Review Article

Conflicting Strategies in the Management of an ARDS Patient with Airway Leak

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Abstract

Acute Respiratory Distress Syndrome is a complex medical condition which, despite variability in its presentation and clinical manifestations, typically necessitates positive pressure mechanical ventilation in affected patients. Advances in clinical practice have significantly improved patient management and reduced mortality. Nevertheless, complications arising from barotrauma, more specifically airway leak, most notably pneumothorax and pneumomediastinum, continue to pose a serious threat to patient outcomes and represent a significant clinical challenge in intensive care management.

Keywords: acute respiratory distress syndrome; barotrauma; airway leak; pneumothorax; pneumomediastinum

1 Introduction

Acute respiratory distress syndrome (ARDS) is a clinical entity of sudden respiratory insufficiency, mostly characterized by a significant hypoxemia. Although initially described in 1967, its current diagnosis is based on the Berlin Definition established in 2012 and which includes (i) symptom appearance in the timeframe of one week after the initial mechanism of distress or worsening of symptoms, (ii) bilateral opacification of lung on radiographic imaging which are not due to exudation, lymph nodules or pulmonary collapse and (iii) formation of pulmonary oedema which isn't cardiogenic or from volume overload. The Berlin Definition also grades the severity of the clinical representation of ARDS into mild, moderate or severe, on the basis of the ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2), taking into account peak end-expiratory pressure (1).

ARDS is characterized by its etiological diversity alongside its clinical variability. It can be caused by numerous conditions, broadly divided in those of direct lung injury and those of

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indirect lung injury including pneumonia, aspiration or lung trauma as a direct lung injuries, while indirect injuries are associated with systemic conditions such as sepsis, pancreatitis, or hemorrhagic shock (2).

The seriousness of ARDS is emphasized by the fact that it's presented in 10% of intensive Care Unit patients, with 25% of them needing mechanical ventilation (3). Complications associated with ARDS are not uncommon, the more serious among which are airway leak syndromes. Bronchopleural fistulas or alveopleural fistulas, which create a communication between the pulmonary airway and the pleural space are presented as pneumothorax, pneumomediastinum, subcutaneous emphysema, or, in rare cases, as pneumopericardium or pneumoperitoneum. The before mentioned communication significantly complicates mechanical ventilation and increases mortality. Gattinoni et al. demonstrated that ARDS associated with pneumothorax is linked to an increased mortality rate of 66%, compared to 46% in patients without pneumothorax (4). Due to the abrupt deterioration in clinical status and the significant challenges in ongoing management, early recognition of airway integrity disorders is of critical importance.

2 Pathophysiology

The main characteristics of ARDS are the pathohistological changes at the level of the alveolo-capillary membrane. The functionality of the tripartite structure, made up of the epithelium, basal membrane, and endothelium, is responsible for appropriate gas exchange, and ARDS is marked by the disruption of all three components. Type 1 and type 2 pneumocytes, constituents of the alveolar epithelium, are destroyed which directly diminishes surfactant production and enhances the release of tissue factors, both of which contribute to a decrease in pulmonary compliance of the affected pulmonary area (5). Associated injury to the endothelial glycocalyx of pulmonary capillaries further impairs surfactant production (6). The basal membrane is also affected, presenting with thickening and increased distance between alveoli and capillaries on the basis of the inflammatory response, increasing tissue factor release, activation of the coagulation cascade and subsequent fibrin deposition (7). The space becomes filled with fluid which more readily passes from the capillaries due to elevated secretion and circulating levels of angiopoietin-2 (8).

The disruption on capillary level is not limited to the increase in permeability, but also includes the expression of adherence molecules on the capillary surface leading to retention of neutrophils and contributes to the destruction of the endothelial glycocalyx (9,10). All aforementioned processes directly impair gas exchange, and the amount of inflammatory mediators, including interleukin-6 and tumor necrosis factor-alpha, are used to grade and phenotype ARDS. The described changes of the alveocapillary membrane do not affect the whole lung, instead the affected regions are interspersed with areas of healthy lung tissue.

The affected lung areas, due to described fibrin deposits and alveolar oedemas, become significantly more challenging to ventilate, which impacts overall pulmonary ventilation. The resulting compliance disparity places greater ventilatory stress on the healthier lung regions

and predispose them to lung injury, leading to disruption of airway membrane continuity and creating a communication between the airways, or the alveoli, and the pleural space. These ruptures can also occur in pathohistologically altered areas, as recently observed in COVID-19 patients who developed pneumothorax in the setting of ARDS, despite not being mechanically ventilated (11). In the context of ARDS airway leaks can be iatrogenic in origin, forming during trauma from intubation, central line placements or bronchoscopy related lacerations. The incidence is influenced by the modalities of mechanical ventilation, the severity of ARDS and the duration of illness. Notably, studies have shown that within the first week of respiratory failure, pneumothorax occurs in approximately 30% of patients, whereas after two weeks, the incidence increases to 87% (4).

The pleural space, formed between the parietal and visceral pleura, is characterized by a pressure that is negative relative to the atmospheric pressure, enabling the movement of the lungs synchronously with the chest wall. During normal breathing the transpulmonary pressure, defined as the difference between airway pressure and pleural pressure, changes based only on the increase of the negative pleural pressure. These cyclical fluctuations in pleural pressure facilitate lung expansion during inspiration and passive recoil to the expiratory volume, enabling effective gas exchange. In the case of a full-thickness defect of the visceral or parietal pleura a communication is established between the pleural spaces and airway or any other positive pressure space and the relative negative pressure is lost. Air entering the pleural space creates pneumothorax, which can be classified as stable or unstable. An unstable pneumothorax is defined by the progressive accumulation of air in the pleural cavity, often arising from trauma or airway leaks (12). In mechanically ventilated patients with positive airway pressures pneumothorax resulting from a full-thickness visceral pleura defect is always unstable. The volume of air entrapped in the pleural space compresses the affected lung, and unlike in normal breathing, the patient with pneumothorax experiences a reduction in lung volumes, decreased airflow, and impaired gas exchange.

3 Airway Leaks in Mechanically Ventilated Patients

Unlike spontaneous breathing which is characterized by the increase of the negativity of pleural pressure, mechanical ventilation functions on the basis of increasing the pressure in the airway leading to insufflation of air into the lungs. Mechanical ventilation is the cornerstone of ARDS patient management (13). The task of mechanical ventilation is to improve gas exchange and decrease the probability of further lung injury, but as with other medical procedures it can lead to further injury (14). Ventilation-induced lung injury (VILI) may occur through one of four mechanisms (i) by volutrauma, meaning by the large tidal volumes which affect the defected connective tissue of the alveoli, (ii) by barotrauma and the effect of large pressure forces which induces changes in viscoelastic forces of the airway and the alveoli, (iii) by atelectrauma induced by strain during the repetitive opening and closing of the atelectasis and (iv) by biotrauma (15). The later mentioned is not induced by physical forces on the lung tissue unlike volutrauma,

barotrauma or atelectrauma, but by the escalation of the inflammatory response caused by air movement (16). VILI is not limited to the before damaged lung tissue, as is the case with ARDS patients, but can be seen in ventilated patients with healthy lungs (17,18).

The goal of mechanical ventilation is to enable as much as of volume to be accessible for ventilation, meaning to increase the pulmonary volume on the end the respiratory cycle the end-expiratory lung volume (EELV) which is decreased in ARDS on the basis of inflammation and oedema. During ventilation EELV is simply increased by increasing PEEP, which not only recruits the closed alveolar units but increases the volume of the opened ones, enabling a larger area for lung exchange. PEEP and its right usage can lead to improvements in the ventilation - perfusion ratio (19), and is recommended in all ARDS guidelines but PEEP misuse can lead to further lung injury. In most modalities of mechanical ventilation PEEP is set as independent parameter. When not properly individualized, inappropriate PEEP levels can contribute to VILI through all three of the aforementioned mechanical mechanisms. Insufficient PEEP levels leave the lungs vulnerable to atelectrauma, while excessively high PEEP levels may increase the transpulmonary pressure, leading to overdistension of ventilated lung units (20), which can result in volutrauma or barotrauma. Those mechanical traumas can lead to iatrogenic fistulations of airway, that further leads to pneumothorax (15). Optimal PEEP titration is not only important for recruitment of the unventilated lung areas and improvements of ventilation-perfusion ratio but also protects the lungs from further VILI.

When observing the lungs from a mechanical perspective they can be analyzed using the term of stress which describes the force applied per unit area and the term of strain which describes the resulting deformation of the object subjected to that force. The force applied on the surface of the airway, the stress, during mechanical ventilation corresponds to the transpulmonary pressure, while strain is defined as the ratio between the lung volume at end-inspiration and the functional residual capacity (FRC). Under normal physiological conditions, the lungs reach total lung capacity during maximal inspiration, and in this state, the strain equals 1, representing the most relaxed configuration of collagen fibers within the lung parenchyma. Introducing PEEP during ventilation enhances the strain on the lungs, and the collagenous and elastic structures of its interstitium. Studies have shown that strain larger than 2, meaning transpulmonary pressure larger than 22 to 23 cmH_2O cause VILI (21), and if total lung capacity is surpassed, alveolar rupture may occur (22). In lungs affected by ARDS the strain rarely reaches those values if the lungs are considered a homogeneous unit, but the ventilation heterogeneity causes the open lung areas to accumulate more of the tidal volume leading to strain values exceeding 2. This cyclic overdistension can progressively damage even healthy parenchyma (23) and, according to animal and in situ studies, may lead to cyclical alveolar air leaks (24).

The communication between the airway and the pleural space during mechanical ventilation results in the loss of applied volume of air into the pleural space. Clinically that is presented as the loss of effective tidal volume, as the loss of PEEP and worsening of the ventilation-perfusion ratio (25). If the patient is ventilated in one of the volume-controlled modalities inspiratory tidal volumes larger than expiration one can be observed, the difference being the volume that

transcends into the pleural space. In cases of large volume pneumothorax or pneumomediastinum the patients become hemodynamically unstable from the compression of trapped air onto the heart and large vessels, which can be presented as jugular veins distension (26).

During positive pressure ventilation in the areas of lung with a visceral pleura defect, specifically in the cases of alveopleural and bronchopleural fistulas, the flow of air is mostly laminar and directly dependent on the size of the defect, on the relative resistance to airflow in the affected lung area, on the compliance of the affected lung area and on the transpulmonary pressure (27). The volume of air that enters the pleural space with every cycle of respiration depends on the transpulmonary pressure and is proportionate to the mean airway pressure (mPaw). In the context of mechanical ventilation mPaw depends on both the peak inspiratory pressure (PIP) and on PEEP. Because the difference in pressures between pleural space and mPaw is the main driver of airflow to the pleural space, it has been researched how do the PIP and PEEP influence the flow through the fistulas. Initial animal studies showed how the flow through the fistula depended on PEEP to a much higher degree, with a lesser influence from PIP while later studies showed a direct connection between mPaw with the airflow, meaning the equivalent importance of PIP and PEEP through the entire respiratory cycle (28). Although human data is limited, case studies from Zimmerman et al. directly showed that increasing PEEP causes an increased airflow through the bronchopleural fistula (29).

4 Management

Understanding the physiology of the fistula is of critical importance in mechanical ventilation, for simultaneously ensuring adequate patient respiration and minimising the airflow through the fistula. Grotberg et al. propose the following strategies within conventional modalities of mechanical ventilation: (i) low PIP, below 30 cmH_2O, (ii) low tidal volume, between 4 and 6 ml/kg of ideal body weight, (iii) minimal possible PEEP, (iv) minimisation of inspiratory volume and (v) low respiratory rate with (vi) permissive hypercapnia (25). In ARDS patients mechanical ventilation recommendations are based on lung protective ventilation and the concept of baby lung, meaning an extremely limited area of normally ventilated lung tissue. Strategies for the two special categories of patients, the ones presenting with ARDS and those presenting with an airway leak, tend to overlap. According to Banavasi et al. ventilation with tidal volumes ranging from 4 to 8 mL/kg of ideal body weight, plateau pressure of 30 cmH_2O and maintaining the difference between plateau pressure and PEEP, the driving pressure, below 15 cmH_2O, are strategies that have been associated with reduced mortality and faster recovery in ARDS patients (30,31). Furthermore, elevated end-inspiratory pressures are directly associated with the incidence of pneumothorax in ARDS patients (32,33). In severe cases of ARDS, PEEP titration to higher values for reducing atelectrauma and improving respiration has proven successful. A meta-analysis by Briel et al. compared the effects of higher and lower PEEP values in ARDS patients, while including only randomized clinical trials in which the difference between the values was equal to or greater than 3 cmH_2O (34). It demonstrated that patients ventilated with

higher PEEP, averaging 15.3 cmH_2O on day one to 10.8 cmH_2O on day seven, showed 10% lower mortality rate compared to those receiving lower PEEP (9.0 cmH_2O on day one to 7.8 cmH_2O on day seven). Interestingly, the incidence of pneumothorax was similar between the groups.

PEEP titration recommendations are individualised, although a clear dichotomy exists between PEEP strategies in ARDS patients and in the management of airway leak. The recruitment manoeuvre is a widely accepted technique in ARDS management, aimed at improving oxygenation. Recent studies do not report mortality benefit of the manoeuvre in severe ARDS, more often reporting an increase in the incidence of pneumothorax, and other barotrauma, and a reduction of 6-month survival (35), the majority still confirm improved oxygenation (30). Considering the physiology of fistulas and taking into account the pressures in the airway, recruitment manoeuvres, whether traditional or stepwise, pose a significant risk in patients with an airway leak. For this reason, ventilation in such patients demands particular caution and often the use of unconventional ventilation modalities.

Transpulmonary pressure manipulation is also achievable by altering pleural pressure using thoracic drainage systems, such as evacuating air from the pleural space to re-establish negative pressure. In cases of large airway leaks, the clinical practice mandates applying suction to thoracic drains with negative pressure of -20 cmH_2O, although physiological pressures in spontaneous breathing vary between 0 and -10 cmH_2O (36). Due to the risk of drain occlusion it is common practice to insert two drains, apically and basally within the pleural cavity (12). In mechanically ventilated patients with pneumothorax managed via suction, expiratory flow, of the air which entered during inspiration through a bronchopleural or alveopleural fistula, may be observed. Increasing pleural pressure during passive expiration may generate sufficient negative pressure for its removal. Thoracic drainage affects not only ventilation but also respiration, which is seen in high-flow fistulas where suction during expiration may excessively remove air from alveolar spaces, potentially reducing alveolar CO_2 partial pressure and causing respiratory alkalosis (37). With an effect on CO_2 partial pressure in arterial blood, excessive suction may also cause hypoxaemia by extracting large portions of tidal volumes and reducing alveolar oxygenation (38,39). To minimise flow through the fistula while still removing excess pleural air, thoracic drainage under positive pressure, which should be lower than PEEP, has been used. This approach may reduce both airflow and trauma to fistulated tissue, potentially enabling faster fistula healing, provided pressures are cautiously and individually adjusted for each patient (38). Air removal from the pleural space also contributes to lung re-expansion, which is linearly dependent on lung compliance. In low-compliance lungs, particularly those of ARDS patients, excessive suction pressure may overload healthy lung tissue and should be applied with caution (12).

In the cases of proximal airway leaks, endobronchial management is possible using occlusive agents such as tetracycline, fibrin glue, cellulose, or blood patches (25). Larger and more proximal defects can be closed with Amplatzer devices or endobronchial valves. Endobronchial valves allow for airflow from the distal airways but prevent air entry, effectively isolating the affected bronchial segment. These demonstrate the best outcomes in patients unfit for surgical management (40). In cases involving large or extensive airway defects or bilateral pneumothoraces, surgical

intervention remains the only viable option, and it includes resection of the affected lung tissue, airway suturing, and pleurodesis (41,42).

Proximal bronchopleural fistulas can be bypassed using double lumen endotracheal tubes, which physically bypass the site of the leak and enable isolation and separate ventilation of each lung. This permits lung sparing on the affected side, as in cases of pneumothorax from alveopleural fistulas (43). For patients that are unable to tolerate single lung ventilation, individualised settings may be applied to each lung using two ventilators. In that case the protected lung may be receiving lower PEEP and tidal volumes and asynchronous ventilation, in which different frequencies are used for each side, can be employed. This type of ventilation is limited by tidal volume differences of up to 100 mL and compliance discrepancies of 20% (44,45).

The need to minimise transpulmonary pressure has led to the use of high-frequency mechanical ventilation for airway leaks. With characteristics such as low maximal pressures, high recruitment pressures, and very small tidal volumes ranging from 2 to 5 mL/kg of ideal body weight with obligatory pairing with high respiratory rates of 100 to 200 breaths per minute to meet minute ventilation requirements, this technique creates optimal conditions for reducing flow through the fistula and facilitating closure (46). Gas exchange occurs via Taylor dispersion, the Pendelluft effect, molecular diffusion, and cardiogenic mixing (25). Two modalities have been used in patients with ARDS and airway leak: (i) high-frequency oscillatory ventilation (HFOV) and (ii) high-frequency jet ventilation (HFJV). While earlier studies suggested deterioration in patients ventilated with HFOV, more recent findings by Meyers et al. (46) and case reports by Galvin et al. (47) and Ranjan et al. (48) demonstrated benefits and potential applications in pneumothorax management among ARDS patients.

The advantages of high-frequency mechanical ventilation include low inspiratory pressures, minimal transpulmonary pressure, and thus minimal flow through fistulated tissues. Small tidal volumes impair gas exchange, which is compensated for by high respiratory rate in the case of high frequency ventilation, or by combining ultraprotective mechanical ventilation with extracorporeal oxygenation or decarbonisation. Using the principles of small tidal volumes, of 3 to 4 mL/kg, and reduced airway pressure, ultraprotective mechanical ventilation combined with extracorporeal membrane oxygenation (ECMO) or extracorporeal carbon dioxide removal ($ECCO_2R$) enables adequate gas exchange in ARDS patients with concurrent airway leaks. Veno-venous ECMO enables reduced ventilatory pressures, tidal volumes and respiratory frequencies, allowing for ultraprotective ventilation and improved healing of airway leaks (49), as confirmed in small case series of patients with refractory bronchopleural fistulas (50). $ECCO_2R$ reduces hypercapnia without affecting hypoxaemia, which commonly burdens patients receiving ultraprotective ventilation (51,52), and has added benefit of simpler implementation compared to ECMO. A case by F. Gómez et al. demonstrated promising outcomes in strain, transpulmonary pressure reduction and successful airway leak management (53).

5 Conclusion

Acute respiratory distress syndrome requires comprehensive management and complicates the clinical course of a significant number of patients, leading to prolonged intensive care stays and increased mortality. Complications such as airway discontinuity, manifesting as pneumothorax or pneumomediastinum, further worsen clinical outcomes. Although new protective ventilation strategies developed over the past two decades have significantly reduced the incidence of barotrauma, these conditions still present a challenge. Effective management demands in-depth understanding of respiratory physiology and prompt intervention, which is key to improving outcomes in each individual patient.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

I.B. and J.P. conceived and designed manuscript. I.B. wrote manuscript. Both authors read and approved the final manuscript.

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