Review Article

Acute respiratory distress syndrome and pneumothorax

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Abstract: Acute respiratory distress syndrome (ARDS) can occur during the treatment of several diseases and in several interventional procedures as a complication. It is a difficult situation to handle and special care should be applied to the patients. Mechanical ventilation is used for these patients and several parameters are changed constantly until compliance is achieved. However, a complication that is observed during the application of positive airway pressure is pneumothorax. In our current work we will present definition and causes of pneumothorax in the setting of intensive care unit (ICU). We will identify differences and similarities of this situation and present treatment options.

Keywords: Acute respiratory distress syndrome (ARDS); pneumothorax; intensive care unit (ICU); recruitment; mechanical ventilation; extracorporeal membrane oxygenation (ECMO)

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Introduction

Acute respiratory distress syndrome (ARDS) is defined as a rapidly progressive acute onset respiratory failure (arterial hypoxemia with PO_2/FiO_2 ratio less than 200 mmHg regardless of PEEP level), with bilateral radiographic infiltrates, without evidence of left atrial hypertension (or pulmonary artery wedge pressure less than 18 mmHg) (1). This complex syndrome, which is characterized by broad clinical presentations, is caused by a variety of insults, such as bacterial or viral pneumonia, non-pulmonary sepsis, major trauma, amniotic fluid embolism, transfusions, aspiration of gastric contents, drug reactions etc., and is associated with high 180-day mortality, approaching 31% in adult patients, according to the most recent report of the ARDS Network clinical trials (2).

Pneumothorax appears as a frequent and potentially fatal complication in patients with ARDS, especially in those who need mechanical ventilation support. Gattinoni *et al.* in a study of 84 patients, who suffered from severe ARDS and were recruited from 48 intensive care units (ICUs), reported a total incidence of pneumothorax of 48.8% of the entire population, having a mortality of 66% *vs.* 46% in patients with ARDS without pneumothorax (3). In another case series of 15 critically ill patients under mechanical ventilation, 88% suffered from pulmonary interstitial emphysema, 77% from pneumothorax and 39% presented pneumomediastinum (4).

Many factors may precipitate the occurrence of pneumothorax in ARDS, such as the mechanical ventilation settings, the clinical severity of ARDS and the underlying pulmonary pathology (like preexisting emphysema). Furthermore, the incidence of pneumothorax seems to be related to the duration of ARDS, varying from 30% of all patients with early ARDS (up to 1 week) to 46% in intermediate ARDS (between 1 to 2 weeks) and complicating a total of 87% of patients with late ARDS (more than 2 weeks) (3). This increase at the incidence of pneumothorax in late ARDS appears to be related to the lung structural changes occurring over time. It must kept in mind, that diagnostic procedures used in patients with ARDS, such as bronchoalveolar lavage (5,6) and lung biopsy (7,8), are accompanied with high risk of pneumothorax development, often with persistent air leaks.

Prompt recognition and treatment of pneumothoraces is necessary in order to minimize morbidity and mortality.

Pathogenesis

It is well previously described that pathophysiologically, ARDS is the result of inflammatory lung injury. It is characterized by increased activation of circulating neutrophils, complement cascade and other proinflammatory mediators, increased microvascular permeability and fluid exudation into the lung parenchyma and loss of surfactant resulting in alveolar atelectasis, destruction and eventually fibrin deposition in the lungs (9). The development of pneumothorax in patients under mechanical ventilation is closely correlated with the underlying pulmonary pathology and it has been proved that ARDS independently correlated with the appearance of this complication (10). As it has been marvelously described by computed tomographic studies in patients with ARDS, the diseased lung parenchyma, seems to have a remarkable heterogenic distribution, with patchy infiltrates, interspersed with areas of normal-appearing lung, resulting in a multi-compartmental lung (11,12). This variable lung structure and function changes markedly with ARDS duration, and the late stages may be described as restrictive lung disease with superimposed emphysema like lesions (3). The aforementioned explains the higher number of bullae formation, preferentially distributed in the dependent lung regions, complicating late ARDS, as well as the increase at the incidence of pneumothorax in this late stage, mentioned above.

Except pneumothorax, in patients with ARDS, many other forms of air leaks can be present, such as subcutaneous emphysema, pneumomediastinum, pneumopericardium and pneumoperitoneum.

Clinical characteristics

The early and accurate diagnosis of pneumothorax in ARDS patients is mandatory since this complication carries an increased mortality. Furthermore, small pneumothoraces in these patients can cause severe hemodynamic or pulmonary compromise. This is the reason why pneumothorax must always be suspected in any patient with ARDS who experiences an acute worsening in respiratory function, accompanied with dyspnea and hypoxemia, which is usually unresponded to oxygen therapy.

Portable chest X-ray is the first diagnostic evaluation imaging being used and the procedure of choice for the documentation of lung underlying pathology or the presents of lines, tubes or devices. Nevertheless, often exhibits diagnostic disadvantages, taking into account that pneumothoraces in ARDS patients may have unusual, as well as subtle features and small sized pneumothoraces or loculated pneumothoraces, can be missed on chest X-ray. Furthermore, other types of air leaks, such as pneumomediastinum and interstitial pulmonary emphysema, may be more difficulty observed by chest radiographs (13). Cases have been described in medical literature, referring to patients presenting clinical deterioration but unchanged chest X-ray and functioning chest drains (14). This is the reason why, especially in patients under mechanical ventilation, serial and daily chest radiographs are necessary in the evaluation of underlying lung pathology.

There for, if a pneumothorax is suspected and is unrevealed on chest X-ray, a more specific diagnostic imaging like chest-computed tomography (CT) is necessary. CT scan in patients with ARDS can reveal a variety of abnormalities, such as ground-glass opacification, consolidation, interstitial thickening, evidence of fibrosis and pulmonary cysts (15-17). Chest CT is helpful in understanding the extent of the underlying lung parenchyma distraction and is quite more sensitive in identifying pneumomediastinum and pneumothorax, which are frequently observed in patients with ARDS (16). In a study of 74 ARDS patients who underwent a chest-CT, 32% of all patients presented a loculated pneumothorax (mostly anteromedial) and 30% had pulmonary air cysts (always multiple and mostly bilateral) (17). Nevertheless, chest-CT evaluation is seldom employed in patients with ARDS, especially patients with severe respiratory failure under mechanical ventilation, mostly due to problems concerning the transfer and monitoring of these critically ill patients (17,18).

Due to these technical difficulties of chest-CT, an essential diagnostic method in critically ill patient gaining respect is lung-ultrasonography, a relatively easy to perform, portable and inexpensive diagnostic imaging. Lung-ultrasonography can prove an alternative diagnostic procedure in the difficult diagnosis of pneumothorax in critically ill patients with severe ARDS, which not only permits bedside assessment of lung pathology but also assists in the evaluation of mechanical ventilation parameters, as well as the evaluation of lung overdistension and PEEP-induced lung recruitment (19).

Treatment

Limited literature exists on when or how to treat pneumothoraces once they have been developed in patients with ARDS (20). Treatment options are varying from simple observations, in case of small spontaneous pneumothoraces without severe respiratory compromise, to traditional tube thoracostomy or open thoracotomy with application of sclerosing agents. Thoracoscopic treatment is another technique commonly applied, especially in cases of recurrences of persistent air leaks, as it permits the prompt recognition of the air leak and the resection of the leaking parenchymal area with parietal partial pleurectomy and application of sclerosing agents.

Among all, one serious problem complicating pneumothorax in ARDS is the persistence of pulmonary air leaks. Persistent air leaks prolong pneumothorax in 2% of cases of ARDS, increasing the rate of mortality by 26% (21). Martínez-Escobar *et al*. reported a series of 27 patients with ARDS and pneumothorax with persistent air leak, managed with pleurodesis using autologous blood, with good results concerning shorter ICU stay, shorter weaning time and lower mortality (21). Surgery may became necessary in various manifestations of barotrauma due to mechanical ventilation in ARDS patients, especially in cases of bronchopleural fistula, persistent air leaks and bilateral pneumothorax, situations that often carry a high frequency of reoperations (22).

ARDS and pneumothorax during mechanical ventilation

Patients with ARDS undergoing mechanical ventilation are considered to be at highest risk for development of barotrauma, with an incidence varying between 0-49% (23). Many radiologic findings, such as vesicular rarefactions, lucent lines toward hilus or lucent halos around vessels, pneumatoceles and emphysema changes, have been described as a result of barotrauma during mechanical ventilation (24). These lesions can precede more serious complications, such as pneumothorax and mediastinal emphysema. The mechanism of this lung damage is not clear and many causes are implicating such as overdistension of alveoli during mechanical ventilation by the use of inappropriately large tidal volumes, shear stresses generated in lung units during the recruitment and de-recruitment maneuvers and necrosis of the collapsed lung due to infection or ischaemia (25).

The development of pneumothorax in an ARDS patient under mechanical ventilation support is a fearful complication as it results in prolongation of mechanical ventilation and increase of morbidity and mortality. This is the reason why a number of mechanical ventilation techniques promising to minimize ventilation-induced lung injury while maintaining adequate oxygenation, are under investigation (26). Many ventilation parameters such as peak inspiratory pressure, positive end-expiratory pressure level, respiratory rate, tidal volume and minute ventilation, are considered to be significant in barotrauma development. From all this ventilation parameters studied, pneumothorax development, seems to correlate strongly with applied end-inspiratory pressure [P(plat)], especially when exceeding 35 cm of water (cm H_2O) and with pulmonary compliance, with high incidence below 30 mL/cm H_2O (25). Furthermore, large tidal volumes might elicit injury to the pulmonary epithelium, therefore tidal volume reduction is another meter presented for the prevention of ventilator-induced injury in ARDS (27).

The use of lung-protective ventilator strategies—the provision of mechanical ventilation with tidal volumes according to predicted body weight and static end-inspiratory pressures [P(plat)] of less than 30 cm H_2O—is strongly associated with a reduced risk of pneumothorax and persistent air leak in ARDS patients (28). For example, in a study by Miller *et al*., in 33 pediatric patients with ARDS, pneumothorax recorded in 55% of all patients managed with conventional ventilation, *versus* 17% of all patients treated with protective lung strategies (29). Even if the outcome of ARDS is unpredictable, ARDS patients need to be ventilated applying "lung protective" strategies (30). Nevertheless, despite the plethora of well documented lung protective ventilation strategies, for patients with acute lung injury (ALI) and acute ARDS, many ICU fail to apply those (31).

Positive end expiratory pressure (PEEP) and pneumothorax in ARDS

The application of PEEP was accused in the past, for the development of pneumothorax in ARDS (3,32-34). It seems that the complication of pneumothorax can occur over a wide variety of mean airway pressures and PEEP. Nevertheless, there are studies concluding that there is a threshold level of peak airway pressure (above 40 cm H_2O), which places the ARDS patients at high risk for developing barotrauma (3,32-34), while others report no correlation between maximal PEEP levels and pneumothorax frequency (10,23,35,36). For example, in a systematic review and meta-analysis by Briel *et al.*, related to patients with ALI and ARDS stratified to treat with higher or lower positive end-expiratory pressure, the incidence of pneumothorax was similar (37).

On the other hand, the use of high levels of PEEP seems to be related with the persistence of lung air leaks. For example, during a study of 53 patients who underwent open lung biopsy for clinical ARDS, a proportion of 30.2% developed an air leak lasting more than 7 days or died with an air leak. The development of this complication was negatively associated with lower peak airway pressure, tidal volume and use of pressure-cycled ventilation. Among all, peak airway pressure remained the significant predictor in multivariated analysis and the risk of prolonged air leak was reduced by 42% for every 5 cm H_2O reduction in peak airway pressure (8).

Finally, recruitment technics using PEEP were found to correlate with significant increase of incidence of pneumothorax (38). But further studies are taking place in order to clarify whether the maximum stepwise alveolar recruitment, associated with PEEP titration, is better than conventional treatment according to ARDSNet strategy in the treatment of ARDS and which is the degree of hazard of each technique applied leading to complications such as pneumothorax or barotrauma (39).

Neuromuscular blocking agents in ARDS

Except from lung protective strategies in ventilated patients with ARDS, many observations have been written down about the beneficial effect of neuromuscular blocking agents, during mechanical ventilation support. In patients with severe ARDS, early administration of a neuromuscular blocking agent, improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness (40). In another study, a prolonged curarization in ARDS patients of 48 h or more was proved to be beneficial regarding systemic oxygenation, even in patients well adapted to their ventilator (41). The use of neuromuscular blocking, like cisatracurium, not only seems to facilitate mechanical ventilation in ARDS patients, but also leads to fewer complications, such as pneumothorax formation (42).

Future lung protective techniques in ARDS

Future lung protective techniques, such as high-frequency ventilation, independent lung ventilation (ILV), partial liquid ventilation, surfactant replacement and extracorporeal membrane oxygenation (ECMO) systems, may contribute to lower barotrauma complications.

High-frequency ventilation

High frequency ventilation, providing low maximal pressures and high recruitment pressures, is considered to reduce ventilator-induced lung injury, especially in patients with ARDS or ALI (43). The two most common forms of high-frequency ventilation are high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). HFOV is a type of lung protective ventilation, used in ARDS patients, to whom conventional ventilation is not effective and classic ventilator settings fail to maintain oxygenation and carbon dioxide (CO_2) removal. This ventilation pattern can be very efficacious and it seems to associate with lower incidence of barotrauma and pneumothorax as well. Early institution of HFOV may be not only an effective rescue therapy, in patients with severe oxygenation failure, but it has been also applied successfully in the management of patients with ARDS and pneumothoraces or severe air-leaks (44). The application of HFOV has been described in many case series of pediatric or adult patients with ARDS. Li *et al.* reported the effectiveness and safeness of HFOV in 10,843 children with severe ARDS unresponsive to conventional ventilation, after open heart surgery, with only 22 reports of pneumothorax as major complication (45). In another study, Martinón Torres *et al.*, reported the application of HFOV in pediatric patients with severe refractory ARDS and gross air-leak syndromes (such as pneumothorax, pneumoperitoneum, pneumomediastinum etc.) (46). In adult critically ill patients the incidence of pneumothorax during HFOV seems to approach 20% (47-49). In a series of 156 adult patients with severe ARDS underwent trials of HFOV after conventional ventilation failure, pneumothorax occurred in 21.8% of patients (49). Nevertheless, in this study, the aforementioned complication was not proved to be an independent predictor of mortality in multivariate analysis.

Concerning HFJV, there are also studies reporting that the application of HFJV early in the course of ARDS complicated by air leak, allowed the reduction of airway pressures, minimizing pulmonary barotrauma and allowing lung recovery (50).

Independent lung ventilation (ILV)

Another ventilation technic reported in patients with post-traumatic ARDS complicated with pneumothorax is the ILV with a double lumen tube, which gives the opportunity to ventilate each lung, using different ventilation parameters (such as PEEP or volume) (51). In this case, ILV with a larger tidal volume and high PEEP may be useful in significant air leak from injured tissue.

Extracorporeal membrane oxygenation (ECMO)

ECMO permits large reductions in lung inflation, avoiding overdistension of the lungs and the use of high oxygen concentrations. This allows the lungs to rest while maintaining acceptable oxygenation. ECMO has been recommended in combination with lung protective ventilation strategies for patients with severe ARDS, taking into account that early institution may decrease mortality and morbitity in rapidly progressing ARDS (52,53). The application of ECMO allows the reduction of peak and mean airway pressures, tidal volumes, ventilator rate, minute volume and inspiratory oxygen concentration (54). Nevertheless, it must be kept in mind that pneumothorax remains one of the most frequent complications and that the application of ECMO may result in chest radiographic patterns, such as mixed alveolar-reticular opacifications, alveolar patterns or reticular opacities, making the diagnosis of pneumothorax difficult from chest X-rays (55).

Partial liquid ventilation

An oxygen soluble flurocarbon can be used in order to provide alveolar recruitment and improved lung mechanics. Partial liquid ventilation with perfluorocarbon has been shown to improve oxygenation and lung compliance, preventing or minimizing the lung damaged, induced by mechanical ventilation (56-78).

Summary

Summarizing all the above mentioned, clinicians must always keep in mind that pneumothorax can be a complication with tragic consequences in a critically ill patient with ARDS, so "lung-protection" during mechanical ventilation support and awareness and prompt recognition of this complication could be lifesaving.

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