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Advances in the Study of Patient Self-inflicted Lung Injury

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Abstract: Patient self-inflicted lung injury (P-SILI) is caused by excessive expansion of the lungs caused by excessive spontaneous breathing and the shear force caused by repeated alveolar atrophy and re-dilation in the gravity-dependent area. There are some benefits of keeping spontaneous breathing in patients with acute respiratory distress syndrome: 1. Reduce the need for sedation; 2. Exercise diaphragm function; 3. Improve the cardiopulmonary function of the patient. However, if the respiratory drive is too high, even with ventilator support, the patient will develop self-induced lung injury. In this review, the current pathophysiology of P-SILI and the indicators of monitoring respiratory drive and measures to reduce respiratory drive are systematically reviewed.

Keywords: Patient Self-inflicted Lung Injury; Respiratory Drive; Airway Occlusion Pressure At 100 Ms; Airway Occlusion Pressure; Prone Position Ventilation.

1. Introduction

Respiratory drive, for which there is no precise definition, is usually thought of as the strength of the impulse emitted by the respiratory center, using the amplitude of the physiological signal as a measure of strength. Respiratory drive determines the strength of the mechanical output of the respiratory muscles (the respiratory effort), but the activity of the respiratory center cannot be measured directly, and so it is measured indirectly by the indicators of the respiratory muscle that performs the respiratory motor output. Jonkma, in his study proposed a definition of respiratory drive: the time integral (the product of signal strength and time) of the output of a network of neurons in the respiratory center obtained by estimating the strength of respiratory effort. Thus, a high respiratory drive may imply that the output of the respiratory center has a higher amplitude, a higher frequency, or both [1].

As research has progressed, it has been noted that sustained vigorous voluntary respiration may be detrimental in the setting of severe lung injury. Changes in transpulmonary pressure have been recognized as a key injury factor in "ventilator-induced lung injury" (VILI) [2]. Transpulmonary pressure is the difference between airway pressure and intrathoracic pressure, generated by the mechanical effort (tensile pressure) acting on the lungs. Patients in the presence of voluntary respiratory effort have an intrathoracic pressure that becomes negative during inspiration, and therefore may bring about a higher transpulmonary pressure compared to those patients who are not breathing spontaneously. As the transpulmonary pressure rises, the tidal volume also rises, leading to further lung injury.

During positive pressure-assisted ventilation, excessive voluntary breathing can cause elevated transpulmonary pressures, increased regional stresses, and overall lung strain can lead to patient-induced lung injury. However, there are no standardized diagnostic criteria or biological markers for self-induced lung injury, so early recognition is very difficult. There is no method to measure the activity of the patient's respiratory center, which can only be quantified by physiological or pathological findings of the patient's breathing. Clinicians should be aware that respiratory-driven monitoring and interventions are very important. In this narrative review, we summarize the pathophysiology of respiratory drive, the indicators of its monitoring, and its control measures. The knowledge provided in this article may help clinicians to early recognize patients at risk for self-induced lung injury and to effectively monitor and apply interventions to prevent the development of irreversible lung injury.

2. Pathophysiology of Self-induced Lung Injury

The pathophysiology of self-induced lung injury is quite complex, involving respiratory neural drive, respiratory muscles, lung physiology, and respiratory mechanics related. From a physiological point of view, three different factors determine the respiratory mechanism: (i) respiratory drive (neural output of the respiratory muscles), (ii) respiratory effort (activity of the respiratory muscles), and (iii) respiratory pattern (respiratory mechanics). Due to the impairment of gas exchange and respiratory mechanics, patients with lung injury usually have higher respiratory drive, and the higher respiratory drive leads to intense inspiratory effort through neuromuscular transmission, which may result in the formation of physiological mechanisms such as lung overdistension, swing respiration, and increase in the pressure difference across the walls of the pulmonary vasculature to exacerbate the lung injury, and the exacerbated lung injury further exacerbates the inspiratory effort through the impairment of gas exchange and respiratory mechanics to create a vicious circle.

2.1. Respiratory Drive

Respiratory drive is defined as the strength of the central

nervous output of respiration, which determines the strength of the respiratory muscles. Respiratory drive is determined by signals from central chemoreceptors, peripheral chemoreceptors, tract receptors in the chest wall and lung tissue, stimulus receptors in the airway epithelium, and cortical and emotional feedback. In pathological states, the respiratory neural-tissue system plays an important role in generating positive feedback, and hypoxemia, hypercarbia and inflammation, and vagal activation further increase respiratory drive [3].

2.2. Inappropriate

lung stress and strain. Stress is the pressure that expands the lungs and chest wall. Numerically, the stress applied to the lung parenchyma is represented by the transpulmonary pressure (PL). Strain is the change in lung volume where the pressure (i.e., tidal volume) exerted on the lung tissue is higher than the end-expiratory lung volume. Both inappropriate stress and strain are associated with the development of VILI and P-SILI. In an injured lung with reduced compliance, higher transpulmonary pressures and work of breathing are required to provide appropriate tidal volumes and ventilation per minute. In addition, the distribution of stresses and strains becomes significantly inhomogeneous under pathological conditions, leading to further detrimental regional amplification of stresses and strains between regions with different mechanical properties [4].

2.3. Oscillatory

breathing. Oscillatory breathing is characterized by redistribution of tidal volume from non-gravity-dependent lung regions to gravity-dependent lung regions due to higher negative pressure in the dependent lung regions. In addition, in patients with greater expiratory effort, de-repression of the dependent lung regions during expiration may increase the subsequent respiratory oscillation during inspiration. Air transfer within the lung tissue results in significant localized hyperexpansion of the dependent regions. Oscillatory breathing increases work of breathing regardless of tidal volume and its frequency and amplitude correlate with increased blood concentrations of inflammatory biomarkers [5].

2.4. Pulmonary Edema

Vigorous inspiratory effort and excessive negative intrathoracic pressure result in increased venous return. This is followed by an increase in left ventricular end-diastolic pressure and pulmonary capillary pressure and an increase in transcapillary pressure. In acute lung injury, capillary permeability increases due to endothelial cell layer dysfunction. Both elevated transcapillary pressure and increased capillary permeability further exacerbate fluid leakage from the pulmonary capillaries into the interstitium [6]. Pulmonary edema in turn increases dyspnea [1], creating a vicious cycle leading to further lung injury.

2.5. Diaphragm Injury

Diaphragmatic atrophy due to prolonged withdrawal of controlled mode mechanical ventilation is thought to be the primary mechanism of ventilatory diaphragmatic injury (VIDI). However, in patients with high respiratory effort excessive contraction of the respiratory muscle fibers causes centripetal loading, and consequent lung injury may also contribute to VIDI. Since diaphragm activity and function are the main factors influencing changes in lung volumes and pressures during spontaneous respiration, avoidance of under- and/or over-exertion of respiratory effort has become the cornerstone of the so-called lung- and diaphragm-protective ventilation strategy[7].

2.6. Person-ventilator Desynchronization During Mechanical Ventilation

refers to a mismatch between the respiratory parameters delivered by the ventilator and the patient's respiratory drive and respiratory force. Person-ventilator dyssynchrony is of clinical significance because the amount and intensity of patient-ventilator dyssynchrony is associated with poor prognostic parameters [8], such as increased mortality or prolonged ventilation due to slower deconditioning[9].

3. Monitoring of Respiratory Drive

It is important to monitor the patient's inspiratory effort during assisted ventilation. It can guide the level of respiratory support and sedation while also helping to predict failure or success of extubation. Insufficient or excessive inspiratory effort is associated with diaphragmatic atrophy or dysfunction. In the presence of hemodynamic abnormalities, the effort made by the inspiratory muscles may be a significant source of oxygen consumption and needs should be reduced by sedation and/or muscle relaxation. Respiratory drive can be assessed in many ways in the clinic by observing the symptoms of respiratory distress, which are all suggestive of increased respiratory drive when the patient exhibits dyspnea, frequent respirations, mobilization of assisted respiratory muscles, and paradoxical chest and abdominal movements. Respiratory drive can also be assessed by measuring some respiratory physiologic indexes such as P0.1, ΔPocc, Edi, etc. They are described in detail below.

3.1. Airway Closure Pressure (P0.1)

is the airway pressure measured within 100ms after blocking the airway in the functional residual airway position. Under the premise of normal respiratory muscle movement, it can reflect the central drive of the patient's voluntary respiration. P0.1, as a commonly used monitoring parameter of mechanical ventilation, can be monitored on top of most of the ventilators in the clinic. In the clinic, after adjusting the trigger sensitivity of the ventilator to pressure trigger and without basic airflow, the ventilator can monitor the value of P0.1 under the premise of the patient's voluntary breathing. In addition to focusing on the size of the value, a more important clinical point is that P0.1 reflects changes in the patient's respiratory center drive and changes in the patient's respiratory work, and its trend may be more conducive to judging the patient's condition. The actual value of P0.1 is negative, but it is customary to use a positive pressure to express. The normal adult reference value of P0.1 is 2-4 cmH20. If P0.1 is lower than normal, it often suggests that the respiratory drive of the respiratory center is reduced, which will easily lead to insufficient ventilation and hypercapnia or hypoxia, and then it is necessary to adjust the depth of sedation or actively deal with the primary factors; if P0.1 is higher than normal, it often suggests that the central respiratory drive is too high, which will make the respiratory system in a high state of stress, and the effective work of the respiratory muscles cannot last. The effective work of

respiratory muscles cannot be sustained. Therefore, adjusting the level of support pressure according to the dynamic monitoring of the change of P0.1 during the withdrawal process is one of the indicators for predicting successful withdrawal. Moreover, the increase of respiratory effort due to excessive respiratory drive will increase the risk of lung injury in patients, while actively dealing with the primary factors causing high respiratory drive, we need to strengthen sedation and muscle relaxation to reduce respiratory drive and reduce the risk of lung injury, if necessary.2022 The study of Irene Telias once again confirmed a good correlation between P0.1 and inspiratory effort of patients[10].

3.2. Airway Block Pressure (ΔPocc)

refers to end-expiratory block measurement maneuver where each block is maintained for a single inspiratory cycle, and the maximum value of the pressure at which the airway pressure falls from the level of PEEP is ΔPocc. Bertoni et al. recently described this new technique for estimating inspiratory Pmus in 2019. For Δpocc can be used to assess Pmus and dynamic transpulmonary driving pressure (ΔPL, dyn), an indicator of the dynamic mechanical stress applied to the lungs during inspiration. Pmus and ΔPes can be estimated from Pocc by those validated correction factors that adjust for differences in chest wall elasticity and chest wall kinematics between obstructive and non-obstructive conditions. ΔPL, dyn can be obtained by subtracting ΔPes from positive airway pressure fluctuations during assisted breathing. it is worth noting that ΔPL, dyn may reflect peaks in localized lung stresses better than the quasi-static trans-lung drive pressure [11]. Although optimal values for these parameters have not been determined, an estimated Pmus >15 cm H2O and an estimated ΔPL, dyn >20 cm H2O suggest that respiratory effort and dynamic lung stress may be excessive, respectively [12].

3.3. Transesophageal Pressure

When it comes to monitoring inspiratory effort, the gold standard is invasive methods, esophageal pressure is now used as a criterion for evaluating our other noninvasive methods, and of course diaphragm electromyography can be used, and transseptal pressure can also be evaluated, but all these methods require special consumables, and the widespread use of special information-gathering instruments in the clinic has not yet been popularized, except in the study of respiratory mechanics in the application of these instruments. In patients with spontaneous respiratory activity, the inspiratory force exerted by the respiratory muscles is an important physiologic mechanism contributing to the development of P-SILI. Esophageal pressure monitoring is considered to be the clinical gold standard for measuring the pressure generated by the respiratory muscles (i.e., respiratory muscle pressure, Pmus.) Changes in Pes (fluctuations in esophageal pressure); ΔPes reflect changes in pleural pressure, and the difference between the airway pressure (Paw) and Pes represents the transpulmonary driving pressure [13]. However, routine bedside Pes monitoring is limited by its invasiveness (esophageal balloon manometry) and potential confounding factors (misplaced probe, technical complications, risk of esophageal pressure sores, etc.).

3.4. Flow Rate Index

A novel noninvasive method to estimate inspiratory force by analyzing the flow-time curve in patients on pressure-support ventilation (PSV). In these patients, the depression in the inspiratory flow-time waveform recorded during pressure-support ventilation reflects inspiratory force because the pressure difference caused by exertion between the airway opening and the alveoli determines the strength of inspiratory flow. The flow index can be calculated with relatively simple software. In small sample clinical trials, the calculation of inspiratory force by flow index is consistent with methods based on esophageal pressure[13].

3.5. Electrical Activity of the Diaphragm (EAdi)

is the ability to continuously monitor diaphragmatic electrical activity using a special catheter with EMG leads. As early as 1978 researchers demonstrated that diaphragmatic electrical activity is more practical compared to trans-diaphragmatic pressure and surface electromyography [14]. The electrical activity of the diaphragm reflects the respiratory drive output (excitation of the diaphragm by the central nervous system) rather than the generation of diaphragmatic force (effort). In healthy individuals in the calm breathing state, EAdi fluctuates between 5 and 30 μV. Due to the high variability of EAdi, it is difficult to specify the value of the target EAdi during mechanical ventilation.EAdi is able to be used to estimate the magnitude of the Pmus at different levels of ventilatory support [15]. Considering that electrical activity and pressure-generated coupling remain constant over time (neuro-mechanical coupling measured by expiratory block = Pmus/EAdi), EAdi can be used to assess Pmus under normal respiratory cycles with each breath.

3.6. Bedside Diaphragm Ultrasound Diaphragm Ultrasound

can be used to assess patient-ventilator interactions with quantitative measurements of diaphragm thickening fraction (TFdi). It can be calculated in M-ultrasound mode as the percentage inspiratory increase in diaphragm thickness relative to end-expiratory thickness during tidal breathing [TFdi = (end-inspiratory thickness - end-expiratory thickness)/end-expiratory thickness × 100%]. The optimal TFdi range is 15-30%. Therefore, if the value is less than 15%, overassistance should be a concern; values greater than 40% indicate underassistance.

4. Measures to Control Respiratory Drive

4.1. Appropriate Sedation

Sedation reduces respiratory drive and may protect lung tissue from further deterioration of P-SILI. However, prolonged sedation is accompanied by an increased risk of ventilator-associated pneumonia, muscle weakness (including diaphragm), and delirium. During the COVID-19 pandemic, high-dose intravenous sedatives and opioids were reported to achieve sedation and suppress patient-ventilator dyssynchrony [16]. The aim of individualized sedation is to maintain person-machine synchronization and to keep the patient's respiratory drive at a safe level while allowing for the presence of spontaneous respiration, an approach known as "lung-protective sedation" [17]. Inhaled sedation allows mechanically ventilated patients to maintain voluntary breathing during deep sedation, and a meta-analysis by Landoni et al. found that the need for intravenous sedation

and opioids was reduced when inhaled sedation was used. In addition to sedation, inhalational anesthetics have the effect of causing bronchodilation, reducing inflammation, improving gas exchange and promoting arousal [18].

4.2. Partial Neuromuscular Blockade

is a pharmacologic strategy for the treatment of high tidal volume and negative pressure fluctuations caused by excessive respiratory effort in partially ventilated support patients. This is achieved by applying low doses of neuromuscular blocking agents to maintain diaphragmatic activity and spontaneous ventilation [19].

4.3. Early Protective Mechanical Ventilation.

Despite evidence from experimental and clinical studies that P-SILI is a serious and life-threatening clinical condition, there is no consensus among critical care specialists as to when to intubate hyperventilated patients. In animal studies of artificially induced lung injury, early use of mechanical ventilation ultimately resulted in less lung injury than if they were allowed to exert themselves on spontaneous ventilation, and self-induced lung injury could be prevented if mechanical ventilation was applied early but did not attenuate such effects if applied later. Therefore, some authors have advocated that mechanical ventilation with lung-protective parameters may be considered a protective therapy to minimize P-SILI in the setting of high respiratory drive and strenuous respiratory effort. Currently, clinical trial data are insufficient to provide evidence-based recommendations and guidelines for autonomic ventilation strategies in mechanically ventilated subjects in the acute phase of ARDS. According to the expert panel, pressure-mode ventilation that allows for autonomous ventilation may be used when ensuring that the tidal volume produced is close to 6 mL/kg (predicted body weight) and does not exceed 8 mL/kg PBW [20].

4.4. Awake Prone Position.

The effect of early prolonged prone positioning was evaluated in 81 awake patients with acute COVID-19-related respiratory failure requiring noninvasive ventilatory support. Prone positioning was associated with a lower incidence of NIV failure (defined as requiring intubation) and mortality. In addition, physiologic effects from prone positioning were observed - significant improvements in lung tissue ventilation (defined by lung ultrasound scores), paO2/FiO2, respiratory rate, and plasma levels of inflammatory biomarkers were observed in patients receiving prone positioning [21]. These effects of the prone position strongly suggest that the prone position is associated with a reduced risk of self-inflicted lung injury [22]. A recent meta-analysis confirmed the favorable effects of the awake prone position on paO2/FiO2 and respiratory rate in spontaneously breathing patients [23].

4.5. Extracorporeal Membrane Pulmonary Oxygenation (ECMO)

The beneficial effect of ECMO is to promote lung rest and healing, rather than as a form of pulmonary therapy. Extracorporeal oxygenation and carbon dioxide elimination can significantly reduce a patient's respiratory drive, thereby reducing the risk of hyperventilation in spontaneously breathing patients [24, 3].

5. Conclusion

Self-induced lung injury is a serious life-threatening complication in patients with acute respiratory distress syndrome. In the process of over-exertion of voluntary breathing, it can aggravate the originally damaged lung tissues, leading to further aggravation of lung tissue injury. This review summarizes the pathophysiology of P-SILI and the monitoring of respiratory drive and measures to control it. The prevention and treatment of P-SILI is very complex and requires analysis and detailed evaluation of respiratory mechanics and causes of respiratory effort. Currently, with the development of artificial intelligence, it is expected that in the future there will be a ventilator to measure respiratory muscle respiratory effort non-invasively at the touch of a button. Future research should favor mechanical, dynamic biomarkers related to self-induced lung injury, knowledge of underlying mechanobiology and aggravation related to microstructural features of self-induced lung injury.

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