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REVIEW ARTICLE

Protective ventilation of patients with acute respiratory distress syndrome

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The majority of patients with acute respiratory distress syndrome (ARDS) require mechanical ventilation. This support provides time for the lungs to heal, but the adverse effects of mechanical ventilation significantly influence patient outcome. Traditionally, these were ascribed to mechanical effects, such as haemodynamic compromise from decreased venous return or gross air leaks induced by large transpulmonary pressures. More recently, however, the ARDS Network study has established the clinical importance of lowering the tidal volume to limit overdistension of the lung when ventilating patients with ARDS. This study suggests that ventilator-associated lung injury (VALI) caused by overdistension of the lung contributes to the mortality of patients with ARDS. Moreover, the results from clinical and basic research have revealed more subtle types of VALI, including upregulation of the inflammatory response in the injured and overdistended lung. This not only damages the lung, but the overflow of inflammatory mediators into the systemic circulation may explain why most patients who die with ARDS succumb to multi-organ failure rather than respiratory failure. The results of these studies, the present understanding of the pathophysiology of VALI, and protective ventilatory strategies are reviewed.

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The acute respiratory distress syndrome (ARDS) in adults was first described in 1967.[9] Only 3 yr later it was observed that pulmonary overdistension may occur during mechanical ventilation of patients with ARDS.[57] The authors speculated that 'mechanical ventilators, by applying high trans-pulmonary pressure to the non-uniformly expanded lungs of some patients who would otherwise die of respiratory insufficiency, may cause the hemorrhage and hyaline membranes found in some patients' lungs at death'. These observations went largely unnoticed for more than two decades. A new era of ventilatory management began in 1990, when it was reported that maintaining limits on tidal volume and airway pressure to minimize pulmonary overdistension, and allowing arterial carbon dioxide tension (Pa_{CO_2}) to rise to a higher level (permissive hypercapnia), caused a 60% decrease in the expected mortality rate among patients with ARDS.[43]

Following this, many clinicians began to adopt ventilatory strategies designed to minimize lung injury, although the clinical importance of ventilator-associated lung injury (VALI) induced by high tidal volumes has only recently been highlighted by the ARDS Network study.[1] This paper establishes that low tidal volume ventilation should now be considered the gold standard ventilation strategy for patients with injured lungs. However, as with any research, this study raises a number of questions, such as the mechanisms underlying the decreased mortality and the appropriate level of positive end-expiratory pressure (PEEP) in patients with ARDS.

'Protective' ventilation trials in ARDS

In 1993, guidelines published from a consensus conference emphasized the importance of limiting airway pressures and

Table 1 Randomized prospective studies of protective ventilatory strategies in patients with ARDS. Vt=tidal volume; PIP=peak inspiratory pressure; Pplat=end-inspiratory plateau pressure; PEEP=positive end-expiratory pressure; LIP=lower inflection point of PV curve

Reference	*n*	'Protective'	Control	Mortality
Stewart (1998)[85]	120	Vt <8 ml kg^{-1} PIP <30 cm H_2O PEEP levels similar in both groups	Vt 10–15 ml kg^{-1} PIP <50 cm H_2O	No difference
Brochard (1998)[14]	116	Vt <10 ml kg^{-1} Pplat <25 cm H_2O PEEP levels similar in both groups	Vt 10 ml kg^{-1} Normocapnia	No difference
Amato (1998)[5]	53	Vt <6 ml kg^{-1} PIP <40 cm H_2O PEEP 2 cm above LIP of static PV curve	Vt 12 ml kg^{-1} Normocapnia	Lower in 'protective' group (45 *vs* 71%)
Brower (1999)[15]	52	Vt 5–8 ml kg^{-1} Pplat <30 cm H_2O PEEP levels similar in both groups	Vt 10–12 ml kg^{-1} Pplat <45–55 cm H_2O	No difference
ARDSNet (2000)[1]	861	Vt 6 ml kg^{-1} Pplat <30 cm H_2O PEEP slightly higher in first few days	Vt 12 ml kg^{-1} Pplat <50 cm H_2O	Lower in 'protective' group (31 *vs* 40%)

alveolar distension in patients with ARDS.[82] However, low tidal volume ventilation may be associated with severe hypercapnia and respiratory acidosis with potentially harmful neurological and cardiovascular sequelae.[43 68 76] Previous strategies used to manage hypercapnia have included increasing tidal volume and airway pressure, or increasing carbon dioxide clearance with techniques such as tracheal gas insufflation or extracorporeal carbon dioxide removal. While carbon dioxide levels of two to three times normal seem to be well tolerated for prolonged periods, presently there are no data to confirm the degree of respiratory acidosis that is safe. Moreover, in a large survey of intensivists' ventilation practices for patients with ARDS published in 1996, most respondents reported using tidal volumes equal to or greater than 10 ml kg^{-1}.[17] Therefore, it was important to compare outcomes of patients randomized with either low tidal volume or traditional ventilation strategies. Five multicentre, randomized clinical trials were conducted recently to address this issue in patients with or at risk of acute lung injury or ARDS (Table 1).[1 5 14 15 85]

The magnitude of the clinical burden of VALI was demonstrated by the ARDS Network study, in which 861 patients with ARDS were randomized to receive either a 'traditional' tidal volume (12 ml kg^{-1} predicted body weight) or a low tidal volume ventilation strategy (6 ml kg^{-1} predicted body weight).[1] In the latter group, the tidal volume was reduced further to 5 ml kg^{-1}, or 4 ml kg^{-1} if necessary to maintain the end-inspiratory plateau pressure at less than 30 cm H_2O (Table 2). Mortality was 39.8% in the traditional group and 31% in the low volume group. There were also more ventilator- and organ failure-free days in survivors in the low volume group. The implication from the ARDS Network study is that by pursuing a normal Pa_{CO_2} tension at the expense of causing VALI, clinicians have inadvertently been contributing to the high mortality associated with the syndrome.

Lowering the tidal volume, however, failed to improve the outcome in three other controlled 'protective' ventilation trials (Table 1).[14 15 85] These discrepant findings

Table 2 The mechanical ventilation strategy from the ARDS Network study[1]

Variable	Setting
Ventilator mode	Volume assist-control
Tidal volume (ml kg^{-1})	6 (adjusted according to plateau pressure)
Plateau pressure (cm H_20)	<30
Rate (bpm)	6–35
I:E ratio	1:1–1:3
Oxygenation target	
Pa_{O_2} (kPa)	7.3–10.7
Sp_{O_2} (%)	88–95
PEEP and FI_{O_2}	Set according to predetermined combinations (PEEP range 5–24 cm H_2O)

can be explained by differences in trial design. The ARDS Network study alone was powered to detect a mortality difference between the two groups, had the largest difference in tidal volume and plateau pressure between the groups, and was the only study to correct respiratory acidosis using sodium bicarbonate infusions.[1] Moreover, in a fourth trial by Amato and colleagues (Table 1),[5] mortality was very high in the traditional ventilation group, making the data difficult to interpret. Therefore, although the ARDS Network trial has established the benefit of lung-protective ventilation, it is not yet clear that hypercapnia and acidosis are without serious consequence.

The results from animal studies have suggested that hypercapnic acidosis may contribute to the benefits of lung-protective ventilation. In isolated perfused rabbit lungs, respiratory acidosis protected the lung from ischaemia–reperfusion injury,[80] whereas respiratory alkalosis potentiated the injury.[49] This protective effect was associated with inhibition of xanthine oxidase and was prevented by buffering the acidosis, suggesting that the acidosis rather than the hypercapnia was protective.[50] Furthermore, in isolated perfused rabbit lungs, hypercapnia was associated with substantially lower concentrations of protein and tumour necrosis factor (TNF)-α in bronchoalveolar lavage fluid (BALF), less pulmonary oedema, better lung compliance, lower lung 8-isoprostane and nitrotyrosine

concentrations (markers of reactions with reactive oxygen and nitrogen species respectively),[69] and less apoptosis than the control group.[51] Despite these experimental observations, we feel that there is no consensus currently concerning the management of respiratory acidosis induced by permissive hypercapnia. However, if bicarbonate is infused, it should be administered slowly to allow carbon dioxide excretion and avoid worsening of intracellular acidosis.

Mechanisms of VALI

Volutrauma: high-volume injury

The relative contributions of pressure and volume to lung injury were first addressed in a comprehensive study in intact animals, which demonstrated that mechanical ventilation may cause pulmonary oedema.[91] Rats were subjected to large or low tidal volume ventilation, but identical peak airway pressures (45 cm H_2O), to distinguish between the effects of lung distension and increased intrathoracic pressure. Low volume ventilation with high airway pressure was achieved by limiting expansion using thoracoabdominal strapping during conventional positive pressure ventilation. The rats subjected to high tidal volume, high pressure ventilation developed permeability pulmonary oedema with ultrastructural abnormalities. In striking contrast, strapped animals ventilated with a high airway pressure but a normal tidal volume had no oedema and their lungs appeared normal on microscopy. Furthermore, permeability oedema also developed in rats ventilated with large tidal volumes but negative airway pressures by means of an iron lung. The conclusion of this study was that the high tidal volume and not the high airway pressure was responsible for ventilator-induced pulmonary oedema.

The main determinant of volutrauma seems to be the end-inspiratory volume (the overall lung distension) rather than the tidal volume or functional residual capacity (FRC), which depends on PEEP. Consequently, guidelines have emphasized the importance of monitoring and maintaining inspiratory plateau pressure (which most accurately reflects end-inspiratory volume) below 35 cm H_2O in ARDS patients by reducing tidal volume to as low as 5 ml kg^{-1}.[83] Peak airway pressure is not solely determined by alveolar pressure as it is influenced by respiratory resistance and the resistance of the ventilator circuit.

Atelectrauma: low-volume injury

Lung damage may also be caused by ventilation at low lung volume (meaning low *absolute* lung volume rather than low tidal volume). This has been well defined in animal models, but the relevance to humans is not firmly established.[8 29 78] Oedema formation in intact rats was less severe when PEEP (10 cm H_2O) was applied during ventilation with 45 cm H_2O peak airway pressure.[91] This beneficial effect of PEEP was attributable to reduced lung tissue stress (by decreasing tidal volume) and capillary filtration (at least in part because of haemodynamic depression), as well as the preservation of surfactant. Ventilation with a high tidal volume and low or zero PEEP therefore appears to be more damaging than low tidal volume and high PEEP, even though both strategies result in similar high levels of end-inspiratory pressure and alveolar distension.

Theoretically, small airways may become occluded by exudate or apposition of their walls, and the airway pressure required to restore patency greatly exceeds that in an unoccluded passage. Cyclic opening and closing (recruitment–derecruitment) of small airways or lung units may lead to increased local shear stress (so-called atelectrauma), particularly if the cycle is repeated with each breath (~20 000 times per day). PEEP effectively works, therefore, by splinting open the distal airways, maintaining recruitment throughout the ventilatory cycle.

Ventilator-induced pulmonary oedema: hydrostatic forces or microvascular permeability?

It has been suggested that hydrostatic mechanisms are responsible for ventilator-induced pulmonary oedema.[91] However, the oedema fluid is rich in protein, suggesting that either increased filtration by hydrostatic forces is very localized, or other mechanisms are involved, especially if one considers the extreme severity of the oedema that may be produced in small species such as rats.[28 29 91] Theoretical considerations based on lung interdependence predict that considerable increases in regional microvascular transmural pressure may occur during the inflation of very heterogeneous lungs.[57] However, increased microvascular permeability is the most likely cause of ventilator-induced pulmonary oedema, and there is probably no large increase in transmural pressure over the whole pulmonary vasculature during high airway pressure ventilation.

Major alterations in pulmonary epithelial and endothelial permeability occur in isolated lungs in animals subjected to high airway pressures. Discontinuities in alveolar type 1 cells have been reported in rabbits ventilated with moderate (20 cm H_2O) peak airway pressure for 6 h,[49] and widespread alterations of epithelial and endothelial barriers were seen when a higher peak airway pressure was used.[28 29] If VALI was the result of changes in hydrostatic forces only, there should be no[25] or little[11] ultrastructural alteration. Ventilation for longer periods resulted in alveolar flooding, diffuse alveolar damage, profound alterations in the epithelial layer, and capillary lesions.[28] The severity of the alterations was unevenly distributed; the epithelial lining appeared to be intact in some areas, whereas there were discontinuities and sometimes almost complete destruction of type 1 cells in many others. Furthermore, alveolar oedema and epithelial lesions were prevented by the application of PEEP (10 cm H_2O).

Biotrauma

The clinical effects of VALI may extend beyond the lungs. The majority of patients with ARDS die not from hypoxaemia but from multi-organ failure (MOF).[59] The mechanisms leading to MOF are probably multifactorial, but there is evidence that lung injury caused by mechanical ventilation can result in the release of several mediators, including proinflammatory cytokines.[84] These mediators may enter the systemic circulation,[19 60 61 88] causing organ dysfunction and ultimately MOF.[84] The term 'biotrauma' has been coined to describe this potentially injurious local and systemic inflammatory response to physical stress. Injurious ventilation of rats, using zero PEEP combined with very high end-inspiratory volumes, was associated with a fifty-fold increase in the recovery from BALF of proinflammatory cytokines, TNF-α, interleukin (IL)-1β, IL-6, macrophage inflammatory protein-2, and a significant increase in serum concentrations of these substances.[86] Similarly, patients with ARDS subjected to lung-protective mechanical ventilation had significantly lower levels of plasma and BALF cytokines and significantly less organ failure.[73 74] The ARDS Network study found that plasma levels of IL-6 were lower in the protective ventilation group.[1] However, it is not clear what role underlying lung bacterial colonization or infection may have played.

In experimental models, bacteraemia is more likely to develop when lungs that have been inoculated with bacteria are ventilated with high tidal volume/zero PEEP, as opposed to less injurious strategies.[73 74 86] The data suggest that overventilation may represent a stimulus for the immune system similar to that elicited by bacterial lipopolysaccharide.[39] Furthermore, these findings suggest that a ventilatory strategy associated with overdistension of the lungs and repetitive opening and closing of alveoli is most likely to facilitate bacterial translocation from the alveoli to the bloodstream. This opens the possibility that inappropriate ventilation strategies may contribute to ventilator-associated pneumonia.

Biotrauma, therefore, may be the missing link between the pulmonary pathophysiology of ARDS and MOF. These concepts may lead to a paradigm shift in which novel therapy for VALI is based not only on minimizing the physical forces causing injury, but also on modulating biotrauma using anti-inflammatory interventions to help limit the consequences of ventilator-associated inflammation.[22]

The injured lung: set up for VALI?

Lung mechanics in ARDS

Susceptibility to VALI is greatly influenced by the condition of the ventilated lung. VALI is apparently not a problem in patients with normal lungs.[13 30 40 62] Under these circumstances, the pressures and flows within the lung closely resemble the physiological situation. However, the grossly abnormal lungs of patients with ARDS are highly susceptible to VALI, and it may be that in some patients no mechanical ventilation strategy is entirely devoid of detrimental effect. An important feature underlying this predisposition to VALI is the uneven distribution of disease, and thus inflation, seen in injured lungs. Diffuse infiltrates on chest radiographs originally led clinicians to believe that lung involvement in ARDS was homogeneous. However, computed tomography (CT) scanning has demonstrated that the posterior, dependent portions of the lung are more severely affected, a distribution determined largely by gravity (Fig. 1).[35] The greater compliance of less affected areas—the so-called baby lung of ARDS—results in their overdistension at the expense of recruiting collapsed and consolidated lung units.[70] Accordingly, CT scans of ARDS survivors have shown greatest abnormality in the anterior parts of the lung even though the posterior areas had been most severely affected in the acute phase.[27]

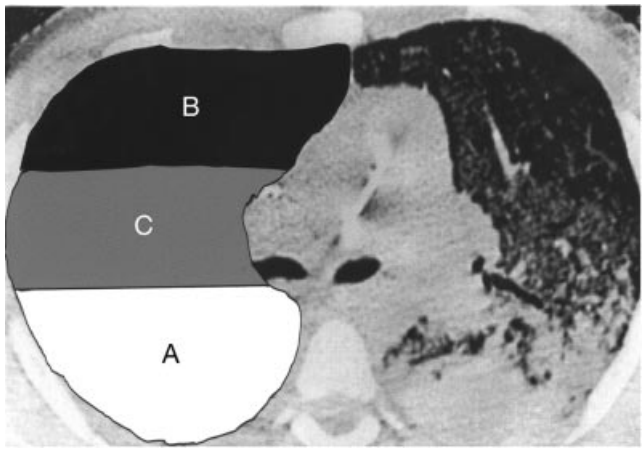

Fig 1 Computerized tomogram of the chest in a patient with ARDS, showing the typical heterogeneous distribution of opacification within the lungs. The increased density of lung tissue in dorsal regions (A) is caused by consolidation and atelectasis. The aerated, ventral regions ('baby lung', (B)) have the highest compliance and tend to become overdistended (volutrauma). The interface between the two areas (C) is prone to cyclic recruitment–derecruitment (atelectrauma).

Inhomogeneity and interdependence

In normal lungs, adjacent alveoli and terminal bronchioles share common walls, so that forces acting on one lung unit are transmitted to those around it. This interdependence is important in maintaining the homogeneity of alveolar size and surfactant function.[57] Normally, all lung units will be subject to a similar transalveolar pressure, approximately equal to the alveolar minus the pleural pressure. However, when an alveolus collapses the traction forces exerted on its walls by adjacent expanded lung units increase, and these are applied to a smaller area. Therefore, if the lung is unevenly expanded, as in ARDS, such forces may vary

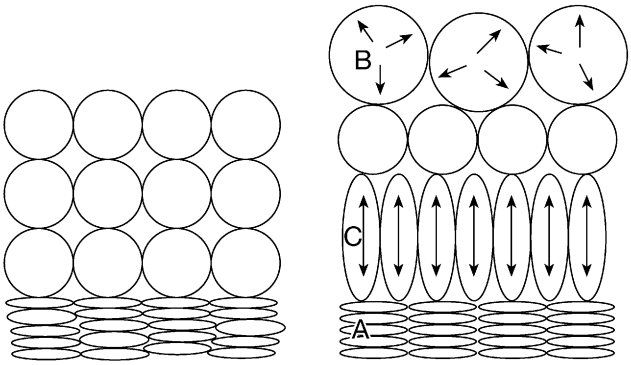

Fig 2 Atelectrauma resulting from interdependence. The left and right panels show the same lung regions at end-expiration and at end-inspiration respectively. At the interface between collapsed/consolidated lung (A) and overdistended lung units (B), lung tissue may be injured by excessive shear stress and stretching caused by the uneven expansion of surrounding zones (C).

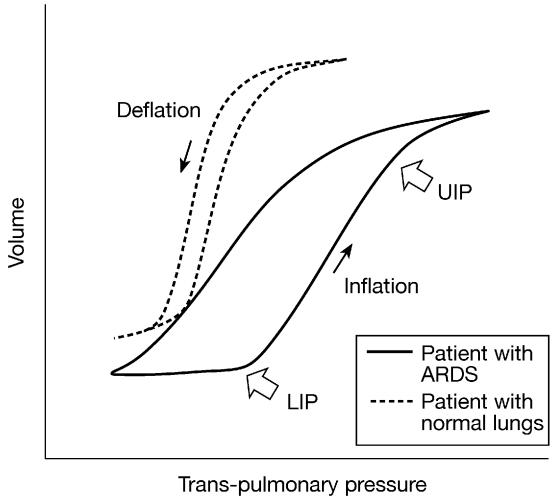

Fig 3 Schematic representation of a static pressure–volume curve of the respiratory system from a patient with normal lungs and from a patient with ARDS. The patient with ARDS has a lower functional residual capacity, decreased compliance and increased hysteresis. Note the lower and upper inflection points of the inspiratory limb in the patient with ARDS. LIP=lower inflection point; UIP=upper inflection point.

considerably. These forces will promote re-expansion at the expense of greatly increased and potentially harmful stress at the interface between collapsed and expanded lung units (Fig. 2).

At a transpulmonary pressure of 30 cm H_2O it has been calculated that re-expansion pressures could reach 140 cm H_2O.[6 57] Furthermore, in an autopsy study of patients who died with ARDS, expanded cavities and pseudocysts were found particularly around atelectatic areas.[77] In a recent study, piglets with multifocal pneumonia were ventilated using a tidal volume of 15 ml kg^{-1} for 43 h.[37] Approximately 75% of the lung was consolidated, so that the residual normally ventilated lung may have received a tidal volume equivalent to 40–50 ml kg^{-1}. In the consolidated areas the alveoli were 'protected' against overdistension, but the bronchioles that remained patent were injured through overdistension and by the forces generated through recruitment–derecruitment.

Pressure–volume curves

The static pressure–volume (PV) curve is often used to illustrate the pathophysiology of injured lung and, in particular, the balance between overdistension and recruitment (Fig. 3). Static PV curves can be obtained by inserting pauses during an inflation–deflation cycle of the respiratory system using a large syringe (super-syringe), or holding a ventilator at end-inspiration of varying tidal volumes. The lower inflection point (LIP) may represent the approximate pressure and volume at which lung units are recruited. The upper inflection point (UIP), at which lung compliance decreases at higher airway pressure, is thought to reflect the point at which alveoli become overdistended, and therefore potentially damaged.[4] Based on these concepts, an ideal ventilation strategy would be one in which the tidal ventilation would take place on the steep, most compliant portion of the PV curve, between LIP and UIP.[23] This may be achieved in part by the application of PEEP, at a level that exceeds the pressure indicated by the LIP, which should prevent the repeated opening and closing of lung units (cyclical atelectasis). This manoeuvre is central to a protective ventilation strategy called 'open lung' ventilation.[4]

The explanation of VALI according to the PV curve is certainly a gross oversimplification. First, the volume history of the lung is an important determinant of the PV relationship. Secondly, recruitment is not necessarily complete at the LIP.[42 70] Similarly, the UIP does not necessarily reflect the onset of overdistension. Instead, it may represent the point at which recruitment is complete and therefore compliance decreases. Thirdly, it is difficult to show that recruitment–derecruitment actually occurs, and dynamic ventilation may not follow the pattern of the static PV curve.[56] Finally, the lack of widespread availability of the super-syringe necessary to generate a PV curve has limited the applicability of this approach. Currently, most ventilators do not have the automated functions required to obtain a static PV curve. The development of a simple tool for determining regional volumes during ventilation would be a major step forward in the search for safer treatment.

Other factors

The surfactant obtained from patients with ARDS shows increased minimal surface tension and decreased hysteresis of the surface tension–surface area relationship, two indicators of surfactant dysfunction.[55] Surfactant dysfunction and deficiency amplify the injurious effects of mechanical ventilation, and mechanical ventilation itself can impair surfactant function. Surfactant dysfunction, in part caused

by plasma proteins in the airspace, may contribute to the pathophysiology of ARDS and VALI via a number of mechanisms, including exacerbation of atelectasis, increased oedema formation, and impairment of the local host defence. Therefore it is logical to propose that increasing the pool of functioning surfactant might lessen lung injury.[48] However, a role for surfactant supplementation in ARDS is not yet established, in part due to difficulties in delivering adequate amounts of active surfactant to damaged and collapsed lung regions.[7]

Current practice in ARDS is to manipulate the level of PEEP and use the lowest $F_{I_{O_2}}$ to give an oxygen saturation of around 90%. Oxygen toxicity may exacerbate lung injury,[81] probably through the increased generation of reactive oxygen species in lung tissue that has been overdistended.[18 24] In humans, no detectable oxygen toxicity occurred in normal subjects when the $F_{I_{O_2}}$ was less than 50%,[20] but impaired gas exchange was apparent after breathing 100% oxygen for approximately 40 h.[12] Although the relationship of $F_{I_{O_2}}$ to oxygen-induced lung injury has not been clearly defined in patients with ARDS, an $F_{I_{O_2}}$ less than 60% is usually considered to be safe.[2]

Finally, changes in the cellular constituents of injured lungs may make them susceptible to further mechanical damage.[67] For example, soon after injury type 1 alveolar epithelial cells die and are replaced by hyperplastic type 2 cells that may respond differently to mechanical strain. Similarly, leucocyte activation and emigration from the pulmonary microvasculature occur almost immediately after lung injury and an influx of myofibroblasts occurs later in the clinical course. This high concentration of cells primed to take part in inflammation may underlie the production of mediators that spill over into the systemic circulation.

Mechanical ventilation strategies in patients with ARDS

Pressure- or volume-controlled ventilation?

Mechanical ventilation of adult patients has traditionally been achieved by determining a set respiratory rate, tidal volume and inspiratory flow. This has the advantage of maintaining a constant minute volume under conditions of changing respiratory system compliance, provided that preset limits of airway pressure are not exceeded. Another strategy that has been used increasingly is pressure-controlled ventilation, in which a decelerating inspiratory flow profile results from the interaction of respiratory mechanics and the applied pressure. More sophisticated mechanical ventilators have allowed adjustment of more variables in each mode and have blurred the distinction between these two types of ventilation. Studies of volume- *vs* pressure-controlled ventilation in ARDS have been too small to detect outcome differences.[32 54 71] The largest study of ventilation in ARDS reported an outcome difference between the two protocols using volume-controlled ventilation, suggesting that settings rather than the mode is the important issue.[1]

Optimizing PEEP

PEEP may improve arterial oxygenation by redistributing lung water from alveolar to interstitial spaces, or by recruiting atelectatic alveoli and thus increasing FRC.[10 79] PEEP-induced improvement in arterial oxygenation in eight patients with ARDS correlated with the volume of lung recruited measured using static PV curves.[72] However, the increase in mean intrathoracic pressure produced by applying PEEP and maintaining the same tidal volume may exacerbate overdistension, increase dead space by occluding pulmonary capillaries, or cause circulatory depression.

Selecting the right level of PEEP for a given patient with ARDS is difficult, because the severity of injury varies throughout the lungs.[23 89] Moreover, there is very little information to guide clinicians on optimizing PEEP in patients with ARDS, and an international survey published in 1996 found wide variations in its use.[17] In theory, setting PEEP above the LIP may prevent derecruitment and atelectrauma. However, in ARDS the linear portion of the PV curve may be very short, so that a tidal volume that would not be deleterious in normal lungs may lead to excessive end-inspiratory volume when the PEEP is set above the LIP. Therefore, tidal volume strongly influences the PEEP level at which optimal compliance is recorded.[31]

In a study involving six patients with ARDS, for example, the use of PEEP at 13 cm H_2O resulted in the recruitment of non-aerated portions of lung, but in three patients overdistension of already aerated portions of lung occurred.[90] Overinflation is probably the explanation for the usual lack of reduction or even the worsening of oedema reported with PEEP during most experiments.[75] The only way to avoid both low- and high-volume lung injury therefore, seems to be to set the PEEP above the LIP and to markedly reduce the tidal volume to minimize overinflation.[5]

Presently, there is no consensus on the optimum level of PEEP in patients with ARDS. The ARDS Network ALVEOLI study, a prospective, randomized, multicentre trial of ARDS patients, comparing hospital or 60-day mortality, using higher PEEP/lower $F_{I_{O_2}}$ *vs* lower PEEP/higher $F_{I_{O_2}}$ ventilation, was recently discontinued prematurely after recruiting 550 patients, due to lack of efficacy.[3]

Prone ventilation

Prone positioning was first reported to improve oxygenation in patients with ARDS in 1976.[66] There is little information to predict which patients will respond positively to prone ventilation. However, the improvements in some patients are quite striking. Recruitment of dorsal lung appears to be the predominant mechanism of improved oxygenation with prone ventilation. In patients with ARDS in the supine

position, ventilation is diverted to the non-dependent part of the lung if the dependent region is consolidated or collapsed. In the prone position, ventilation is more evenly distributed because of changes in gravitational distribution of pleural pressure, and reduction of pleural pressure in the dorsal region of the lung.[52] This suggests that prone ventilation could prevent VALI by promoting more uniform distribution of tidal volume and by recruiting dorsal lung regions, preventing repeated opening and closing of small airways or excessive stretch at margins between aerated and atelectatic dorsal lung units. Furthermore, it has recently been suggested that the addition of a recruitment manoeuvre, such as cyclical sighs during ventilation in the prone position, may provide optimal lung recruitment in the early stages of ARDS.[64]

Potential problems of prone positioning are dislodgement of tracheal tubes and intravascular catheters, increased intra-abdominal pressure, facial oedema, and eye damage. A multicentre randomized controlled trial of prone positioning for patients with acute respiratory failure has recently been completed.[36] Patients randomized to prone positioning were assessed daily for the first 10 days and turned prone for at least 6 h each day if severity criteria were met. However, despite a significant improvement in oxygenation, no differences in clinical outcome were observed. Therefore, at present, prone positioning is a useful adjunct to ventilation that may help to improve oxygenation and pulmonary mechanics, but has not yet been shown to alter outcome in ARDS.

Recruitment manoeuvres

One means of minimizing the loss of lung volume from low tidal volume ventilation is by the use of sighs, involving the delivery of intermittent breaths of large tidal volume, administered either via the ventilator or by hand.[63] In one study, increasing the plateau pressure by at least 10 cm H_2O during sighs, applied three times a minute over a period of 1 h, caused a 26% decrease in shunting with a 50% increase in oxygenation.[65] However, it is unknown whether sighs used at this frequency cause injury from alveolar overdistension. Furthermore, recruitment manoeuvres may improve oxygenation only in patients with early ARDS who do not have impairment of chest wall mechanics and who have a large potential for recruitment.[38]

Sustained inflation or continuous positive airway pressure (CPAP) is another form of recruitment manoeuvre. It is well recognized that even a single breath without PEEP results in derecruitment. Therefore, when a patient requiring lung-protective ventilation is disconnected from the ventilator, for suctioning for example, a recruitment manoeuvre utilizing a CPAP of 35–40 cm H_2O for 30–40 s before reinstituting the previous level of PEEP has been suggested.[53] However, at present there are no published data from randomized studies to indicate whether recruitment manoeuvres, of whatever form, influence outcome.

High-frequency ventilation (HFV)

HFV uses very small tidal volumes with very high respiratory rates (>60 per minute). HFV offers potentially all the goals of lung-protective ventilation, with minimum tidal volume (1–5 ml kg^{-1}) while maintaining maximal recruitment (the 'open lung'), provided sufficient end-expiratory lung volume is maintained.[34] There has been a resurgence of interest in HFV over the last few years. Initial enthusiasm had been tempered by practical difficulties and the lack of clinical outcome data showing any advantage over conventional ventilation. High-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV) are the two most commonly used modes.

HFJV uses a high-pressure gas jet delivered into a tracheal tube at high frequency (100–200 Hz). The tidal volume produced can be adjusted by altering the inspiratory time and/or driving pressure. During HFJV, expiration occurs passively. HFJV has been investigated in two large randomized studies. In one study of 309 patients, the use of HFJV resulted in no significant outcome differences.[16] Similarly, a study of 113 patients at risk of ARDS demonstrated similar clinical outcomes in groups that were ventilated conventionally and in those in whom HFJV was used.[47] However, these studies did not use recruitment manoeuvres that may be beneficial when used in conjunction with HFJV,[41] and they were underpowered with respect to clinical outcomes such as mortality.

HFOV differs from HFJV in a number of important aspects. Tidal volume (1–3 ml kg^{-1}) is generated by the excursion of an oscillator within a ventilator circuit similar to that used for CPAP and is varied by altering the frequency, inspiratory time and oscillator amplitude. The use of an oscillator to generate tidal volume results in active expiration. HFOV is very frequently used in hyaline membrane disease of neonates to avoid end-inspiratory lung overstretching (by greatly reducing the tidal volume), although it has not been shown to be better than conventional mechanical ventilation in terms of morbidity and mortality.[44]

The first randomized controlled trial comparing HFOV with a conventional ventilation strategy in 148 adults with early ARDS has recently been completed.[26] Although this study expands on two recent studies showing HFOV to be effective and safe,[33 58] there was no significant difference in mortality between the groups.[26] One of the limitations of this (and almost all other older studies of ventilation strategy) was that HFOV was not compared with the current gold standard, low tidal volume ventilation used in the ARDS Network trial.

Liquid ventilation

Filling the lung with liquid removes the air–liquid interface and supports alveoli preferentially in the dependent lung regions that are most susceptible to collapse.

Perfluorocarbons (PFCs) have been used because they have a low surface tension, and they dissolve both oxygen and carbon dioxide readily.

Total liquid ventilation involves filling the entire lung with liquid and uses a special ventilator to oxygenate the PFC, a technique that is both difficult and expensive. In partial liquid ventilation (PLV), the lung is filled to FRC with liquid and ventilated with a conventional ventilator. The appropriate dose of PFC during PLV remains to be determined. Concerns over air and PFC leaks have been reported with large doses of PFC.[21] Moreover, improvement in lung mechanics using lower doses of PFC has been demonstrated, which also has financial implications.[87] Although PLV has been shown to be practical and safe,[45] a recent randomized, prospective study against conventional ventilation showed no difference in outcome.[46] However, no attempt to control tidal volume was made in this study.

Conclusions

The clinical importance of lowering the tidal volume to limit overdistension of the lung when ventilating patients with ARDS has recently been established.[1] No other treatment or supportive modality has been shown to affect the outcome of patients with ARDS. With few exceptions, for example patients with underlying conditions that would be exacerbated by hypercapnia (e.g. raised intracranial pressure), the low tidal volume strategy should be used for all patients with injured lungs. It is tempting to speculate that the lower mortality using a protective ventilation strategy may be related to the decrease in serum cytokines, but a definite answer to this question requires a study that specifically targets these mediators and examines changes in outcome. If this hypothesis is correct, anti-inflammatory therapies may prove to be useful adjuncts to lung protective strategies, possibly by preventing distal organ injury.

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