Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Optimizing Mechanical Ventilation in Refractory ARDS

Nicolas Terzi, Médecine Intensive Réanimation, CHU Grenoble-Alpes, Grenoble, France; Université de Grenoble-Alpes, Grenoble, France; and HP2 INSERM 1042, Grenoble, France

Claude Guérin, Médecine Intensive Réanimation, CHU Lyon, Medical ICU, University Hospital of Lyon, Lyon, France; University of Lyon, Lyon, France; and INSERM 955, Créteil, France

© 2022 Elsevier Ltd. All rights reserved.

Introduction

In this review, we will define refractory acute respiratory distress syndrome (ARDS) as a refractory hypoxemia occurring in ARDS patients. Although ARDS is defined from the Berlin criteria (Ranieri et al., 2012) as PaO2/FIO2 ratio ≤ 300 mmHg at positive end-expiratory pressure (PEEP) ≥ 5 cmH2O, the definition of refractory hypoxemia is not unique in the literature. In this review, we will use PaO2 < 60 mmHg with an FIO2 of 1, and hence as a sustained PaO2/FIO2 ratio < 60 mmHg, to define refractory hypoxemia in ARDS. This definition has been used in a recent prospective observational study (Duan et al., 2017). Furthermore, we will deal with ARDS patients receiving invasive mechanical ventilation. Defining refractory ARDS from severity of hypoxemia is obviously too simple as important pathophysiologic findings are missed, like the amount of non-aerated tissue or the nature of lung inflammation. In the future, better definition refractory ARDS would include additional assessment, like lung imaging (Bellani et al., 2017) and biomarkers (Jabaudon et al., 2018).

When ARDS accounts for 10% of all intensive care unit (ICU) admissions (Bellani et al., 2016), refractory hypoxemia has been found to occur in 21% of ARDS (Duan et al., 2017). In this study the mortality in patients with refractory hypoxemia was 60.1% versus 49.1% in severe ARDS (PaO2/FIO2 < 100 mmHg) and 33.3% in moderate ARDS (PaO2/FIO2 ≤ 200 mmHg) (Duan et al., 2017). Therefore, refractory hypoxemia is a significant clinical problem.

This review primarily intends to focus on the optimization of conventional mechanical ventilation, and also to include some adjunct treatments during refractory hypoxemia in ARDS. We will not cover extracorporeal membrane oxygenation. It is assumed, from the very onset, that a complete check-up has been done to rule out causes of refractory hypoxemia that need specific management, like acute pulmonary embolism, patent foramen ovale, pneumothorax, or massive fluid overload. Beyond the scope of this review is the indication of specific medication (steroids or other immunosuppressive drugs) in case of immunologic underlying cause of ARDS (Guerin et al., 2015, Aublanc et al., 2017).

Optimization of Ventilator Settings During Conventional Mechanical Ventilation

Conventional mechanical ventilation is the mechanical ventilation delivered by an ICU ventilator set in volume- or-pressure controlled mode. Provided that tidal volume (VT) and positive end expiratory pressure (PEEP) are similar both modes are equivalent in terms of respiratory mechanics and oxygenation (Lessard et al., 1994). Trials comparing them found that outcome was not different (Rittayamai et al., 2015). Therefore, we will deal with the ventilator settings in volume-controlled mode. The primary target of the optimization process is to simultaneously protect the lung by preventing ventilator-induced lung injury (VILI) and provide safe oxygenation. For the first objective, VILI can be prevented by reduced the lung stress and strain (Chiumello et al., 2008). For the second objective, it is worth noticing that safe oxygenation threshold is largely unknown. The 55–80 mmHg PaO2 range was used in a large number of studies following the landmark ARMA trial that introduced it (ARDSnet, 2000).
Tidal Volume

VT is the primary factor that contributes to VILI (Slutsky and Ranieri, 2013). Use of low VT, around 6 mL/kg predicted body weight (PBW), is strongly recommended in any ARDS patient (ARDSnet, 2000; Fan et al., 2017). PBW is computed from body height and is equal to 0.91 (height in cm—152.4) (ARDSnet, 2000). The value is multiplied by 50 for men and 45.5 for women. In clinical practice, the VT set in ARDS patients averaged 7.6 mL/kg PBW (Bellani et al., 2016), and more importantly, was not different across ARDS stages. In the landmark ARMA trial the goal in the lower VT group was to set VT to 6 mL/kg PBW and to maintain the end-inspiratory elastic recoil pressure of the respiratory system, the so-called plateau pressure (Pplat), equal to or lower than 30 cmH2O (ARDSnet, 2000). VT could be lowered further to 4 mL/kg PBW if Pplat exceeded this value provided pH was above 7.15.

Ideally, the size of VT should be adjusted according to the size of the baby lung to prevent tidal overinflation (Terragni et al., 2007). In ARDS with refractory hypoxemia it is highly likely that the size of the baby lung is markedly reduced making the use of low VT highly relevant and, hence VT lower than 6 mL/kg PBW can even be used. The gold standard for assessing baby lung size is lung CT. However, for obvious practical reasons VT cannot be tailored according to CT on a daily basis. Therefore, assessing the size of baby lung at the bedside should be done by using other tools. As mentioned above, VT could be titrated to reduce lung stress and strain. Lung strain is the amount of lung deformation at the end of inspiration due to the inflation of VT above the functional residual capacity (FRC). Even though there is no clear harmful threshold of strain, any strain that would make the end-inspiratory lung volume close to the total lung capacity (TLC) is harmful. A strain of two corresponds to a doubling of FRC and could be an upper safety limit (Caironi et al., 2009; Protti et al., 2011). This approach is limited by the need to measure FRC and tidal recruitment and by the difference between static and dynamic strain. Static strain is due to PEEP whilst dynamic strain is the change in lung volume above aerated lung. Dynamic strain may be more harmful than static strain (Protti et al., 2013). Strain can be assessed indirectly by computing the driving pressure (DP), which is the difference between Pplat and PEEP. Indeed, since DP is the ratio of VT to compliance of the respiratory system (Crs) and that Crs correlates with the size of baby lung (Gattinoni et al., 1987), DP is an indirect reflection of strain. DP was the strongest predictor of mortality and the mediator of the effects of VT and PEEP in ARDS (Amato et al., 2015). A threshold in the vicinity of 15 cmH2O has been suggested above which the relative risk of mortality significantly increased (Amato et al., 2015). There is, however, no recommendation to titrate VT based on DP to maintain below this value. The shortcomings of this approach are that lung protection can be obtained independently on DP (Tojo et al., 2018; Samary et al., 2015) and different values of DP can result from using total PEEP instead of PEEP or earlier Pplat measurement within the zero flow period after insufflation of VT (Mezidi et al., 2016). VT can be titrated to reduce the lung stress. Lung stress is the trans-pulmonary end-inspiratory pressure (PLie) that results from lung strain. There are two methods to measure lung stress based on the measurement of esophageal pressure (Pes), an estimate of pleural pressure, at end-inspiration and zero flow (Pes,ei), i.e., in static conditions (Fig. 1). The first is the absolute method (PLie, ABS = Pplat – Pes,ei) and the second the elastance derived method (PLie, ER = Pplat × EL/Ers) where EL and Ers are lung and total respiratory system elastance (Ers = 1/Crs). The difference in PLie between the two methods can be substantial due to differences in chest wall elastance (Ecw) across patients (Gattinoni et al., 1998;
that P_L,ee was frequently negative in ARDS (Talmor et al., 2006). Talmor and colleagues proposed to maintain P_L,ee above 20 cmH₂O (Gattinoni et al., 1993; Pelosi et al., 1994). Three large trials comparing low (around 9 cmH₂O) and high (around 15 cmH₂O) levels of PEEP have been conducted, each reporting an advantage of high PEEP over low PEEP in terms of improving patient outcome (Goligher et al., 2014). In the Lung Safe study the average PEEP was 10 cmH₂O in severe ARDS and more importantly was not different from that in the moderate group (Bellani et al., 2016). This indicates that clinicians managed hypoxemia primarily by increasing FIO₂ as it averaged 0.90 in this group.

Among the several other strategies to set PEEP than the two discussed above (Gattinoni et al., 2017), one based on the measurement of P_{es} and calculation of end-expiratory PL (P_L,ee) in static conditions is particularly useful (Fig. 2). Stemming from the observation that P_L,ee was frequently negative in ARDS (Talmor et al., 2006). Talmor and colleagues proposed to maintain P_L,ee above 0 cmH₂O assuming that this would keep some lung regions open (Talmor et al., 2008). They found that keeping P_L,ee positive with the P_{es} strategy resulted in better oxygenation and Crs and improved patient outcome in ARDS patients with an indirect lung injury (Talmor et al., 2008). In this study PEEP was higher than that in the control group (a PEEP/FIO₂ table) by 7 cmH₂O. In the second strategy, from VT set at 6 mL/kg PBW PEEP was 5–9 cmH₂O in the low PEEP group and titrated to reach 28 cmH₂O P_{plat}. FIO₂ was set according to the same oxygenation target as in the two previous trials. With this strategy higher PEEP was beneficial to patient outcome only if DP goes down (Amato et al., 2015). Beyond the role of the level of PEEP per se a secondary analysis of the three trials found that the response to PEEP in terms of oxygenation was associated with improved patient outcome (Goligher et al., 2014). In the Lung Safe study the average PEEP was 10 cmH₂O in severe ARDS and more importantly was not different from that in the moderate group (Bellani et al., 2016). This indicates that clinicians managed hypoxemia primarily by increasing FIO₂ as it averaged 0.90 in this group.

Positive End-Expiratory Pressure

As already mentioned PEEP of at least 5 cmH₂O is mandatory in the Berlin definition for making the diagnosis of ARDS. However, higher PEEP can be required to counterbalance the superimposed pressure due to the increased lung weight in ARDS (Cressoni et al., 2014; Gattinoni et al., 1993; Pelosi et al., 1994). Three large trials comparing low (around 9 cmH₂O) and high (around 15 cmH₂O) levels of PEEP in patients with acute lung injury/ARDS, with VT around 6 mL/kg PBW in each group, found no difference in mortality between groups (Mercat et al., 2008; Meade et al., 2008; Brower et al., 2004). The meta-analysis of these trials at the individual patient level found a slight (5%) but statistically significant reduction in absolute mortality in the high PEEP group in ARDS patients (PaO₂/FIO₂ < 200 mmHg regardless PEEP) (Briel et al., 2010). Two strategies of PEEP selection were used in these trials. One is a PEEP/FIO₂ table in two trials (Brower et al., 2004; Meade et al., 2008), the other is an augmented recruitment strategy (Mercat et al., 2008). In the first strategy, PEEP and FIO₂ were set concurrently for one group to receive high PEEP and low FIO₂ and the opposite combination for the other group. Oxygenation target was similar in both groups with PaO₂ in the range 55–80 mmHg. In the second strategy, from VT set at 6 mL/kg PBW PEEP was 5–9 cmH₂O in the low PEEP group and titrated to reach 28 cmH₂O P_{plat}. FIO₂ was set according to the same oxygenation target as in the two previous trials. With this strategy PEEP level is dependent on Crs and potential of tidal recruitment but patients were not stratified accordingly. According to Amato et al., higher PEEP is beneficial to patient outcome only if DP goes down (Amato et al., 2015). Beyond the role of the level of PEEP per se a secondary analysis of the three trials found that the response to PEEP in terms of oxygenation was associated with improved patient outcome (Goligher et al., 2014). In the Lung Safe study the average PEEP was 10 cmH₂O in severe ARDS and more importantly was not different from that in the moderate group (Bellani et al., 2016). This indicates that clinicians managed hypoxemia primarily by increasing FIO₂ as it averaged 0.90 in this group.

In conclusion, in refractory ARDS VT should be set initially at 6 mL/kg PBW and confronted to a measurement of P_{plat}, which should be maintained equal to or lower than 30 cmH₂O. VT can be further declined to lower value in order to keep P_{plat} at this value. Systematically setting VT to 4 mL/kg PBW in any ARDS patient with refractory hypoxemia is an open issue. The size of VT is tightly linked to the amount of PEEP.
Recruitment Maneuvers

Recruitment maneuvers (RM) is a method that aims at voluntary increase intrans-pulmonary pressure (PL) and transpulmonary plateau pressure (Pplat) by increasing airway pressure from the ICU ventilator (Guerin et al., 2011). Practice of RM follows the concept of "open the lung and keep it open" (Lachmann, 1992), and as such, is tightly linked with use of PEEP, which should be greater after than before the RM (Suzumura et al., 2016). To open the lung the airway pressure must surpass lung critical closing pressure and to maintain it open it has to be greater than lung critical closing pressure (Crotti et al., 2001). The amount of airway pressure to deliver during RM depends on these critical pressures and there is some discrepant results regarding them (Gattinoni et al., 2006; Borges et al., 2006a,b). Furthermore, the key pressure is PL and not airway pressure (Grasso et al., 2002). There are different methods to perform RM, such as sighs (Pelosi et al., 1999), sustained inflation (Lapinsky et al., 1999), extended sighs (Lim et al., 2001) and maximal recruitment strategy (Borges et al., 2006a,b) and their effects to the lung are not the same (Badet et al., 2009; Constantin et al., 2010; Grasso et al., 2009). For a given RM there are specific considerations to take into account. By stimulating the production of surfactant by pneumocytes II sighs can promote lung recruitment by preventing alveolar collapse (Albert, 2012). However, the rate and pressure of sighs delivery are critical to reach this goal (Steimback et al., 2009). Sustained inflation delivers a target pressure during a certain period of time, usually 40 cmH2O for 30–40 s. However, the maximal gain in lung recruitment is obtained after a few seconds and the remaining time under RM is spent for the harms (Arnal et al., 2011). The whole picture of the benefits (lung recruitment, lung homogenization, VILI prevention, improvement in gas exchange) and risks (hemodynamic impairment, volutrauma) must be well balanced (Constantin et al., 2017). Recently, the amount of recruited lung tissue measured by the CT scan was found markedly different depending on the ARDS severity stage (Cressoni et al., 2017). When airway pressure is increased from 27 to 40 cmH2O recruited lung mass is nil in mild ARDS and slight in moderate ARDS (Cressoni et al., 2017). By contrast, patients with severe ARDS had a large increase in lung recruitment. A conventional meta-analysis found a positive signal on mortality favoring RM (Suzumura et al., 2014). However, this study was limited by the small sample size in trials, the lack of large trial in which RM was the real intervention tested against a control group, the heterogeneity of RM and the lack of high quality trials. The OLA trial was included in this meta-analysis (Kacmarek et al., 2016). Done over 200 ARDS patients it found a higher, but not statistically significant survival in the open lung approach (sustained inflation) as compared to a control group that received lung protective ventilation (Kacmarek et al., 2016). More recently the ART trial compared a maximal recruitment strategy to a control group (Cavalcanti et al., 2017). The maximal recruitment strategy included the use of PEEP up to 45 cmH2O under pressure controlled ventilation with fixed DP to 15 cmH2O, followed by a decremental PEEP trial that allowed the selection of PEEP based on the best Crs. The average PEEP in the maximal strategy group one hour after inclusion was 16 cmH2O vs. 13 cmH2O in the control group. The maximal recruitment strategy group resulted in significantly higher mortality at day 28 (primary end-point).
presumably due to barotrauma and shock, amounting to 55.3% vs. 49.3% in the control group ($P = 0.041$). Surprisingly, the experts made a conditional recommendation for RM (Fan et al., 2017) but this was made before the publication of the ART trial.

To conclude, RM could be used in refractory ARDS with caution, on a case-by-case basis, but must avoid higher PEEP and include a close monitoring of both oxygenation response (to not repeat if nonresponsive) and hemodynamic condition.

**Apparatus Dead Space and Respiratory Rate**

Physiologic dead space, the sum of apparatus, anatomic and alveolar dead space, is markedly increased in ARDS patients as a result from higher alveolar dead space due to microthrombi in the lung vasculature and alveolar overdistension stretching the alveolar vessels. It is a marker of poor outcome (Nuckton et al., 2002). High alveolar dead space and lower VT contribute to hypercapnia and respiratory acidosis. Reducing apparatus dead space is a simple method to reduce the physiologic dead space and increase the $CO_2$ washout. This can be done by using heated-humidifier and connecting endotracheal tube as close as possible to the Y piece of the ventilator circuit. Then, the increase in respiratory rate would be more efficient to remove $CO_2$. The risk of increasing respiratory rate is to promote intrinsic PEEP and to increase mechanical power. The ARMA trial protocol planned a 6–35 breaths/min set respiratory rate window. At day 1, respiratory rate was $29 \pm 7$ breaths/min in the lower VT group vs. $16 \pm 6$ in the higher VT group, on average. As patients could breathe spontaneously higher total rate would be expected. The rationale of increasing respiratory rate is that hypercapnia is harmful. Even hypercapnia may not be dangerous and may even protect the lung (Kavanagh, 2002; Laffey et al., 2000, 2003, 2004), recent observational data suggest that it is associated with poor outcome (Nin et al., 2017). Actually, the variable to be used to set the respiratory rate should be the plasma pH rather than the $PaCO_2$ per se. In the ARMA trial and further studies (Mercat et al., 2008) the range of pH that should target the above respiratory rate window was 7.30–7.45. A lower safety threshold of 7.20 plasma pH was used in recent trials in ARDS (Guerin et al., 2013; Papazian et al., 2010). The ARMA trial protocol allowed to increase VT up to 8 mL/kg PBW if pH was as low as 7.15 provided Pplat remained in the safe range.

To conclude, apparatus dead space should be minimized and respiratory rate adjusted to maintain plasma pH $\geq 7.20$.

**Inspiratory Flow Rate**

In volume-controlled mode mean inspiratory flow should be set directly in most of current ICU ventilators. If inspiratory flow is square shaped the mean inspiratory flow is constantly delivered during the insufflation phase. If a decelerating inspiratory flow pattern is used in volume-controlled mode, the mean flow is reached at the time of mid-insufflation. A period of zero flow after the insufflation phase may result from the selection of inspiratory flow rate, respiratory rate and inspiratory time. It can be taken advantage of to monitor Pplat breath by breath. The common range of set inspiratory flow rate is between 30 and 60 L/min but is not evidence-based. With the new concept of mechanical power this setting should receive more attention.

**High Frequency Oscillation Ventilation**

High frequency oscillation ventilation (HFOV) is not a form of conventional mechanical ventilation as it requires a specific device. The rationale for using HFO in ARDS patients, which was attractive, was that it delivered very low VT at high respiratory rate that would promote and maintain lung recruitment. Therefore, HFOV was thought as acting at both sides of the VILI. Recent trials were disappointing showing that HFOV was either harmful or neutral to patient outcome in adult patients with ARDS. The primary reason for these negative results was thought in the hemodynamic compromise due to excessive mean airway pressure. It could be that HFOV increased the mechanical power.

Therefore, HFOV should not be recommended in adult patients with ARDS (Goligher et al., 2017).

**Adjunct Treatments**

Three adjunct therapies, which are not mechanical ventilation per se, are worth mentioning in the management of refractory ARDS, namely pharmacologic neuromuscular blockade (NMB), prone position (PP) and inhaled nitric oxide (NOI).

**Pharmacologic Neuromuscular Blockade**

The continuous IV infusion of NMB as compared to placebo has been shown to improve oxygenation (Gainnier et al., 2004), reduce lung and systemic inflammation (Forel et al., 2006) and eventually improve survival (Papazian et al., 2010) when used early, for 48 h, in ARDS with $PaO_2/FIO_2$ ratio $< 150$ mmHg. Patients with $PaO_2/FIO_2$ ratio $< 120$ mmHg had the most important benefit in terms of survival. The rate of pneumothorax was lower than in the placebo group and muscular weakness was similar in both groups at 3 months (Papazian et al., 2010). Mechanisms of action may include reduction in regional P, ei, reduction of asynchronies in particular double triggering, reduction in expiratory respiratory muscles activity, which would decrease end-expiratory lung volume (Slutsky, 2010). Double triggering may make a patient receiving VT twice higher than set by the caregiver, and hence at risk of volutrauma. Double triggering may stem from a very peculiar kind of asynchrony, i.e., reverse triggering (Akoumi, 2013; Yonis et al., 2015). With reverse triggering followed by double triggering a patient is going to receive twice VT even though he/
she is doing no effort. NMB is the treatment of choice in this situation. Therefore, NMB should be recommended in this specific setting of ARDS. A large RCT to reassess NMB is ongoing in the US (NCT02509078).

**Prone Position**

Delivering mechanical ventilation in the prone position (PP) in refractory ARDS is evidence-based in ARDS patients with moderate to severe ARDS (Cattinoni et al., 2010; Guerin et al., 2013). PP can improve oxygenation, sometimes dramatically, and does this by recruiting dependent dorsal lung regions that continue to receive most of the pulmonary perfusion. It can also homogenize the distribution of ventilation and perfusion throughout the lung. Furthermore PP contributes to protect the lung from VILI by homogenization of lung stress and strain and lowering inflammation. Hemodynamic also get improved or stabilized in PP. From the supine position, PP increases chest wall elastance (Est,cw), which reduces right ventricle preload. Increase in Est,cw results in decrease in PL,ei, which reduces right ventricle afterload. The right ventricle performs better and becomes sensitive to preload dependence, which can be increased by the higher abdominal pressure in PP. All these physiologic benefits translated into better survival. Experts made a strong recommendation to prone ARDS patient if PaO2/FIO2 < 100 mmHg (Fan et al., 2017). Others (Alessandri et al., 2018) advised using PP in ARDS patients with PaO2/FIO2 < 150 mmHg according to the Proseva trial (Guerin et al., 2013). In this trial mortality as low as 6.8% in the PP group vs. 30% in the supine group was observed in the 105–124 mmHg PaO2/FIO2 ratio quartile at the time of randomization. In practice the rate of use of PP has been found as low as 13.4% in severe ARDS patients in the Lung safe study (Bellani et al., 2016). This rate was higher in a more recent study, amounting to 32% (Guerin et al., 2018). In another recent study the rate of use of PP was 10% over all the patients and stepped up to 23.8% once these patients met the criterion of refractory hypoxemia (Duan et al., 2017). When used PP should be planned for long sessions, at least 16 h. The response to the first PP session in one trial in terms of gas exchange did not correlate to survival (Albert et al., 2014). Therefore, PP should be continued regardless oxygenation response.

In conclusion PP should be used in refractory ARDS.

**Spontaneous Breathing: Is There a Place in Refractory ARDS?**

Maintaining spontaneous respiratory efforts during mechanical ventilation has long been recognized to improve oxygenation, and because oxygenation is a key target in patient management, such efforts may seem beneficial. Also disuse and loss of peripheral muscles and diaphragmatic function are increasingly recognized, and thus spontaneous breathing may confer additional advantage (Jaber et al., 2011).

Recently, in mechanically ventilated rabbits Yoshida et al. (2012, 2013) demonstrated that vigorous spontaneous effort did not change Pplat but did worsen injury. In a clinical study, strong spontaneous effort can injure not only the lung but also the diaphragm (Goligher et al., 2015).

The mechanisms whereby spontaneous breathing (SB) may worsen lung injury are complex and manifold: generation of substantial negative pleural pressures, generation of pendelluft phenomenon, increased lung perfusion, increase of patient-ventilator asynchrony and expiratory muscles (de Vries et al., 2018).

Even if SB is common in patients with ARDS during the first 48 h of mechanical ventilation (van Haren et al., 2019) without negative impact on outcomes further prospective studies incorporating the magnitude of inspiratory effort and adjusting for all potential severity confounders are required.

To conclude, SB should not be used in refractory ARDS.

**Conclusions**

Optimization of mechanical ventilation during refractory ARDS requires precise management. It includes low VT and high PEEP to maintain plateau pressure below 30 cmH2O. Measuring and monitoring trans-pulmonary pressure allows the intensivist assessing the lung stress and further optimizing VT and PEE levels. Neuromuscular blockade is recommended in addition to sedation. Use of PP for long sessions should be done early.

**References**

Akoumianaki, E., Lyazidi, A., Rey, N., Matamis, D., Perez-Martinez, N., Giraud, R., Mancebo, J., Brochard, L., Marie Richard, J.C., 2013. Mechanical ventilation-induced reverse-triggered breaths: A frequently unrecognized form of neuromechanical coupling. Chest 143, 927–938.

Albert, R.K., 2012. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine 185, 702–708.

Albert, R.K., Keniston, A., Baboi, L., Ayaz, L., Guerin, C., 2014. Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine 189, 494–496.

Alessandri, F., Fugliose, F., Ranieri, V.M., 2018. The role of rescue therapies in the treatment of severe ARDS. Respiratory Care 63, 92–101.
