Optimizing Mechanical Ventilation in Refractory ARDS

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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 PaO_2/FIO_2 ratio ≤ 300 mmHg at positive end-expiratory pressure (PEEP) ≥ 5 cmH_2O, the definition of refractory hypoxemia is not unique in the literature. In this review, we will use $PaO_2 < 60$ mmHg with an FIO_2 of 1, and hence as a sustained PaO_2/FIO_2 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 ($PaO_2/FIO_2 < 100$ mmHg) and 33.3% in moderate ARDS ($PaO_2/FIO_2 \leq 200$ 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).

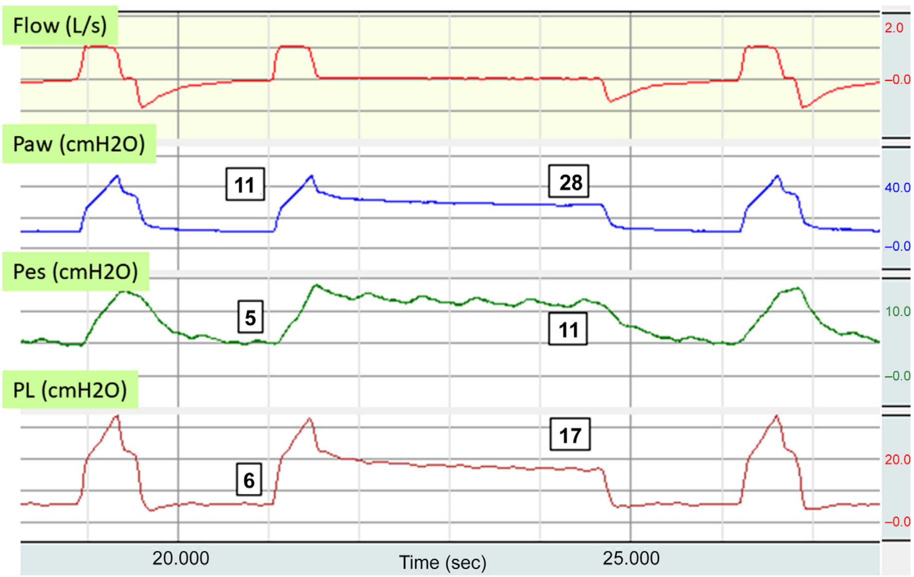
Optimization of Ventilator Settings During Conventional Mechanical Ventilation

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 PaO_2 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 cmH_2O (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 cmH_2O 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 (PL,ei) 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 (PL,ei_ABS = Pplat−Pes,ei) and the second the elastance derived method (PL,ei_ER = Pplat × EL/Ers) where EL and Ers are lung and total respiratory system elastance (Ers = 1/Crs). The difference in PL,ei between the two methods can be substantial due to differences in chest wall elastance (Ecw) across patients (Gattinoni et al., 1998;



$$Ers = \frac{(28-11)}{0.42} = 40\ cmH2O/L \qquad E_L = \frac{(28-11)-(11-5)}{0.42} = 26\ cmH2O/L \qquad \frac{E_L}{E_{rs}} = 0.65$$

Fig. 1 Lung CT scan in a patient with ARDS showing a massive loss of aeration due to bilateral consolidation. The size of the baby lung on this slide is very small (upper left handside).

Chiumello et al., 2008). There is, however, no clear threshold of PL,ei to recommend to date, as values as different as 15 cmH_2O (Gattinoni et al., 2003) and 27 cmH_2O (Chiumello et al., 2008) are mentioned in the literature. It is worth noticing that PL,ei may inform on regional lung stress as PL,ei_ABS correlated with dependent lung stress and PL,ei_ER with non-dependent lung stress when PL,ei was computed by using a direct measurement of pleural pressure in experimental acute lung injury in pigs (Yoshida et al., 2018). The most recent concept of VILI involves the transfer of mechanical power from the ventilator to the lung (Gattinoni et al., 2016). VT is the main component of mechanical power, which increases exponentially with higher VT. A threshold of mechanical power of 22 J/min has been shown harmful in animals with normal lungs and injured with combinations of VT, PEEP, and respiratory rate (RR) (Cressoni et al., 2016). However, there is no current recommendation to titrate VT from mechanical power.

It is worth mentioning that even though VT is carefully lowered patients may receive twice set VT in case of double triggering or of reverse triggering (Akoumianaki et al., 2013). Double triggering can be treated by increasing insufflation time or increasing inspiratory flow (Chanques et al., 2013). Reverse triggering should be treated by neuromuscular blockade if it is followed by double triggering.

Finally, two technical remarks relevant to the accuracy of VT delivery should be mentioned. The compensation for circuit compliance must be activated at the time of ventilator checking (Lyazidi et al., 2010). The caregiver should select the appropriate expression of gas volume measurement (ATPD, BTPS) (Moro et al., 2018).

In conclusion, in refractory ARDS VT should be set initially at 6 mL/kg PBW and confronted to a measurement of Pplat, which should be maintained equal to or lower than 30 cmH_2O. VT can be further declined to lower value in order to keep Pplat 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.

Positive End-Expiratory Pressure

As already mentioned PEEP of at least 5 cmH_2O 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 cmH_2O) and high (around 15 cmH_2O) 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 ($PaO_2/FIO_2 < 200$ mmHg regardless PEEP) (Briel et al., 2010). Two strategies of PEEP selection were used in these trials. One is a PEEP/FIO_2 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 FIO_2 were set concurrently for one group to receive high PEEP and low FIO_2 and the opposite combination for the other group. Oxygenation target was similar in both groups with PaO_2 in the range 55–80 mmHg. In the second strategy, from VT set at 6 mL/kg PBW PEEP was 5–9 cmH_2O in the low PEEP group and titrated to reach 28 cmH_2O Pplat. FIO_2 was set according to the same oxygenation target as in the two previous trials. With to 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 cmH_2O 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 FIO_2 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 Pes and calculation of end-expiratory PL (PL,ee) in static conditions is particularly (**Fig. 2**). Stemming from the observation that PL,ee was frequently negative in ARDS (Talmor et al., 2006) Talmor and colleagues proposed to maintain PL,ee above 0 cmH_2O assuming that this would keep some lung regions open (Talmor et al., 2008). They found that keeping PL,ee positive with the Pes 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/FIO_2 table) by 7 cmH_2O or nearly so. In a recent study on ARDS patients with mostly primary ARDS we found that negative PL,ee was less frequent than in the previous study and that, on average, PEEP was higher than the PEEP/FIO_2 table by 2 cmH_2O. However, the Pes strategy allowed adjusting PEEP patient by patient. An interesting observational study suggested that Pes-guided PEEP should be considered in the setting of refractory ARDS (Grasso et al., 2012). Patients referred to ECMO for severe ARDS were subdivided between those with PL,ei equal to or higher 25 cmH_2O and those with PL,ei lower, with seven patients falling in each group. The patients with PL,ei equal to or higher than 25 cmH_2O were therefore optimized in terms of mechanical ventilation and moved to ECMO. In the remaining 7 PEEP was further increased from 18 to 22 cmH_2O in order to make PL,ei of 25 cmH_2O. This resulted in a marked increase in PaO_2/FIO_2 preventing them to undergo ECMO. In these latter patients, chest wall elastance (Est,cw) was impaired and some of PEEP and Pplat dissipated into the chest wall.

Another method to titrate PEEP at the patient level is the use of electrical impedance tomography (Zhao et al., 2010) but it is less available in the clinical field than the Pes.

To conclude, in refractory ARDS PEEP should be high, with high meaning values above 12 cmH_2O, the primary goal being still to maintain Pplat below 30 cmH_2O. Experts made a conditional recommendation of higher rather than lower PEEP in patients with

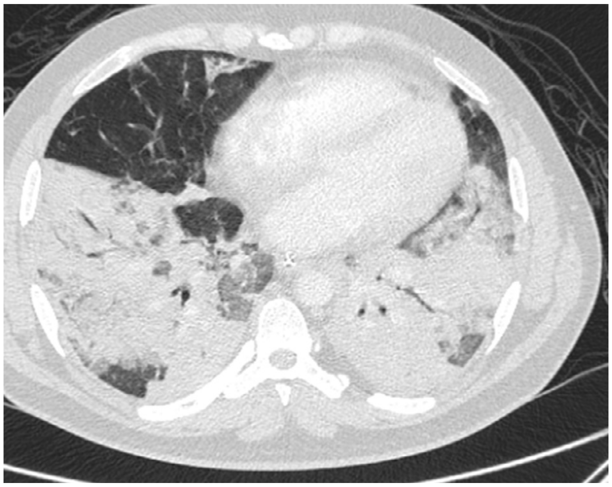


Fig. 2 Respiratory mechanics measured at the bedside in a patient with ARDS receiving invasive mechanical ventilation in volume-controlled mode at constant flow inflation with a tidal volume of 0.42 L. From top to bottom, signals of flow, airway pressure (Paw), esophageal pressure (Pes) and transpulmonary pressure (PL) against time. After one baseline breath the airways are occluded at the end of inspiration for 5 s. This allows measuring plateau pressure for the respiratory system, chest wall and lung, which amounted to 28, 11 and 17 cmH_2O, respectively. This latter value of trans-pulmonary pressure was obtained with the absolute method. The corresponding values of end-expiratory pressure were 11, 5, and 6 cmH_2O. The lung elastance (EL) and respiratory system elastance (Ers) were computed and their ratio multiplied by the plateau pressure of respiratory system gave 18.2 cmH_2O trans-pulmonary plateau pressure with the elastance method.

moderate to severe ARDS (Fan et al., 2017). The Pes-guided PEEP strategy should be considered making of PL,e and PL,ei the new targets and setting up Pplat above 30 cmH_2O.

Recruitment Maneuvers

Recruitment maneuvers (RM) is a method that aims at voluntary increase Pplat and PL,ei well above the recommended upper safety limits discussed previously by increasing airway pressure from the ICU ventilator (Guerin et al., 2011). Practice of RM follows the concept of "open the lung and keeping 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., 2006b) and their effects to the lung are not the same (Badet et al., 2009; Constantin et al., 2008). The direct or indirect nature of ARDS also influences the impact of RM (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 cmH_2O 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 cmH_2O 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 cmH_2O under pressure controlled ventilation with fixed DP to 15 cmH_2O, 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 cmH_2O vs. 13 cmH_2O 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 ± 7 breaths/min in the lower VT group vs. 16 ± 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 ≥ 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 PL,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 (Akoumianaki et al., 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 (Gattinoni 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 $PaO_2/FIO_2 < 100$ mmHg (Fan et al., 2017). Others (Alessandri et al., 2018) advised using PP in ARDS patients with $PaO_2/FIO_2 < 150$ 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 PaO_2/FIO_2 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 cmH_2O. 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.

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