Editorial

Low tidal volume ventilation in acute respiratory distress syndrome

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Ashbaug first described acute respiratory distress syndrome (ARDS) in 1967[1] in patients having acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on the chest radiograph. The definitions have evolved since then to the recent most accepted one proposed by the American-European Consensus Conference Committee.[2]. The definition has an advantage: it recognizes that the severity of the clinical lung injury varies; the patients with less severe hypoxemia with the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) less than or equal to 300 are considered to have acute lung injury (ALI) and those with more severe hypoxemia with PaO_2/FiO_2 less than or equal to 200 are considered to have ARDS.

The syndrome has been frustratingly resistant to treatment and the mortality from ARDS still remains very high. Years of clinical research have led to conceptual clarification of the etiopathogenesis of the lung injury in ALI/ARDS. Studies in experimental models strongly suggest that the traditional mechanical ventilation approaches could actually cause ventilator-induced lung injury.[3,4] Besides this, the lung injury which was believed to be diffuse and homogenous on the chest radiographs is actually patchy.[5]. There is, hence, a preferential distribution of large tidal volumes and higher inspiratory pressures to the normal alveoli, causing overdistension and stretch injury. In addition, the repeated cyclic opening and closing of alveoli during mechanical ventilation subjected the lung to shear injury.

Characteristic pressure–volume curves have described the mechanics of lung injury in ALI/ARDS.[6] In the sigmoid-shaped pressure–volume curve, ventilatory pressures higher than the upper inflection point cause overdistension and stretch. Lowering the end-expiratory pressures below the lower inflection point causes repeated collapse and reopening causing shear injury.

Clinical trials and research have ushered in the hope of improving survival rates by newer protective lung strategies aimed at preventing the stretch and shear injury. Interestingly, a recent study even found that a strategy of protective ventilation could reduce both the pulmonary and systemic cytokine response.[7] The protective lung strategies essentially recommend a gentler ventilation using lower tidal volumes, limiting the inspiratory and plateau pressures, and in that process accept permissive levels of hypercapnia. With this ventilation strategy, protection of lungs from excessive stretch is given higher priority than the attainment of normal partial pressure of arterial carbon dioxide (pCO_2) and pH with the traditional approach.

In 1990, Hickling *et al.*[8] reported clinical experiences in severe ARDS patients using low tidal volumes and pressure-limited ventilation with permissive hypercapnia aimed at reducing ventilator-associated lung injury. The mortality was found to be lower in the study group in this retrospective study.[8]

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This concept was exciting and led to further clinical trials conducted to replicate the benefits of low tidal volumes,[9–13] with conflicting results.

Stewart and co-workers, in 1998, randomized patients at a high risk of ARDS within 24 h of intubation[9] into a control group that received conventional ventilation with mean tidal volumes of 10.8 ml/kg body weight and a peak inspiratory pressure limit of 50 cm H_2O. The study group received protective ventilation with a mean tidal volume of 7.2 ml/kg of body weight and a peak inspiratory limit of 30 cm H_2O. No difference in mortality was found in the two groups. In fact, the morbidity in the study group was higher with more patients needing dialysis for renal failure. The plateau pressure in the control group was 28.8 cm H_2O, which was significantly below the limit of 35 cm H_2O, associated with lung injury. It was hence concluded that mechanical ventilation limiting tidal volumes and inspiratory pressures is unlikely to be beneficial and is not warranted for routine use in such patients. This conclusion was also supported by similar findings in two trials conducted by Brower *et al.*[10] and Brochard *et al.*[11]

The trial conducted by Amato and co-workers on 53 patients revealed strikingly different findings.[12] The study was designed to limit lung injury from overdistending volumes and high inspiratory pressures and maintaining a level of positive-end expiratory pressure (PEEP) that prevented the majority of alveoli from collapsing at end exhalation. PEEP in the protective ventilation group was set just above the lower inflection point of the pressure volume curve. Tidal volumes and inspiratory pressures were also substantially reduced. The protective ventilation approach was associated with significant improvements in 28-day survival rates, rates of weaning, and frequency of barotrauma.

A large multicentre randomized trial was conducted by the ARDS Network to study the effects of lower tidal volumes in ventilating patients with ALI and ARDS.[13] The trial compared traditional ventilation (initial tidal volume of 12 ml/kg of predicted body weight and a plateau pressure of 50 cm H_2O or less) *vs* ventilation with lower tidal volume (initial tidal volume of 6 ml/kg of predicted body weight and a plateau pressure of 30 cm H_2O or less).

The first primary outcome was death before a patient was discharged home and was breathing without assistance. The second primary outcome was the number of days without ventilator use from day 1 to day 28.

The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes (31% *vs* 39%) and the days without ventilator use during the first 28 days after randomizaton was greater in this group. The mean tidal volumes were 6.2 ± 0.8 and 11 ± 0.8 ml/kg of predicted body weight, and the plateau pressures were 25 ± 6 and 33 ± 8 cm H_2O, respectively. Thus, mortality was reduced by 22% and the number of ventilator-free days was greater in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes.

These benefits were observed despite the higher requirements for PEEP and FiO_2 and the lower PaO_2/FiO_2 in the group treated with lower tidal volumes. These were coupled with greater reductions in the concentrations of plasma interleukin 6 in the group reflecting a reduced systemic inflammatory response to lung injury. The lower output of inflammatory mediators could contribute to the higher number of days without organ system failure and the lower mortality in the group treated with lower tidal volumes.[14]

Following the conclusions made by the ARDS Network Trial, important issues were raised regarding the credibility and the interpretation of these landmark clinical trials[12,13] of patients with ARDS.

Eichacker pointed out that the trials showing low tidal volumes to be beneficial did not use control arms that reflected the current best practice standards at the time.[15] Instead, the trials compared very low tidal volumes (5–7 ml/kg of measured body weight) with traditional tidal volumes (10 ml/kg or more), which were higher than those routinely used.[16–19] A meta-analysis of the two beneficial trials[12,13] and the nonbeneficial trials[9–11] suggests that there were important postrandomization differences in airway pressures in the control arms of the five trials.[15] The three nonbeneficial trials used control tidal volumes that resulted in lower airway pressures (28–32 cm H_2O), consistent with routine care at the time of the studies.[17] Compared with these controls, low tidal

volumes did not improve outcomes. However, the two beneficial trials compared low tidal volume ventilation with control arms with airway pressures high enough (34–37 cm H_2O) to potentially increase control mortality rates. In this setting, low tidal volumes may mistakenly appear beneficial. This concern of unconventionally high plateau pressures in the group treated with traditional volumes that may account for the different outcomes in the ARDS Network Trial was also voiced by others.[20]

The meta-analysis failed to prove the superiority of the low tidal volumes over the current traditional practice method. However, it clearly indicated that using very high tidal volumes associated with high plateau pressures (>34 cm H_2O) was harmful and should be avoided.[15] Besides, the nonbeneficial trials used control arms that closely reflected the practice of the physicians treating ALI/ARDS.[17–19] These trials established that as long as tidal volumes produce airway pressures between 28 and 32 cm H_2O there is no benefit in using low tidal volumes. The ARDS Network Trial protocol not only specified a "traditional" high tidal volume for control subjects (rather than current practice in the study centers), but also restricted the physician's ability to adjust tidal volumes unless airway pressures were very high (more than 50 cm H_2O). Moreover, this study design may have resulted in inferior treatment conferred on the patients in the control arm of the study.

As a result, the meta-analysis concluded that neither of the two beneficial trials can determine whether raising tidal volumes and airway pressure worsened outcomes or lowering tidal volumes and airway pressures improved them compared with the practice that was current among participating physicians at the study centers. Further, even if low tidal volumes are beneficial and improve clinically important outcomes, this study might have overestimated the effects of low tidal volumes because of the unusually high tidal volumes and high plateau pressures used in the group treated with traditional tidal volumes.[15]

In spite of the fact that the meta-analysis did not show any benefits of using lower tidal volumes for ALI/ARDS patients, it had its own limitations and pitfalls. The lack of standard control in the studies relevant to the prevailing practice at the time as pointed in the meta-analysis is largely based on an international survey of ventilation practices conducted by Carmichael and co-workers.[16] Variability in the reported practice was profound and a wide disparity existed in the selection of tidal volumes. Over half of the respondents in the survey reported using tidal volumes that were high or higher than those received by the traditional group. Also, the use of plateau pressures that influenced the adjustment of tidal volumes was not systematic. Two general approaches seemed to be prevalent at the time as per differing clinical priorities. One approach used generous tidal volumes with high plateau pressures in order to maintain gas exchange and breathing comfort.[21,22] The other approach[8] used lower tidal volumes and inspiratory pressures to prevent overdistension and lung injury as per experimental evidence.[4] The disparity in physician-selected tidal volumes and the absence of a clear plateau pressure limit indicate the lack of any prevailing standard practice at the time which could have any relevance to the results of the trials, thus refuting any claims made by Eichacker and co-workers.[15]

There were views[23] that in addition to the low tidal volumes and plateau pressures, other factors also may have played an important part in improving the outcomes of the ARDS Network Trial. The significantly higher PEEP used in the study group with low tidal volumes provided the lung recruitment and was actually protective and necessary for lung protection when tidal volumes were reduced.[12] The nonstandardized partial buffering of hypercapnic acidosis associated with low tidal volumes also seemed to affect the outcomes; given the evidence that academia, in general,[24] and hypercapnic acidosis may have beneficial effects.[25] Another possible explanation given for the lower mortality rates with lower tidal volumes is improved systemic oxygen delivery. Reduced inspiratory airway pressures in patients receiving low tidal volumes may increase cardiac output and diminish the need for exogenous vasopressor drugs. Decreased use of these drugs would improve microvascular organ perfusion.[26]

Additionally, as observed by Brower and co-workers,[27] the three nonbeneficial studies were too small to provide convincing evidence for the lack of efficacy. Even if these studies were combined, the difference between the higher and lower tidal volume groups was

not statistically significant.[27]

A recent trial[28] has given additional weight to the ARDS network study. Similar to the ARDS network trial, Kallet and co-workers conclude that despite the heterogeneity of underlying lung injury typically present in this patient population, their findings strongly suggest that the low tidal volume strategy may benefit all patients with ALI or ARDS..[28] Other leaders in the field believe that tidal volumes in patients with ALI and ARDS should be titrated based on surrogate markers of lung injury, such as airway pressures or lung strain.[29–32] These physicians indicate that although some patients, such as those with poor pulmonary compliance and high airway pressures, would benefit from very low tidal volume, others with less severe lung injury may require larger volumes to maintain ventilation and avoid alveolar collapse.

In a recent major study on outcome of patients with ALI/ARDS, a multivariable logistic regression analysis showed that the independent risks for mortality included, use of tidal volumes higher than those used by the $ARDS_{net}$ study.[33]

Some investigators have used a meta-analysis of all low *vs* high tidal volume ARDS trials to argue that P_{PLAT} alone would be an adequate target, independent of V_T, and 6 ml/kg V_T could be problematic in patients who had already achieved an inspiratory plateau pressure target of 28–32 cm H_2O.[15] Those who counter that argument point to an analysis of the effect of low *vs* high tidal volumes across the four quartiles of P_{PLAT} levels in the $ARDS_{net}$ low V_T trial, demonstrating a beneficial effect of 6 ml/kg V_T in all four quartiles of P_{PLAT}.[34] In addition, a beneficial effect of lower tidal excursion independent of P_{PLAT} could be important.

Thus, after what was termed the culmination in an era of research , several questions arise. How do the results of the ARDS Network Trial affect the routine ventilator care of patients with ARDS? Has the trial established a new standard of care for mechanical ventilation of patients with ARDS? If not, can clinicians justify the failure to apply what some would consider as evidence-based medicine?[32]

An alternative approach to mechanical ventilation that has generated a great deal of interest over the past decade is high-frequency ventilation (HFV). Broadly speaking, HFV is defined as mechanical ventilatory support using higher than normal frequencies generally >100 breaths/min in adult and >300 breaths/min in pediatric population. When these frequencies are used, tidal volumes are much smaller than normal, may be less than the anatomic dead space and airway pressure swings are consequently less. The smaller tidal pressure swings coupled with appropriate baseline pressure elevations, create a conceptually ideal " lung protective strategy." Specifically, the combination of applied and intrinsic PEEP provides alveolar recruitment and the smaller tidal pressure swings prevent overdistension. The rapid flow pattern in HFV may enhance gas exchange and improve ventilation-perfusion matching.

Adult experience with HFV has been limited and literature does not show improvement in outcome.[35] Thus, more clinical data should be available to make it applicable as standard care for ARDS. The interesting perspective of HFV here is that perhaps the efficacy of HFV will throw more light on how much tidal volume is desirable and how low can we go.

Conclusion

Since the time that ARDS/ALI was first understood as an entity by Ashbaug,[1] considerable progress has been made in understanding the pathogenesis. Extensive research has been carried out to characterize subgroup of patients, identify patients at high risk early in the course of their illness, delineate the biology and mechanics of alveolar damage, and define molecular markers and mediators. However, strategies for betterment of outcomes have more or less remained a matter of debate. More than 30 years of research in formulating new therapies in the form of ways to improve oxygen delivery, nitric oxide, glucocorticoids, prostacyclins, etc., have yet to yield tangible results.

The five clinical trials[9–13] provide a platform for development of better strategies for mechanical ventilation in ARDS. Notwithstanding the debatable issues revolving around the trials, the ARDS Network Trial is the culmination of a series of mechanistic physiologic studies that have elucidated the new principle.[36]

There are lessons to be learnt from this breakthrough trial[13] that provide a new strategy for healing injured

lungs. The goal of ventilatory strategy henceforth should be to minimize lung injury by reducing the tidal volumes and keeping the plateau pressures below 32 cm H_2O and provide a gentler ventilation.[36]

Despite extensive discussions and debates on this strategy, we have examples of both low and high rates of compliance with the use of low tidal volumes for patients with ALI.[28,37]

Until another ventilatory strategy proves clear survival benefits for patients of ARDS, low tidal volumes (6–8 ml/kg of predicted body weight) should be regarded as a standard approach to ventilating patients of ARDS.

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