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REVIEW ARTICLE

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UPDATE IN ACUTE RESPIRATORY DISTRESS SYNDROME – CLINICAL VENTILATOR MANAGEMENT AND PRONE VENTILATION

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ABSTRACT

The acute respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure. Its development leads to high rates of mortality, as well as short- and long-term complications, such as physical and cognitive impairment. Key components of a strategy include avoiding lung overdistension by limiting tidal volumes and airway pressures, and the use of positive endexpiratory pressure with or without lung recruitment manoeuvres in patients with severe ARDS.In this review article, we describe updated concepts in ARDS. Specifically, we discuss the new definition of ARDS, its risk factors and pathophysiology, and current evidence regarding ventilation management, prone ventilation, and intervention required in refractory hypoxemia.

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance. ARDS was first described by Ashbaugh and Petty in 1967 in a case series of 12 ICU patients who shared the common features of unusually persistent tachypnea and hypoxemia accompanied by opacification on chest radiographs and poor lung compliance, despite different underlying causes for more than 20 years, there was no common definition of ARDS inconsistent definitions led to the published prevalence in ICU ranging from 10 to 90% of patients. The 1994 AECC definition became globally accepted, but had limitations. The current definition is the 'Berlin Definition' published in 2013, which was created by a consensus panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine)

The Berlin Definition (2013)

ARDS is an acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance. ARDS represents a complex response to local and systemic inflammatory factors. Regardless of the underlying insult, the pathophysiological correlate of ARDS – alveolar damage – involves neutrophil activation and endothelial injury, leading to noncardiogenic pulmonary edema and atelectasis (Johnson, 2010). Studies using computed tomography have demonstrated that, in contrast to chest radiograph appearances, the distribution of disease is heterogeneous with atelectatic-dependent regions and relatively well-aerated 'baby lungs' in nondependent areas (Gattinoni, 2001 and Gattinoni, 1999). Recognition of the

heterogeneity of disease distribution has led to the concept of recruitable lung regions and the need to deliver lower than historical tidal volumes to avoid overdistension of the baby lung. The majority of patients with ARDS will require invasive mechanical ventilation, although the successful use of non-invasive ventilation has also been described (Rocker, 1999). ARDS may resolve with supportive treatment, heal with interstitial fibrosis, or contribute to systemic inflammation and death. We review current evidencebased practices for invasive ventilation and discuss adjunctive therapies for ARDS.

Pathogenesis of ARDS: In addition to the classical views of ARDS including the role of cellular and humoral mediators, the role of the renin-angiotensin system (RAS) has been highlighted. The RAS is thought to contribute to the pathophysiology of ARDS by increasing vascular permeability. Angiotensin-converting enzyme (ACE) is a key enzyme of the RAS that converts inactive angiotensin I to the vasoactive and aldosterone-stimulating peptide angiotensin II and also metabolizes kinins along with many other biologically active peptides. ACE is found in varying levels on the surface of lung epithelial and endothelial cells (Igic, 2003). Angiotensin II induces apoptosis of lung epithelial and endothelial cells and is a potent fibrogenic factor (Wang, 2000). Based on these biological properties of ACE, there is considerable interest in its potential involvement in acute lung injury (ALI)/ARDS (Imai *et al*., 2005 and Lambert et al., 2010).

Diagnosis and early intervention

Differential diagnosis between cardiogenic pulmonary edema (CPE) and ARDS is sometimes not easy. The accuracy of the portable chest radiograph to detect pulmonary abnormalities consistent with ARDS is significantly limited (Figueroa-Casas, 2013). In a study using chest computed tomography, upper-lobe-predominant ground-glass attenuation, central-predominant ground-glass attenuation, and central airspace consolidation were associated with high positive predictive values (95.2%, 92.3%, and 92.0%, respectively) and moderate negative predictive values (47.5%, 51.4%, and 50.0%, respectively) to diagnose CPE (Komiya, 2013). Measurement of the extravascular lung water index and the pulmonary vascular permeability index (PVPI) (Kushimoto, 2012), using a transpulmonarythermodilution method seemed to be a useful quantitative diagnostic tool for ARDS in patients with hypoxemic respiratory failure and radiologic infiltrates. In one study, A PVPI value of 2.6–2.85 provided a definitive diagnosis of ALI/ARDS (specificity, 0.90–0.95), and a value <1.7 ruled out an ALI/ARDS diagnosis (specificity, 0.95) (The Acute Respiratory Distress Syndrome Network, 2000).

Clinical Mechanical ventilation Management

Numerous lines of evidence have demonstrated that inappropriate mechanical ventilatory settings can produce further lung damage to patients with ARDS. Ventilator-induced lung injury seems to be attributed to end-inspiratory overdistension and a low end-expiratory lung volume, allowing repeated collapse and re-expansion with each respiratory cycle (tidal recruitment). Tidal recruitment results in high shear force on alveolar walls and small airways during inflation, especially at the interfaces between collapsed and aerated alveoli. Therefore, low tidal volume (6 mL/kg of predicted body weight), limitation of plateau pressure (less than 28–30 cm H_2O), and appropriate PEEP is a key component of a lung-protective ventilatory strategy (LPVS) (The Acute Respiratory Distress Syndrome Network, 2000). Since then, the lung-protective mechanical ventilation strategy has been the standard practice for the management of ARDS. In a retrospective observational study of 104 patients with ARDS caused by pandemic influenza A/H1N1 infection admitted to 28 ICUs in South Korea, low-tidal volume (TV) mechanical ventilation still benefited patients with ARDS caused by viral pneumonia. Patients with TV less than or equal to 7 mL/kg required ventilation, ICU admission, and hospitalization for fewer days than those with TV greater than 7 mL/kg (11.4 vs. 6.1 days for 28-day ventilator-free days, 9.7 vs. 4.9 days for 28-day ICU-free days, and 5.2 vs. 2.4 days for 28-day hospital-free days, respectively). A tidal volume greater than 9 mL/kg (hazard ratio, 2.459; $P = 0.003$) and the Sequential Organ Failure Assessment score (hazard rate, 1.158; $P = 0.014$) were significant predictors of 28-day ICU mortality (Oh, 2013). The lung-protective ventilation strategy is both safe and potentially beneficial in patients who do not have ARDS at the onset of mechanical ventilation. In mechanically ventilated patients without ARDS at the time of endotracheal intubation, the majority of data favors lower tidal volume to reduce progression to ARDS (Fuller, 2013). Septic patients without ARDS who were ventilated with a protective strategy using a plateau pressure <30 cmH_2O showed better outcomes and a lower incidence of ARDS than those ventilated without this limit on plateau pressure (Martin-Loeches, 2013). A recent meta-analysis also showed that protective ventilation with low tidal volumes was associated better clinical outcomes even in patients without ARDS (Neto, 2012). The use of very low TV combined with extracorporeal CO_2 removal has the potential to further reduce ventilator-associated lung injury. Whether this strategy will improve survival in ARDS patients remains to be determined (Prone Positioning in Severe Acute Respiratory Distress Syndrome, 2013). To select the optimal PEEP level to prevent the undesirable tidal recruitment together with the minimization of alveolar overdistension is not easy. Traditionally, the level of PEEP has been set according to the required level of FiO_2. Simple elevation of the PEEP level which is more than that of the ARDSnet clinical trial group of low TV was shown to not improve clinical outcome (Brower, 2004). Another way to set the PEEP level is to employ a decremental PEEP trial after alveolar recruitment maneuvers (ARM). An ARM has the advantage of standardizing the history of lung volume and to let the lung remain more open at the end of expiration. However, the application of early ARM with low tidal volume has not been proved efficacious for the reduction of mortality (Huh, 2009 and Lamm, 1994). The PEEP level could be set according to a level of transpulmonary pressure during expiration. One study demonstrated the efficacy of esophageal pressure-guided PEEP on the improvement of oxygenation and lung compliance in ALI (Talmor, 2008). The researchers set the PEEP at a level to guarantee that transpulmonary pressure during end-expiratory occlusion would stay between 0 and 10 cm H_2O as well as keep transpulmonary pressure during end-inspiratory occlusion at less than 25 cm H_2O (Talmor, 2008). A problem with setting the PEEP according to the transpulmonary pressure is the technical difficulty in achieving accurate esophageal pressure using an esophageal balloon catheter (Benditt, 2005). Recently, electrical impedance tomography has been introduced as a true bedside technique,

which provides information on regional ventilation distribution (Moerer, 2011).

Prone ventilation

Prone position reduces the transpulmonary pressure gradient, recruiting collapsed regions of the lung without increasing airway pressure or hyperinflation. Prone ventilation showed improved oxygenation and improved outcomes in severe hypoxemic patients with ARDS (Guerin, 2013). Prone ventilation was more effective in obese patients with ARDS than in non-obese ARDS patients (De Jong, 2013). In a study investigating whether there is any interdependence between the effects of PEEP and prone positioning, prone positioning further decreased non-aerated tissue (322 ± 132 to 290 ± 141 g, $P = 0.028$) and reduced tidal hyperinflation observed at PEEP 15 in the supine position ($0.57\% \pm 0.30\%$ to $0.41\% \pm 0.22\%$) (Cornejo, 2013). Cyclic recruitment/de-recruitment only decreased when high PEEP and prone positioning were applied together ($4.1\% \pm 1.9\%$ to $2.9\% \pm 0.9\%$, $P = 0.003$), especially in patients with high lung recruitability (Cornejo, 2013). These results showed that prone ventilation decreases alveolar instability and hyperinflation observed at high PEEP in ARDS patients. Recently published paper "Prone Positioning in Severe Acute Respiratory Distress Syndrome" (Prone Positioning in Severe Acute Respiratory Distress Syndrome, 2013). Guérin and colleagues present the results of the PROSEVA trial, a prospective, multicentre RCT investigating the impact of early application of prone positioning on severe ARDS patients outcome. 466 patients were recruited from 27 “experienced” ICUs (where prone positioning had been used in daily practice for more than 5 years) and randomised to undergo daily prone-positioning sessions of at least 16 hours or to be left in the supine position. Mortality at day 28 was significantly lower in the prone group than in the supine group: 16.0% versus 32.8% ($p<0.001$). Ventilation-free days at day 28 and 90 were more ($p<0.001$) in the prone group.

Distribution of alveolar inflation in the prone position

In supine position alveolar inflation is heterogeneous and there will be over distension of some of the alveolar and it is depends on transpulmonary pressure. As we discussed earlier in prone position there will be a homogeneous distribution of gases and transpulmonary pressure (Mutoh, 1994). During the prone ventilation can also observe the movement of the chest wall and lung densities from dorsal region to ventral regions. Distribution of ventilation and alveolar recruitment can be seen in figure-1.There are many factors which are responsible for the changes of transpulmonary pressure during the prone ventilation. Which include weight of the heart will be on the sternum bone, reduces from 30 to 40 % of the weight, abdominal content moves downward so less effects of intraabdominal pressure on the diaphragm, mechanical properties and shape of the chest wall helps in homogeneous distribution of gases, transpulmonary pressure and alveolar inflation.

Distribution of ventilation in the prone position

Unfortunately, no data regarding the distribution of ventilation in the prone position are currently available.

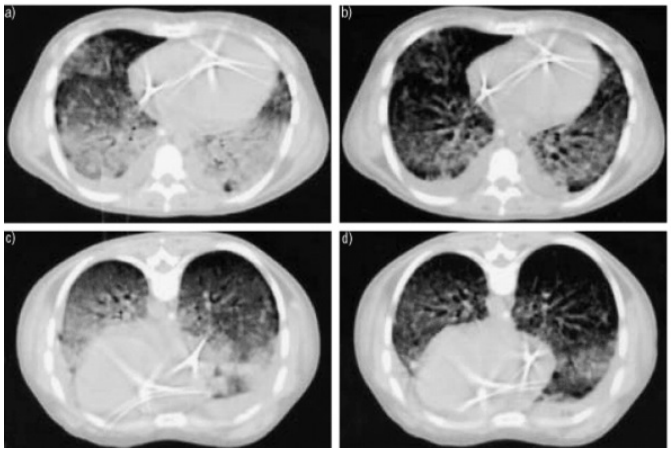

Figure 1. A and B. Supine position C and D Prone position

However, from regional inflation data, the authors infer that ventilation should redistribute from ventral (collapsed in the prone position) to dorsal regions (recruited in the prone position). Moreover, as regional inflation is more uniform in the prone position, ventilation is expected to be more uniform. To conclude, in patients with ARDS in the prone position, ventilation is probably more homogeneous and dorsally distributed.

Distribution of perfusion in prone position

To the best of the authors' knowledge, no data regarding the distribution of perfusion in the prone position are available. However, experimental evidence in dogs suggests that perfusion to dorsal regions is greater in the prone position, and that perfusion is overall more homogeneous, suggesting that mechanisms other than gravity may operate in this situation (Lamm, 1994). To conclude, in patients with ARDS in the prone position, perfusion is probably more homogeneous and not dependent on gravity.

Effects on respiratory mechanics

Respiratory mechanics have rarely been assessed in patients with ARDS in the prone position. Recently, the authors investigated modifications in respiratory mechanics in a group of patients with “primary” ARDS (following a direct pulmonary insult) (Pelosi, 1998). They found that prone positioning decreased thoraco-abdominal compliance but did not affect total respiratory system compliance. The reduction in thoraco-abdominal compliance could be explained by a decrease in thoracic wall and/or diaphragmatic wall compliance. Assuming that overall compliance of the diaphragmatic wall remains unchanged in the prone position, since the intra-abdominal pressure did not change, it could be supposed that the decrease in thoraco-abdominal compliance arises through a greater stiffness of the posterior, compared to the anterior, wall of the thorax when free to move. Other authors have shown an improvement in respiratory system compliance in the prone position, but their data mainly refer to patients with “secondary” ARDS (nonpulmonary insult) (Blanch, 1997 and Guerin, 1999). Interestingly, respiratory system compliance is improved when patients are returned to the supine position (Gattinoni, 1991). This indicates that structural beneficial effects can occur on the lung parenchyma in the prone position. To conclude, total

respiratory system mechanics are not modified in the prone position but seem to improve after repositioning to supine.

Effects on lung volume and alveolar recruitment

The effects of prone positioning on lung volume and alveolar recruitment are unclear. Using CT scanning, the authors observed that the total amount of density was similar in supine and prone positions, suggesting no alveolar recruitment (Gattinoni, 1991). On average, lung volume and alveolar recruitment are unaffected by the posture change in patients with primary ARDS (Mure, 1998). Other authors have reported alveolar recruitment, correlated to the improvement in oxygenation, in a group of patients with prevalent secondary ARDS (Guerin, 1999). To conclude, in patients with primary ARDS, prone positioning does not markedly influence lung volume and total alveolar recruitment. In patients with secondary ARDS, prone positioning is more likely to induce increases in lung volume and alveolar recruitment.

Mechanisms of improvement in oxygenation in the prone position

From a pathophysiological point of view, hypoxaemia in ARDS follows a reduction in the ventilation/perfusion ratio (V′/Q′) and the presence of a true shunt (alveolar units are not ventilated but remain perfused, V′/Q′=0). The combination of these two factors is called "physiological shunt". Prone positioning can improve oxygenation owing to several mechanisms that improve V′/Q′, in general, and consequently cause a reduction in physiological shunt. These include increased lung volume, redistribution of perfusion, recruitment of dorsal lung regions and a more homogeneous distribution of ventilation.

Increase in lung volume

An increase in lung volume was amongst the first mechanisms hypothesised to explain the improvements in oxygenation in the prone position. Increased lung volume should be attributable to an unloading of diaphragmatic movement in the prone position, owing to a reduction in the forces opposing the passive movements of the dorsal regions. This hypothesis has not been confirmed in human studies, including those in patients with primary ARDS, since the improvement in oxygenation was not correlated with lung volume or alveolar recruitment. On the contrary, in secondary ARDS the improvement in oxygenation correlated with alveolar recruitment (Guerin, 1999). To conclude, the increase in lung volume and alveolar recruitment that occurs in the prone position, if present, does not entirely explain the improvement in oxygenation in primary ARDS. An increase in lung volume and alveolar recruitment may explain the improvement in oxygenation seen in secondary ARDS.

Redistribution of perfusion

This hypothesis is based on the fact that perfusion in the supine position is gravity-dependent, greatest to the most dependent part of the lung, and that lung densities are also greatest in dependent regions. Thus, in the supine position, perfusion is greatest in the most diseased lung regions with a consequent increase in shunt (reduced V′/Q′). If the patient is turned and densities remain in the dorsal part, whilst perfusion following a gravitational gradient is increased ventrally, an improvement of V′/Q′ correlating with increased oxygenation should be expected. Unfortunately, this simple and attractive mechanism does not apply to the majority of patients with ARDS. In fact, when patients are in the prone position, although maximum perfusion is likely to remain dorsally, lung densities redistribute from dorsal to ventral regions.

Recruitment of dorsal lung with more homogeneous distribution of ventilation and perfusion

This seems to be one of the most probable causes of increased oxygenation in the prone position. In the prone position, densities in the dorsal part of the lung decrease causing more homogeneous distribution of alveolar inflation and ventilation, whilst perfusion probably remains greatest in the dorsal lung regions. Thus, V′/Q′ improves with a consequent increase in oxygenation. Recently, the authors found, in a group of patients with primary ARDS, that basal chest wall compliance and its changes played a role in determining oxygenation response to prone positioning (the lower the chest wall compliance in the supine position, the lower the improvement in oxygenation) (Pelosi, 1998). In addition, the magnitude of the decrease in thoraco-abdominal compliance observed in the prone position was related to the improvement in oxygenation. These findings, in patients with ARDS, are in line with experimental data and highlight the importance of the interactions between the rib cage, lungs and abdomen during prone positioning (Mure, 1998). Moreover, the more triangular the thoracic shape in the supine position (apex on the top and base on the bottom), the greater the response in oxygenation in the prone position **7**. The improvement in oxygenation probably results from a redistribution of blood flow away from unventilated areas to regions with normal V′/Q′, most probably resulting from alveolar recruitment in previously atelectatic, but healthy and well-perfused alveoli (Lamm, 1994). Interestingly, in some studies, the improvement in oxygenation was partially maintained even when the patients were repositioned supine (Langer, 1988 and Gattinoni, 1997). To conclude, redistribution of ventilation (more homogeneous and increased in the dorsal regions), associated with a more uniform distribution of perfusion, seems to be the main cause of the improvement in oxygenation seen in the prone position. The improvement can be maintained even when patients are repositioned supine.

Extracorporeal membrane oxygenation and high-frequency oscillatory ventilation for ARDS

Extracorporeal membrane oxygenation (ECMO) is a therapy that has been used in severe cases of ARDS when patients fail to improve with traditional management. Major technological improvements in ECMO machines and the positive results of the conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial (Peek, 2009), have reignited interest in veno-venous ECMO in patients with severe ARDS. Recent literature shows varying mortality rates for the use of ECMO for ARDS. Although transfer of patients to an ECMO center for treatment using specific criteria and indications may improve outcomes, credible evidence supporting a mortality benefit of ECMO is lacking. Further research is needed regarding the timing of the initiation of ECMO, the standardization of therapy and monitoring, and understanding which type of ECMO reduces morbidity and mortality rates in patients with ARDS.

Conclusions

In conclusion, PP reduced mortality among patients with severe ARDS and patients receiving relatively high PEEP levels. In spite of the remarkable advancements in the understanding of ARDS pathogenesis, the only effective therapeutic measure to decrease mortality is low-tidal volume mechanical ventilation and prone ventilation for severe ARDS cases. In extreme, life-threatening cases, ECMO seems to serve as a bridge to recovery and enables lung-protective ventilation. There is now a large body of evidence supporting the fact that prone positioning decreases mortality rate in patients with severe ARDS. Accordingly, prone positioning should be used as a first-line therapy. Moreover, long-term PP improved the survival of ARDS patients.

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