Recent advances in mechanical ventilation in patients with acute respiratory distress syndrome

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ABSTRACT Acute respiratory distress syndrome (ARDS) is characterised by different degrees of severity and different stages. Understanding these differences can help to better adapt the ventilatory settings to protect the lung from ventilator-induced lung injury by reducing hyperinflation or keeping the lung open when it is possible. The same therapies may be useful and beneficial in certain forms of ARDS, and risky or harmful at other stages: this includes high positive end-expiratory pressure, allowance of spontaneous breathing activity or use of noninvasive ventilation. The severity of the disease is the primary indicator to individualise treatment. Monitoring tools such as oesophageal pressure or lung volume measurements may also help to set the ventilator. At an earlier stage, an adequate lung protective strategy may also help to prevent the development of ARDS.

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Introduction

Mechanical ventilation is a cornerstone in the management of patients with acute respiratory distress syndrome (ARDS). We now know that mechanical ventilation *per se* can aggravate lung injury, a process referred to as ventilator-induced lung injury (VILI), through several mechanisms including volutrauma, barotrauma and biotrauma [1–4]. Dynamic lung distension and repeated opening and closing of recruitable lung units are considered the two main mechanisms contributing to lung injury. The lung protective ventilation strategy using low tidal volume and limiting plateau pressure (P_{plat}) has been proven to improve survival in patients with ARDS in a large randomised controlled study and was confirmed in a

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meta-analysis [5, 6]. Current research still suggests that further reducing ventilator-associated or -induced lung injury is the main avenue to further reduce mortality in this syndrome.

For a clinician in 2015, the main consequences of making the diagnosis of ARDS concern the supportive therapy he or she will apply to the patient. The clinician is essentially managing the consequences of ARDS. These result from three major physiological derangements: 1) a major defect in oxygenation; 2) a poor efficiency of the lungs at eliminating CO_2; and 3) a major reduction in lung volumes and compliance making ARDS a severe restrictive lung disease. For each component the key issue in daily management is the price to pay to improve the physiological consequences of these problems [5]. It took many years to realise that the price of normalising physiological parameters was often unacceptably high and to put the problem of VILI central to our clinical approach [7]. Thus, evaluating the three components is essential since the management strategy may be based on this assessment: 1) assessment of gas exchange and oxygenation, which includes the influence of haemodynamics or intracardiac shunt; 2) dead space, which can be assessed grossly by calculating the "corrected" level of minute ventilation that would be needed for normalising arterial CO_2 tension [8]; and 3) lung volume, assessed indirectly through the decrease in compliance or directly by measuring end-expiratory lung volume [9]. Measurement of oesophageal pressure (P_{oes}) as a surrogate for pleural pressure helps to determine the lung mechanics and separate the effect of the chest wall [10]. In addition, the assessment of lung recruitability may be of great help to individualise the settings for mechanical ventilation and choose the level of positive end-expiratory pressure (PEEP) needed to keep the lung sufficiently open to minimise the risks of repeated opening and closing of alveoli. In addition, we now have better knowledge of what may worsen ARDS and this knowledge has been used to try to prevent the development of ARDS.

An individualisation of therapy is essential since application of the same concepts may be beneficial in certain forms of ARDS or at certain stages, and may be risky or harmful in others. This is the case for spontaneous breathing activity, noninvasive ventilation (NIV) and high PEEP, which we will discuss below.

Preventing ARDS

Early identification of patients at risk for developing ARDS and implementation of preventive strategies becomes an important approach for critically ill patients admitted to intensive care units (ICU), particularly patients receiving mechanical ventilation. ARDS is not frequently present at the time of visiting the emergency room or hospital admission and it frequently occurs over a period of hours to days following the clinical insult [11–14]. Many clinical risk factors are associated with the development of ARDS such as sepsis, shock, pneumonia, pancreatitis, aspiration, high-risk trauma and surgery, and multiple blood transfusions. A large multicentre observation study demonstrated that ARDS develops within a median of 2 days after hospital admission and also markedly increases in-hospital mortality in this patient population [14]. Many patients, therefore, develop ARDS during hospital admission because of a second-hit, but from potentially preventable exposures. AHMED *et al.* [11] demonstrated that inadequate antimicrobial therapy, medical and surgical adverse events, hospital-acquired aspiration, ventilation with high tidal volumes, and greater volumes of blood transfusion and fluid administration were significantly associated with the secondary development of ARDS. Prompt resuscitation to reach the goal within 6 h, early administration of effective antimicrobials, and appropriate source control could help to prevent the development of ARDS. Similarly, optimal fluid and transfusion management (*i.e.* early fluid resuscitation during periods of septic shock and avoiding positive fluid balance after periods of shock) and monitoring of fluid balance, such as extravascular lung water, in mechanically ventilated patients might prevent the development of ARDS.

A lung protective ventilation strategy using low tidal volume and limiting P_{plat} is now proposed in patients with ARDS. Potentially injurious ventilator settings might also be associated with secondary development of ARDS in mechanically ventilated patient without ARDS at the onset. Observational studies demonstrated that high tidal volume and P_{plat} are major risk factors for the secondary development of ARDS [15, 16]. Thus, the lung protective ventilation strategy may also prevent lung injury in mechanically ventilated patients without ARDS. A randomised controlled study comparing low *versus* conventional tidal volumes (6 *versus* 10 mL·kg^{-1} predicted body weight (PBW)) in critically ill patients without acute lung injury at the onset of mechanical ventilation found that the level of systemic inflammatory cytokines decreased significantly in the low tidal volume group and development of lung injury was higher in the conventional tidal volume group (13.5 *versus* 2.6%; p=0.01) [17]. A recent systematic review and meta-analyses suggested that using lower tidal volumes ($\leqslant$6 *versus* $\geqslant$10 mL·kg^{-1} PBW) in patients without ARDS was associated with better clinical outcomes, including development of ARDS, mortality and duration of mechanical ventilation [16]. Strong evidence is still lacking, but it is possible that implementing the lung protective strategy and also applying an appropriate PEEP level may be needed in patients requiring mechanical ventilation in whom it is expected to be required for >48 h.

NIV in ARDS

NIV has been increasingly used in the ICU as a first-line therapy for 15–20% of critically ill patients with acute respiratory failure [18, 19]. NIV has demonstrated survival benefits in specific patient groups including acute exacerbations of chronic obstructive pulmonary disease and acute cardiogenic pulmonary oedema, and for facilitating extubation in hypercapnic respiratory failure. In acute hypoxaemic respiratory failure, a meta-analysis from five randomised studies found that NIV significantly reduced the rate of intubation and also mortality rate [20]. The heterogeneity of diagnoses of hypoxaemic respiratory failure, however, makes it difficult to interpret the benefits of NIV in this patient group, and a specific risk of delaying intubation has also been described in this group [21]. ARDS is one of the most severe forms of hypoxaemic respiratory failure and the role of NIV is still inconclusive. A multicentre, randomised study by DELCLAUX *et al.* [22] comparing continuous positive airway pressure (CPAP) with standard oxygen therapy in 123 patients (83% were patients with acute lung injury) failed to demonstrate any benefit of CPAP in terms of intubation rate, ICU length of stay, and ICU and hospital mortality. In addition, patients receiving NIV developed a higher number of adverse events than standard oxygen therapy. A multicentre cohort study by ANTONELLI *et al.* [23] surveying the use of NIV as first-line therapy for ARDS demonstrated that NIV was followed by intubation in 46% of patients. A high SAPS (Simplified Acute Physiology Score) II score and an arterial O_2 tension (P_{aO_2}) to inspiratory O_2 fraction (F_{iO_2}) ratio ⩽175 after 1 h of NIV were associated with NIV failure and the requirement for endotracheal intubation. A recent observational study by THILLE *et al.* [24] in 113 patients requiring NIV for hypoxaemic respiratory failure (82 patients with ARDS) found that ARDS patients had a significantly higher intubation and ICU mortality rate than non-ARDS patients. P_{aO_2}/F_{iO_2} <150 was associated with a high intubation rate. Thus, the evidence for using NIV in patients with ARDS is limited, and may be discussed probably only in mild-to-moderate ARDS patients (P_{aO_2}/F_{iO_2} >150). The risk of VILI associated with the large tidal volumes favoured by NIV probably exists, although this has not been proven [21]. In addition, close monitoring and prompt intubation in patients without improvement in oxygenation and clinical parameters within the first hour should be considered.

Spontaneous *versus* passive breathing in ARDS

Passive mechanical ventilation in ARDS

The lung protective ventilation strategy is now proposed as standard care for patients presenting with ARDS by using low tidal volume of 6 mL·kg^{-1} PBW and limiting the inspiratory P_{plat} to <28–30 cmH_2O. Implementation of the lung protective ventilation strategy in patients exhibiting high respiratory drive and work of breathing may often lead to development of patient–ventilator dyssynchrony, such as double triggering, despite administration of sedative and analgesic agents [25]. Neuromuscular blocking agents (NMBAs) have been used for decades to correct this problem and can facilitate low tidal volume ventilation. Data from several randomised controlled studies in ARDS demonstrated that 25–55% of patients routinely received a NMBA [26–28]. Concerns about the safety of administration have been raised, especially since we know that diaphragm atrophy can rapidly occur in case of disuse. GAINNIER *et al.* [29] conducted a pilot randomised controlled study by enrolling 56 patients with moderate-to-severe ARDS (P_{aO_2}/F_{iO_2} <150) to receive cisatracurium or placebo for 48 h. They showed that patients in the NMBA group had a sustained improvement in oxygenation and a lower P_{plat} after 48 h of randomisation. A second randomised controlled study by FOREL *et al.* [30] demonstrated the same result associated with a decreased concentration of proinflammatory cytokines (interleukin (IL)-1β, IL-6 and IL-8) in both bronchoalveolar lavage fluid and serum. A larger multicentre randomised controlled trial (the ACURASYS study) by the same group enrolled 340 patients with moderate-to-severe ARDS (P_{aO_2}/F_{iO_2} <150 with PEEP >5 cmH_2O) presenting within 48 h to receive cisatracurium or placebo for 48 h [31]. The early administration of cisatracurium reduced adjusted 90-day mortality and barotrauma, and also increased ventilator free days without increasing muscle weakness (although this was assessed subjectively). In a *post hoc* analysis, the mortality benefit of cisatracurium was limited to patients with a P_{aO_2}/F_{iO_2} ratio <120. The important concern about using NMBAs is the development of ICU-acquired weakness, which led to long-term morbidity in patient with ARDS [32, 33]. The data from both experimental and clinical studies suggest that cisatracurium is not associated with ICU-acquired weakness when used for a short period of time. The mechanisms of NMBAs for improving gas exchange and outcomes are not completely clear [34]. Proposed mechanisms include minimising VILI by minimising the transpulmonary pressure changes during assisted breathing and reducing patient–ventilator asynchrony, decreasing oxygen consumption of respiratory muscles, and reducing pulmonary and systemic inflammation. Thus, NMBAs should be considered for early and short-term use in patients with severe ARDS.

Maintaining spontaneous breathing in ARDS

Complete inactivity of the diaphragm results in disuse atrophy and muscle weakness, referred to as ventilator-induced diaphragmatic dysfunction (VIDD), after as little as 18–24 h of mechanical ventilation [35, 36].

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This can contribute to weaning problems and poorer prognosis. In experimental studies, allowance of spontaneous breathing using either assist-control ventilation or pressure support ventilation can reduce VIDD [37, 38]. The place and timing of spontaneous breathing in patients with ARDS has been debated for several years. Experimental lung injury models of ARDS demonstrated that preserving spontaneous breathing was associated with: 1) reduced markers of lung inflammation and epithelial cell damage; 2) improved tidal ventilation, gas exchange and oxygen delivery; and 3) increased systemic blood flow. NEUMANN *et al.* [39] and PUTENSEN *et al.* [40] demonstrated that partial ventilatory support with airway pressure release ventilation (APRV) promoted alveolar recruitment in juxta-diaphragmatic areas, improved ventilation/perfusion matching and gas exchange, and increased oxygen delivery in comparison with controlled mechanical ventilation. It should be noted that among the studies described above, the study populations had a mild-to-moderate degree of lung injury. The impact of spontaneous breathing in severe ARDS may be completely different and may be harmful. YOSHIDA and co-workers [41, 42] found that spontaneous breathing in a model of severe lung injury caused high transpulmonary pressure, worsened oxygenation and lung damage, and could also cause local injury by internal redistribution of volume. Thus, from the body of evidence, allowance of spontaneous breathing should be limited to mild-to-moderate ARDS. By contrast, early use of NMBAs should be considered in patients with severe ARDS.

One important consideration when a patient with ARDS generates spontaneous breathing efforts is that the real transpulmonary pressure becomes the sum of the pressure generated by the ventilator and by the patient's respiratory muscles. Clinicians should be aware that, when using pressure-targeted modes of ventilation including pressure assist/control ventilation (PACV) and pressure support ventilation, the true driving pressure is higher than the airway pressure (P_{aw}) displayed by the ventilator. This scenario is different from volume-controlled ventilation in which transpulmonary pressure and tidal volume are kept constant irrespective of muscular pressure (fig. 1). In addition, during PACV, when the patient makes a strong effort, transpulmonary pressure and tidal volume increase substantially which may be potentially harmful (fig. 2). In an experimental and clinical study by RICHARD *et al.* [43], nonsynchronised pressure-targeted modes of ventilation, such as APRV, resulted in lower tidal volumes and transpulmonary pressure than fully synchronised and partially synchronised pressure-targeted modes of ventilation, such as PACV and biphasic airway pressure, despite similar pressure settings on the ventilator and the patient's effort. An ongoing large multicentre randomised controlled study (Early Spontaneous Breathing in Acute Respiratory Distress Syndrome (BiRDS) study; ClinicalTrials.gov identifier: NCT01862016) will examine the efficacy and safety of early spontaneous breathing with APRV mode using normal inspiratory to expiratory ratios in comparison with controlled mechanical ventilation. The evidence for new modes of ventilation including proportional assist ventilation and neurally adjusted ventilatory assist, in which the patient selects his/her own tidal volume, and noisy pressure support ventilation, which introduces variability, is limited to experimental or physiological studies and still lack clinical data.

In summary, in severe ARDS complete relaxation of the respiratory muscles may be needed to ensure lung protection, while in less severe forms or at a later stage spontaneous breathing should be allowed with great caution to minimise the risk of amplifying transpulmonary pressure. A nonsynchronised mode may be preferable in this regard.

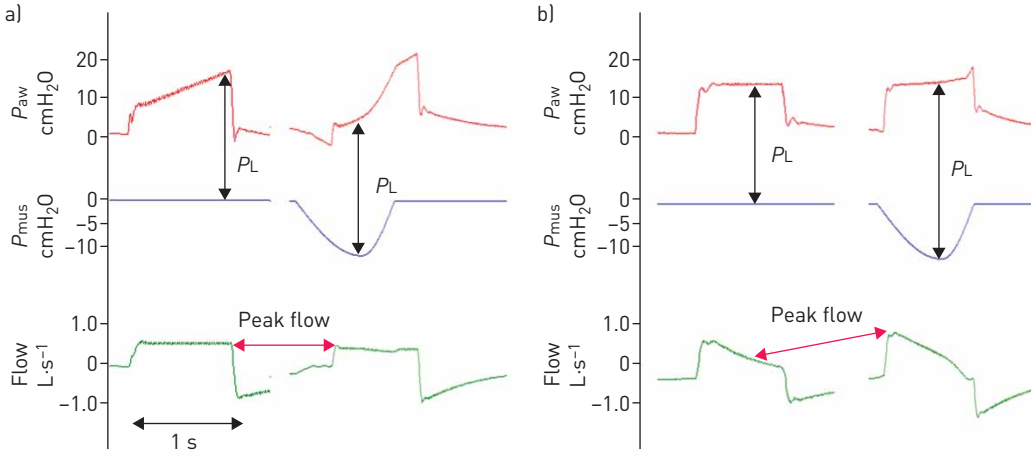

FIGURE 1 Change in transpulmonary pressure (P_L) from passive to active breathing during a) volume control ventilation (VCV) and b) pressure control ventilation (PCV). By contrast to VCV, with PCV an increasing effort will increase the flow and volume delivered. P_{aw}: airway pressure; P_{mus}: muscular pressure.

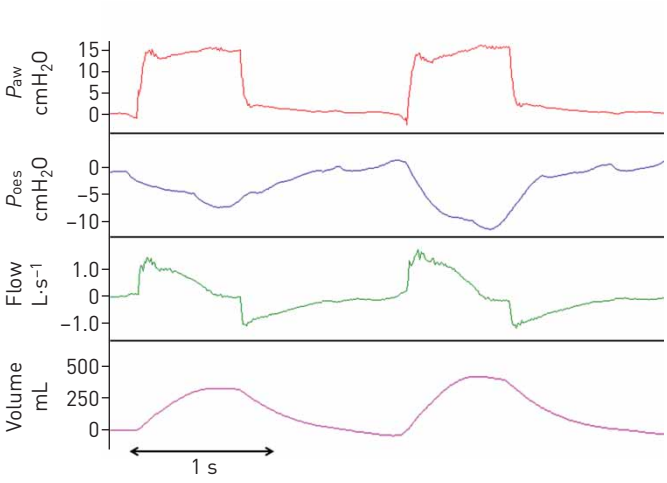

FIGURE 2 Effect of increasing inspiratory effort on delivered tidal volume during pressure-targeted ventilation. P_{aw}: airway pressure; P_{oes}: oesophageal pressure.

Titrating PEEP

ARDS is characterised by a major loss of lung volume due to alveolar flooding, atelectasis and consolidation. Since the first description of ARDS, the use of PEEP has been proposed to combat hypoxaemia and atelectasis [44]. Three large multicentre randomised trials have tested higher *versus* lower levels of PEEP while limiting tidal volumes in all patients: ALVEOLI (Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury) [45], ExPress (Expiratory Pressure) [28], and LOVS (Lung Open Ventilation Study) [27]. They found no significant improvement in mortality, although the ExPress trial found an improvement in ventilator-free days [28]. An individual patient-based meta-analysis [26] combining these data, however, found a modest but significant reduction in mortality for patients with moderate and severe ARDS assigned to higher PEEP. There is ongoing research into how best to individualise PEEP at the bedside and to set high PEEP only in those who will benefit.

The aim of PEEP in ARDS is to recruit (or maintain recruitment of) atelectatic or flooded lung. Initial studies looking at the effects of PEEP described adverse haemodynamic effects at high levels, leading to a reduction in cardiac output and oxygen delivery [46–48]. In the best cases, PEEP is able to keep the recruited lung areas reopened by the ventilator, and thus improve gas exchange in patients with ARDS and reduce the risk of repeated opening and closure [44]. A wide variability in the amount of recruitable lung exists among patients, and between 0% and 50% of potentially recruitable lung has been described [49]. High PEEP may be able to keep the lung open only if the lung is recruitable. A major challenge to protocolising PEEP titration is, therefore, the heterogeneity with which patients respond. While effective application of higher PEEP will reduce alveolar stress and improve gas exchange, it can fail to recruit or be harmful causing regional lung over-distension or haemodynamic depression. Therefore, a positive response to increased PEEP is expected in some, but not all, patients. The impact of PEEP on VILI and mortality may depend on this response.

The main physiological consequence of PEEP is the increase in end-expiratory lung volume (EELV). In a highly recruitable patient, a substantial part of the increase in EELV can be due to reopening of previously collapsed lung tissue, referred to as recruitment. This will have potential benefits and minimal risk. In a poorly recruitable patient, most of the increase in EELV is generated by inflation of previously open lung tissue potentially leading to overdistension (volutrauma, a major mechanism of VILI [50, 51]), and with very little potential benefit, failing to recruit the collapsed tissue. Therefore, the potential effectiveness and benefit of high PEEP levels depends on the patient's recruitability.

Clinical trials have suggested that a similar target for PEEP settings in all ARDS patients without a valid assessment of individual recruitability may not be very efficient for improving survival [27, 28, 45]. This may explain why the effect in terms of improved survival with high PEEP originating from randomised controlled trials is small [26]. In this regard, assessment of the individual recruitability may be essential for individualised PEEP settings to better decide the PEEP level based on the beneficial and deleterious effects of PEEP. Different techniques have been proposed: multiple pressure–volume curves, measurement of lung volume, use of P_{oes} and transpulmonary pressure, use of lung ultrasound and use of a physiological test based on oxygenation. In research studies, alveolar recruitability has been assessed using computed tomography (CT) [52]. This technique necessitates scanning patients at different static pressure levels (45 cmH_2O and 5–15 cmH_2O, respectively) and a detailed analysis of the CT scan cuts to compare aeration [49]. Although it provides the most visual way to detect recruitability, the individual analysis of

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each CT scan cut is extremely time-consuming and not applicable to clinical practice. It also exposes patients to the risk of repeated radiation exposure.

Multiple pressure–volume curves technique

This approach consists of plotting several pressure–volume curves obtained at different PEEP levels on the same volume axis, measuring or estimating the volume above functional residual capacity (FRC), *i.e.* the relaxation volume at zero end-expiratory pressure (ZEEP), at each PEEP level [53, 54]. Elastic pressure–volume curves can be obtained using low flow inflation. With this technique it is then possible to compare the lung volume above FRC in different conditions but always at the same pressure (*e.g.* 15 or 20 cmH_2O). The change in lung volume induced by PEEP can be measured by a prolonged expiration from higher PEEP to lower PEEP or FRC. When reducing PEEP to ZEEP during a prolonged expiration, the lung volume expired is the volume above FRC at that PEEP level. Numerous studies have demonstrated good reproducibility of pressure–volume curves for assessment of alveolar recruitability [55–57]. Due to its relative complexity, however, this technique often remains limited to research areas.

P_{oes} *monitoring*

Measuring P_{oes} to estimate pleural pressure and then estimating transpulmonary pressure at end-inspiration and expiration from the difference between P_{plat} or PEEP and oesophageal pressures is a proposed method to titrate PEEP and adjust pressures: transpulmonary pressure=P_{aw}–P_{oes} [10]. The usefulness of P_{oes} in guiding PEEP therapy in ARDS has been shown in the EPVent (Esophageal Pressure directed Ventilation) study [58]. Because of reduced chest wall compliance, oedema or abdominal distension, P_{oes} is often elevated in patients with ARDS and the calculated transpulmonary pressure can be negative at end-expiration. This may indicate closed or compressed airways or atelectatic lung. Thus, PEEP could be increased until transpulmonary pressure becomes positive at end-expiration to keep the airways open (with the caveat that positive values do not assure open alveoli in the zones distal to the sampling catheter). In a single centre, randomised controlled trial, investigators compared mechanical ventilation guided by P_{oes} measurements (experimental arm) with ventilation based on the protocol of the US National Institutes of Health sponsored ARDSNetwork (control arm) [5]. Patients who had PEEP titrated to ensure a positive end-expiratory transpulmonary pressure experienced a higher P_{aO_2}/F_{iO_2}, better respiratory system compliance as a possible consequence of improved recruitment, and a trend towards reduced 28-day mortality. This research may be considered proof of concept for the usefulness of P_{oes} measurements in ARDS but more data are needed before widespread clinical use.

Other investigators have used an elastance-based method to estimate transpulmonary pressure, which neglects the absolute values and relies on the tidal P_{oes} swings to calculate chest wall elastance [59]. This method estimates the lung distending pressure applied by positive pressure inflation during mechanical ventilation, *i.e.* eliminating the influence of the chest wall. Since any positive pressure applied at the airway opening acts on two elastic structures connected in series (the lung and the chest wall), P_{aw} is distributed between chest wall and lung elastance. The ratio of lung to respiratory system elastance can be used to better interpret the effect of P_{aw}. The latter method for partitioning lung and chest wall elastance has been used to guide a transpulmonary "open lung" approach in a cohort of patients with severe ARDS related to influenza A (H1N1) [60]. This assessment helped clinicians to decide, in severely hypoxaemic patients requiring high P_{aw} pressures, whether it was appropriate to further increase pressures on the ventilator or whether an extracorporeal oxygenation technique was preferable. While further studies are needed to test alternative methods of calculating transpulmonary pressure, the results from such studies support the use of P_{oes} measurement in sedated and paralysed subjects when titrating ventilator settings in ARDS.

Lung volume measurement using the nitrogen washout/wash-in technique

Direct measurement of lung volume is now feasible and allows measurement of FRC and/or EELV at each PEEP level and calculation of the strain, *i.e.* the change in lung volume relative to FRC. Recently, washout/wash-in techniques using nitrogen or O_2 and CO_2 sensors have been available in ICU ventilators, allowing bedside lung volume measurement [9, 61]. The washout/wash-in technique has shown good correlations with helium dilution or CT scans for EELV measurement [62]. The technique uses a change in F_{iO_2} to allow the calculation of nitrogen washout and then wash-in of the aerated lung volume. Although measuring changes in lung volume by itself is not sufficient to assess recruitment, a relatively simple method has been described as follows. Comparison of the change in lung volume with the expected change in lung volume based on the change in pressure and the static compliance gives a reasonable estimate at the bedside of the amount of recruitment occurring when changing PEEP [9]. Thus, this technique can directly quantify alveolar recruitment.

Lung ultrasound

Some interesting data suggest that evaluating the response to PEEP could be done by assessing the lung reaeration with lung ultrasound. Bouhemad *et al.* [63] have used a specific score based on the repeated examination of six lung regions in each lung, before and after increasing PEEP. Their results suggested that the transthoracic lung ultrasound technique is a method equivalent to the pressure–volume curve method for quantitative assessment of PEEP-induced lung recruitment. More data will be needed to assess the reproducibility and feasibility of this technique, but its noninvasive nature is attractive.

Oxygenation response to PEEP

Clinicians use oxygenation to titrate PEEP, but we know this has many drawbacks including the possible presence of intracardiac shunt, the influence of haemodynamics, and a significant but relatively poor correlation existing between recruitment and oxygenation [48, 55, 64]. The oxygenation response after a change in PEEP varies widely. The preceding randomised controlled trials assessing PEEP often tried to increase oxygenation based on a fixed target and a progressive increase in PEEP. They did not try to offer high PEEP to responders and low PEEP to nonresponders. A recent *post hoc* analysis of the published trials suggested that among patients in whom PEEP was increased after randomisation, the higher the increase in oxygenation after PEEP the higher the reduction in mortality associated with PEEP. These findings suggest that a better way to design a trial with PEEP may be to use the physiological response to PEEP as a marker of the need for high PEEP.

In summary, high PEEP has been shown to be beneficial in patients with ARDS. A better individualisation of therapy using bedside methods to assess recruitability seems necessary. Changes in lung volume, multiple pressure–volume curves and lung ultrasound are attractive methods. The oxygenation response to PEEP may also be used as a guide for titration. These approaches will need further validation.

Reducing the burden of ventilation by extracorporeal CO_2 removal

Extracorporeal CO_2 removal ($ECCO_2R$) uses a veno–venous (or arterio–venous) extracorporeal device at low blood flow rates (300–1000 $mL \cdot min^{-1}$). This low flow rate is adequate for substantial CO_2 removal but will allow only minimal blood oxygenation [65, 66]. Types of cannulae and insertion location vary, and are currently evolving. If proven to be effective, $ECCO_2R$ could potentially be used in an approach that is similar to continuous renal replacement techniques and be available in most ICUs. $ECCO_2R$ could be used technically like a simple continuous veno–venous haemofiltration circuit, but for which the primary goal would be to eliminate CO_2 from the blood. The major difference with the technique described as veno–venous extracorporeal membrane oxygenation (ECMO) is that much lower blood flows are needed to remove CO_2, compared with 3–5 $L \cdot min^{-1}$ with ECMO. The advantage of the low flow is that relatively small vascular cannulas can be used for this amount of blood flow. Potentially, removing CO_2 with an extracorporeal device could facilitate generalised use of protective or ultraprotective lung ventilation in many patients with ARDS. In addition, the decrease in tidal volume, down to 4 $mL \cdot kg^{-1}$ PBW, could facilitate an increase in PEEP.

In a prospective cohort study, Terragni *et al.* [66] used a CO_2 removal device to reduce tidal volume to <6 $mL \cdot kg^{-1}$ PBW and observed an improvement of morphological markers of lung protection. A randomised control trial compared a ventilation strategy with a very low tidal volume (3 $mL \cdot kg^{-1}$ PBW) combined with a pump-less $ECCO_2R$ device *versus* conventional protective ventilation in 79 patients with severe ARDS [65]. Ventilation with 3 $mL \cdot kg^{-1}$ PBW combined with arterio–venous $ECCO_2R$ was safe and feasible, and did not result in physiologically relevant hypercapnia/acidosis. The use of extracorporeal CO_2 elimination was associated with a significant reduction in analgesic and sedative use, and resulted in an increased ratio of spontaneous breathing compared with controls. The serum levels of the pro-inflammatory cytokine IL-6 were significantly reduced early in the study period in patients treated with very low tidal volumes compared with control patients. Mechanical ventilation using lower tidal volumes and extracorporeal CO_2 removal was not associated with a significant reduction of mechanical ventilation or ICU and hospital stay, but a *post hoc* analysis indicated that ARDS patients who were more hypoxaemic (P_{aO_2}/F_{iO_2} <150) and treated with the low tidal volume strategy had a significantly shorter ventilation period [65]. Some complications were noted. This approach is, therefore, promising but it is too early for it to be applied.

Conclusion

Major advances have been made in our understanding of the pathophysiological abnormalities present at the different stages of ARDS. We have evidence for the benefits of using high PEEP but also understand that it needs to be based on a more individualised response. Spontaneous breathing may need to be avoided at an early and severe stage, while it may be favoured cautiously in milder and later stages of ARDS. New monitoring tools, including P_{oes} measurements may considerably help in this regard.

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