdistension (volutrauma), interfaces between collapsed or edema-filled alveoli and surrounding open alveoli, acting as stress raisers (barotrauma), alveoli that continuously open and close with tidal breathing (atelectotrauma), and

systemic inflammatory response (biotrauma) [7,12-16]. Other mechanisms, which are currently studies, may include heterogeneous local lung mechanics, alveolar stress frequency, and stress failure of pulmonary capillaries [4]. Furthermore, variation in the expression of genetically determined inflammatory mediators has shown to affect VILI susceptibility [17]. It is important to be able to recognize and manage VILI to improve gas exchange and prevent the progression of lung damage, especially in the presence of significant lung disease.

The incidence of VILI is still unclear, both in adult and pediatric patients. However, in the adult population, this injury expected to be more frequent in ARDS patients receiving mechanical ventilation [5,18]. When the lungs injured, mechanical ventilation will further damage them, in the absence of lung-protective strategies [5]. A study conducted on 332 mechanically ventilated patients without acute lung injury at the beginning of ventilation found the development of VILI in 24% of patients within the first five days [19].

Conclusion

Barotrauma has been employed in studies as a surrogate measure of VALI, because it has a specific radiologic and clinical definition. However, its relationship to the microstructural lesions of VALI is unknown [19]. The incidence of barotrauma in patients with ARDS has decreased markedly in recent years due to changes in the approach to mechanical ventilation, with reduction of tidal volume and the use of lower plateau pressures. Prospective ARDS studies report an incidence of barotrauma ranging from 5-10% (in meta-analyses) and from 5-6% (in clinical trials) [20-22]. No geographic influences are known to affect the incidence of barotrauma. Age, sex, or ethnicity not expected to influence barotrauma. However, it is known that lung compliance tends to decrease with age, which may play a role in the risk for barotrauma in older patients [23].

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Chapter 2

Dyspnea in Spontaneous Acute Lung Injury: Pathophysiology

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Abstract

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent spectrums of a complex process of progressive respiratory failure, leading to low alveolar ventilation/perfusion ratios (VA/Q), and abnormal shunting of O_2, loss of control of vascular ton, and right ventricular failure. Clinically it may present with dyspnea, a subjective awareness of the sensation of uncomfortable breathing, that results from a mismatch between afferent receptors and central respiratory motor activity and a dissociation between pulmonary ventilation and respiratory drive. Multiple factors in lung ventilation influence the appearance and intensity dyspnea, through activation of mechanoreceptors int the lung, airways and chest wall and chemoreceptors in the carotid bodies and through exaggerated ventilatory response.

Keywords: acute respiratory distress syndrome, acute lung injury, dyspnea, hypoxemia, ventilation-perfusion mismatch

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent spectrums of a complex process of progressive respiratory failure,

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characterized by rapid onset, diffuse, bilateral alveolar damage, capillary leakage and protein rich pulmonary oedema leading to low alveolar ventilation/perfusion ratios (VA/Q), and abnormal shunting of O_2. Clinically it is characterized by dyspnea, tachypnea and cyanosis refractory to oxygen therapy, and on chest X-ray it shows diffuse alveolar infiltrates with non-cardiogenic pulmonary edema. ALI can be caused by multiple mechanisms, including pulmonary and extra-pulmonary illness. The most frequent causes are pulmonary-specific: pneumonia, aspiration, pulmonary embolism, chest trauma or inhaled noxious gases. Systemic conditions include sepsis, burns, massive transfusions, pancreatitis and hemorrhagic shock [1, 2].

Clinical Definition of ALI/ARDS

Since its first description by Ashbaugh *et al*. [3] in 1967, the definition of ALI/ARDS has undergone several changes. The updated and revised Berlin definition for ALI/ARDS [4] is an approach of combining consensus discussions with empirical evaluation in order to standardize and validate this syndrome, recognized as a major clinical problem worldwide. Table 1 shows Berlin criteria for acute respiratory distress syndrome.

Table 1. Berlin criteria for acute respiratory distress syndrome

Onset	Within 1 week of a known clinical insult or new or worsening respiratory symptoms.
Oxygenation	Mild ARDS: $PaO_2/FiO_2 > 200mmHg \leq 300mmHg$. Moderate ARDS: $PaO_2/FiO_2 > 100mmHg \leq 200mmHg$. Severe ARDS $PaO_2/FiO_2 \leq 100mmHg$.
PEEP	Minimum $5cmH_20$ PEEP by invasive mechanical ventilation or noninvasive ventilation.
Chest imaging	Bilateral opacities not fully explained by effusions, lung collapse or nodules on chest X-ray or CT.
Origin of oedema	Respiratoy failure not fully explained by cardiac failure of fluid overload (echocardiography excluding hydrostatic oedema if no risk factor present).

Abbreviations: PEEP: positive end-expiratory pressure; PaO_2: arterial oxygen tension; FiO_2: inspiratory oxygen fraction; CT: computed tomography.

Pathophysiology of ALI/ARDS

Acute lung injury processes through several phases after an injury. The acute, exudative phase (up to 7 days) is characterized by rapid onset of respiratory dysfunction. In this phase there is activation of alveolar macrophages, neutrophils, platelets, and epithelial cells, which secrete inflammatory mediators and cells, leading to increased vascular permeability through destruction of epithelial-endothelial barrier and leak of protein-rich fluid and blood cells into the interstitium and alveoli. These changes result in damage of surfactant-producing alveolar type II cells with surfactant loss, formation of hyaline membranes, alveolar atelectasis and hemorrhage, pulmonary oedema, and decreased lung compliance [5, 6]. Alveolar vascular damage also leads to altered vasomotor tone (vasoconstriction and vasodilation) and formation of microthrombi. This results in pulmonary hypertension with increasing right ventricular afterload and ventricular dysfunction. Combined endothelial and epithelial damage ends up with worsening ventilation-perfusion mismatch, loss of hypoxic pulmonary vasoconstriction and refractory hypoxia [7, 8].

The proliferative phase takes two to three weeks and initiates the repair process of the lung. Anti-inflammatory cytokines and cells deactivate neutrophils and macrophages; type II alveolar cells proliferate and establish the epithelial lining and surfactant production.

The excess fluid in the alveoli and interstitium is drawn by re-expressed alveolar ion channels and aquaporins and the endothelial cells reestablish vascular integrity [6, 7].

The fibrotic phase, only occur in some patients with ongoing inflammation and persistent endothelial and epithelial damage and is associated with increased morbidity and mortality [7].

Clinical Presentation in ALI/ARDS

In ALI/ARDS most patients follow similar clinical courses. Patients typically present with dyspnea, hypoxemia and cyanosis. On examination patients may have tachypnea, tachycardia, diffuse crackles over the chest, increased work of breathing, and use of accessory respiratory muscles. Laboratory changes are nonspecific and include leukocytosis, evidence of disseminated intravascular coagulation, and lactic acidosis. Blood gases may show severe

hypoxemia, decreased PaO2/FiO2, and acute respiratory acidosis. On the chest X-ray, interstitial pulmonary oedema with bilateral diffuse infiltrates may be identified [8].

Dyspnea in ALI/ARDS

Dyspnea, also known as shortness of breath, is a subjective awareness of the sensation of uncomfortable breathing. Dyspnea begins with a physiological impairment (either respiratory, cardiovascular or metabolic derangements) that stimulates pulmonary and extrapulmonary afferent receptors, which are responsible for the transmission of the information to the cerebral cortex, where the sensation of discomfort (increased respiratory work/effort, tightness, or air hunger) is perceived.

The mismatch between afferent receptors and central respiratory motor activity leads to a dissociation between pulmonary ventilation and respiratory drive [9].

Several afferent pathways are responsible for the perception of breathlessness: Atelectasis and pulmonary oedema activates juxta capillary receptors; bronchoconstriction signal stretch receptors in the lung; and the tension on respiratory muscles activates muscle spindles in the chest wall; the metabolic derangements stimulate the chemoreceptors in the carotid bodies and medulla, which stimulate breathing by changing the sensitivity of central chemoreceptors.

The efferent signals are the motor neuronal signals that send information to the respiratory muscles [9, 10].

Dyspnea occurs when there is an increase above usual levels of afferent information from the peripheral sensors and the central neural output does not produce the expected result of motor commands to the ventilatory muscles (airflow or ventilation).

The extent of the mismatch of this information determines the intensity of dyspnea. The sensory cortex is simultaneously activated when motor signals are sent to the chest wall, resulting in the conscious sensation of muscular effort and breathlessness [10, 11].

In ALI/ARDS several changes in lung ventilation influence the appearance of dyspnea:

1) *VA/Q mismatch and physiological shunting*: In ARDS, atelectasis, pulmonary oedema, and air space consolidation, results in increased

dead space and shunt, where a lung unit is not ventilated and perfusion is preserved. In severe cases of ARDS, the shunt area may exced 50% of the lung, leading to severe hypoxemia. Also the diffusion between capillaries and alveoli may be affected: the fluid in the lungs increases the effective thickness of the alveolar wall and decreases the area of gas exchange, resulting in perfusion without ventilation and shunting, leading to hypoxemia and hypercapnia [12].

2) *Decreased lung compliance*: The alveolar epithelium destruction and alveolar flooding leads to surfactant loss, increased surface tension and alveolar atelectasis during end-expiration, which fail to expand during inspiration due to high alveolar opening pressures. This results in decreased lung compliance, which, in turn, originates rapid, shallow breathing, and reduced functional residual capacity, aggravating dyspnea [13].
3) *Pulmonary hypertension and right ventricular failure*: Activation of pulmonary microvascular endothelium leads to imbalance between vasodilating and vasoconstricting mediators and a shift to a prothrombotic phenotype. It results in capillary and larger pulmonary arteries, veins, and lymphatics occlusion due to thromboemboli and fibrinous obliteration. A loss of control of vascular tone, with an excess of pulmonary vasoconstrictor over vasodilator substances increases vascular tone, leading to acute rises in pulmonary vascular resistance, and later, to vascular remodeling, with increased thickness of the pulmonary arterial smooth muscle layer, and neomuscularization of previously non muscularized vessels. These pathological factors contribute to VA/Q mismatch and right ventricular dysfunction. This also result in hypoxemia, which stimulates chemoreceptors in the carotid bodies and medulla [13].

These conditions together will activate the mechanoreceptors in the lungs, airways and chest wall and the chemoreceptors in the carotid bodies and medullae.

However, the response to this afferent information may be compromised due to exaggerated ventilatory response in the brain (secondary to systemic inflammation and organ dysfunction, acidosis and shock) and to increased respiratory load and muscle weakness. The consequence is a rapid shallow breathing with increased respiratory rate but decreased tidal volume. This mismatch of information and deranged response determines the emergence and intensity of dyspnea [14].

Treatment of Dyspnea

Opioids have been the most widely studied drug in the treatment of dyspnea in patients with a variety of conditions. However, evidence of long-term efficacy is limited and conflicting. In addition, opioids are associated with several adverse effects [9]. The treatment of dyspnea involves treating the underlying pathology. In the case of ARDS, it will include oxygen therapy, non-invasive ventilation, or even invasive mechanical ventilation in the more severe cases, antibiotic therapy, corticosteroid therapy and sedation when necessary, and other treatments aimed at the initial insult that triggered the ARDS.

Conclusion

Acute lung injury and acute respiratory distress syndrome represent two spectrums of a complex process of progressive respiratory failure, and it is a major clinical problem worldwide. It is characterized by rapid onset, diffuse, bilateral alveolar damage, capillary leakage and protein rich pulmonary oedema. Acute lung injury processes through several phases after an injury: the exudative phase, the proliferative phase and the fibrotic phase where there is activation of multiple inflammatory mediators and cells leading to alveolar damage and atelectasis, pulmonary oedema, altered vasomotor tone, decreased lung compliance formation of microthrombi and right ventricular dysfunction and ultimately leading to severe respiratory dysfunction.

Dyspnea, also known as shortness of breath, is a subjective awareness of the sensation of uncomfortable breathing and is a common symptom in ARDS. It occurs when there is an increase above usual levels of afferent information from the peripheral sensors and the central neural output does not produce the expected result of motor commands to the ventilatory muscles (airflow or ventilation). The extent of the mismatch of this information determines the intensity of dyspnea.

Multiple factors in ARDS influence the appearance of dyspnea: VA/Q mismatch and physiological shunting, impaired diffusion, decreased lung compliance, microthrombi formation, pulmonary hypertension and right ventricular failure, and the exaggerated ventilatory response in the brain due to systemic inflammation, organ dysfunction, acidosis and shock. The treatment of dyspnea involves treating the underlying pathology. In the case