Ventilator-Induced Lung Injury and Implications for Clinical Management

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ABSTRACT

Objective: *To review recent studies in pathogenesis and management of ventilator-induced lung injury.*

Data sources: *Articles and published reviews on ventilator-induced lung injury, barotrauma and acute lung injury.*

Summary of review: *This review summarises the important differences between clinically apparent 'barotrauma' and the more subtle changes in lung structure and function associated with ventilation. Of great importance is the understanding that as the underlying lung injury worsens, the degree of injury from mechanical ventilation increases. An inflammatory process results from mechanical stimuli and this may contribute to distant organ dysfunction.*

A great deal of knowledge has been obtained from the use of animal models, however, one must be cautious about extrapolating these findings directly to the clinical setting without the use of adequately designed clinical trials. Tidal volume reduction and higher levels of PEEP and recruitment manoeuvres should be employed given the available evidence. The use of high frequency techniques, surfactant therapy despite their past track record, may prove to be exciting 're-discoveries'.

Conclusions: *Ventilator- induced lung injury is an iatrogenic disturbance that increases morbidity and mortality associated with acute respiratory distress syndrome. Tidal volume reduction and increased levels of PEEP reduce the plasma levels of inflammatory mediators and the mortality associated with ARDS.* (**Critical Care and Resuscitation 2000; 2: 269-277**)

Key words: Ventilator-induced lung injury, adult respiratory distress syndrome, PEEP

Barotrauma during mechanical ventilation has long been defined as the clinical appearance of extra-pulmonary air (e.g. pneumothorax, pneumo-mediastinum and subcutaneous emphysema) and until recently, was thought to be directly related to airway pressure and positive end expiratory pressure (PEEP) level.[1] Macklin in 1939 hypothesised that a pressure gradient between the alveolus and the bronchovascular sheath allowed air to track towards the mediastinum,[2] and Bouhuys[3] recognised the importance of trans-pulmonary pressure (i.e. alveolar minus intra-pleural pressure) rather than airway opening pressure in the pathogenesis of barotrauma. The recognition that microvascular injury and diffuse alveolar damage can result from mechanical ventilation in animal models has led to a large research effort in the last two decades. The morphologic and physiological changes seen in animal lungs, termed ventilator-induced lung injury (VILI) are almost indistinguishable from those seen with human acute respiratory distress syndrome (ARDS). The pathological mechanisms are unrelated to those responsible for classical clinical barotrauma.[4]

Webb and Tierney,[5] in 1974, described the onset of pulmonary oedema in rats during mechanical ventilation. This work was largely ignored until the 1980's when Parker *et al*,[6] demonstrated an increase in capillary filtration coefficient in isolated dog lungs when ventilated with peak airway pressures (P_{pk}) > 20cm H_20, and Kolobow *et al*,[7] demonstrated similar changes in larger animals. Dreyfuss *et al*,[8,9] found that lung stretch rather than distending pressure was the major variable in producing VILI and coined the term 'volutrauma'. Since

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this pioneering work there has been an explosion of knowledge of VILI pathophysiology. The most important concepts include:

a) Pre-existing acute lung injury is the greatest predisposing factor to VILI. The concept of the 'baby-lung' and regional overdistension or volutrauma has led to the use of tidal volume (V_T) reduction, and permissive hypercapnia as a protective ventilatory strategy.

b) Atelectasis predisposes to tidal opening and closing of distal lung units producing a shear stress injury termed 'atelectrauma' or 'low-volume lung injury'. An appropriate level of PEEP protects against this injury.

c) Up-regulation of an inflammatory response, following mechanical stimuli to the lungs occurs, and may perpetuate VILI and contribute to distant organ dysfunction ('biotrauma').

The term VILI has been restricted to describe the damage seen in animal lungs as a direct consequence of mechanical ventilation. In humans, it is impossible to obtain definitive evidence that ventilation causes these lesions as it is difficult to delineate between morphological changes induced by the underlying illness (e.g. ARDS) from those due to ventilation. To describe the worsening of lung injury caused by mechanical ventilation in humans, the term VALI (ventilator-associated lung injury) is preferred.[4] For simplicity, we will use only the term VILI in this article. The recent NIH/NHLBI ARDS network study has provided convincing evidence that VILI is a clinically relevant entity that affects outcome.[10]

This review focuses upon the latest pathophysiological mechanisms of VILI and how this knowledge together with data from many clinical trials utilising protective ventilatory strategies is changing our practice.

MORPHOLOGICAL CHANGES IN VILI

Areas of oedema, atelectasis, enlargement and congestion, are readily apparent on initial inspection of animal lungs damaged by ventilation.[5] There may or may not be evidence of macrobarotrauma, such as pneumatocoeles, but loss of lobular and alveolar structure with local emphysema invariably occurs. Microscopically, interstitial and alveolar eosinophilic oedema is present along with peri-bronchovascular cuffing. In more severe injury, diffuse alveolar damage (DAD), hyaline membranes, and alveolar haemorrhage with neutrophilic infiltrates are seen, all of which occur in early ARDS. Capillary endothelial cell basement membrane detachments and blebbing occur which is not seen in pure hydrostatic pulmonary oedema with capillary stress failure.[8] Destruction of alveolar Type 1 cells occurs and, later on, Type 2 cell and fibroblastic proliferation is seen. There appears to be a tendency for lesions to predominate in the dependent areas of the lung,[11] possibly due to the increased local vascular pressures and atelectasis.

PATHOGENESIS OF VILI (Figure 1)

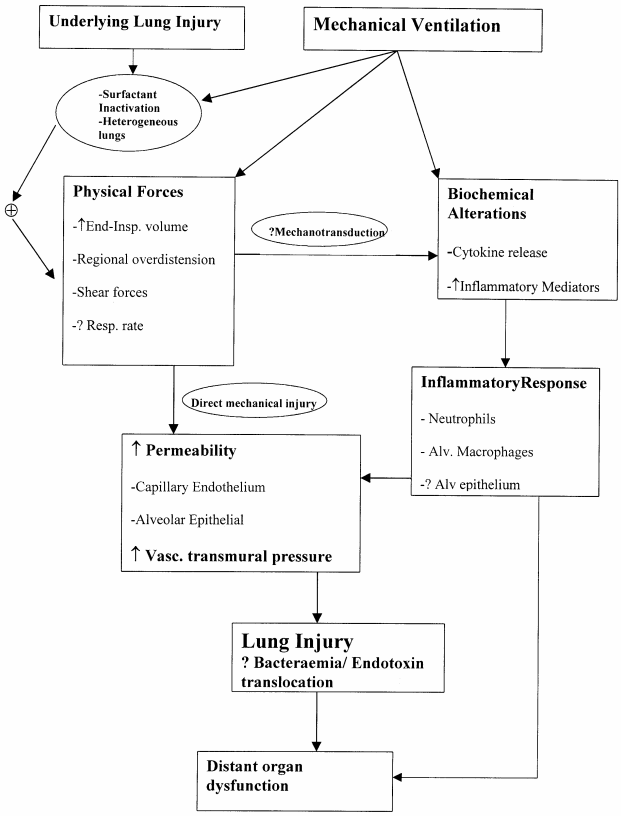

Figure 1. This figure demonstrates the complex interaction between underlying lung injury and mechanical ventilation in the pathogenesis of ventilator-induced lung injury (VILI). The underlying lung injury, through loss of surfactant function and heterogeneous mechanical properties, accentuates VILI by amplifying the effects of physical forces. End-inspiratory stretch and regional overdistension (i.e. 'baby-lung') together with shear forces from repeated tidal opening and collapse of distal lung units causes direct mechanical injury, resulting in increased capillary permeability and transmural pressure. An inflammatory response is upregulated possibly through direct sensing of physical forces (e.g. mechanotransduction) or as a result of direct lung damage. This inflammatory response may contribute to multiple organ dysfunction.

Direct mechanical injury

Lung injury in small animals occurs very rapidly over the course of minutes with little histological evidence of inflammatory activity. This implies that direct mechanical injury is a major factor.

'Volutrauma' or 'high volume lung injury'

Dreyfuss *et al*,[12] showed that lung volume (or more correctly end-inspiratory volume) was a crucial variable

in the genesis of VILI. They showed that rats ventilated at high airway pressure but with thoraco-abdominal strapping developed no lung oedema compared with those that were ventilated at high volume with positive or negative pressure (Figure 2). Hernandez *et al*,[13] demonstrated this again in rabbits with chest wall restriction by plaster casts. Therefore, chest wall and lung compliance will determine the degree of stretch injury for any given inspiratory pressure.[14] Computed tomography (CT) studies in acute lung injury performed by Gattinoni *et al*,[15] introduced the concept of 'baby lung', where areas of collapsed non-recruitable lung coexisted with normally aerated lung. Overdistension and 'volutrauma' to the normal lung areas would then occur if tidal volumes were not concomitantly reduced.

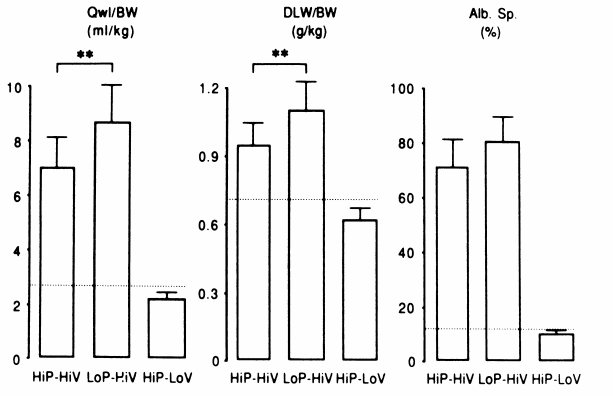

Figure 2. Comparisons of the effects of high-pressure-high-volume ventilation (HiP-HiV) with those of negative inspiratory airway pressure high tidal volume ventilation (e.g. iron lung ventilation = LoP-HiV) and of high-pressure-low-volume ventilation (e.g. thoracoabdominal strapping = HiP-LoV). The dotted lines represent the upper 95% confidence limit for control values. Qw = extravascular lung water, BW = body weight, DLW = dry bloodless lung weight, Alb. Space = I^{125} distribution volume. Permeability oedema occurred in both groups receiving high tidal volume (V_T) ventilation. Animals ventilated with a high peak pressure and a normal V_T had no oedema. (Modified from Dreyfuss, et al. Am Rev Respir Dis 1988;137:1159-1164).

'Low volume lung injury'.

Ventilation at low lung volumes leads to atelectasis due to inhibition of surfactant release or loss from the alveolus into the airway. The force required to reopen these units is great. Mead *et al*,[16] proposed that a collapsed lung region completely surrounded by expanded airspaces could be exposed to a pressure as much as five times greater than the transpulmonary pressure. Robertson was the first to implicate large shear forces caused by repeated opening and closing of distal airways as an explanation for worsening lung injury in neonatal respiratory distress syndrome.[17] Muscedere *et al*,[18] using an *ex vivo* rat lung model, and Argiras *et al*,[19] using an *in vivo* surfactant deficient rabbit model, showed that ventilation using PEEP at a level above the lower inflection point (P_{lip}) on the static pressure-volume (PV) curve lessened the deterioration in lung compliance and pathologic evidence of lung injury. Other workers have shown the importance of maintaining open airways and lung units (the so-called 'open lung approach') with both conventional ventilation and high frequency ventilation.

Role of PEEP

The direct effects of PEEP are to increase the functional residual capacity and splint the lung open. The end-inspiratory volume increases if V_T is not reduced and this may counteract any beneficial effects. Worsening of lung oedema with PEEP may reflect end-inspiratory overdistension, which occurs in open-chested animal experiments. Indirectly, PEEP (in closed chested models) increases mean intrathoracic pressure, which depresses pulmonary blood flow and capillary surface area, reducing filtration and lung water as well as increasing surfactant production.[5] However, most studies in intact animals do not show a change,[20] or only a slight increase,[21] in extravascular lung water. Therefore the overall effect of PEEP on lung injury is a balance between the detrimental effects of an increase in end-inspiratory volume and the benefits of reduced capillary filtration and 'lung opening' properties.

Role of airway pressure

Preliminary data from Broccard *et al*,[22] showed that isolated constant flow perfused rabbit lungs ventilated with higher mean airway pressure (P_{mean}) developed a greater increase in permeability and lung haemorrhage, independent of V_T. It was hypothesised that a higher P_{mean} increased pulmonary vascular resistance and increased capillary pressures. The effect of P_{mean} on capillary pressures in this model may not be relevant in intact animals. Further studies are required.

Role of respiratory rate

Little emphasis has been placed on respiratory rate in the pathogenesis of lung injury. It is entirely possible that the higher the respiratory rate the greater the cumulative lung insult. Recent work by Hotchkiss *et al*,[23] concluded that decreasing respiratory frequency can improve the indices of lung damage in isolated perfused rabbit lungs ventilated at a given V_T and mean airway pressure.

Mechanisms of lung oedema

The weight of experimental evidence suggests that ventilation causes lung injury by mechanisms that increase permeability across the alveolar-capillary

barrier. Increases in vascular transmural pressure play a secondary pathogenic role,[24] as the observed capillary lesions (e.g. endothelial blebbing, cell swelling/lysis) that occur with mechanical ventilation differ slightly to those seen purely due to high capillary pressure (i.e. 'capillary stress failure').[8]

Increased alveolar-capillary permeability

Experimental data shows that a major increase in alveolar-capillary barrier permeability is the critical factor in the genesis of VILI. The reader is referred to an extensive review of this topic by Dreyfuss and Saumon.[24]

Role of surfactant. Although mechanical ventilation increases surfactant release, it is inactivated by compression, which causes rupture of the film. In addition, surfactant may be lost into the airways.[24] Surfactant inactivation plays a central role in the increased permeability of both alveolar epithelial and capillary endothelial cells. Increased surface tension results in an uneven distribution of ventilation and regional overinflation, which leads to damage of the alveolar epithelial cells. Capillary endothelial permeability may increase secondary to increased radial traction on microvessels.

Role of inflammatory cells, cytokines and mediators in VILI. In larger animals and in humans, an inflammatory response characterised by neutrophil priming, activation and infiltration occurs. This was first described by Woo and Hedley-White,[25] and later by Hamilton and co-workers,[26] who found an increased number of neutrophils in the lavage specimens of patients assigned to a potentially injurious ventilatory strategy. The central role of the neutrophil in mediating VILI was illustrated by the work of Kawano *et al*,[27] who showed markedly better lung function and less histologic evidence of lung injury in neutrophil-depleted animals compared with control animals subjected to mechanical ventilation. Other cells (e.g. capillary endothelial cells, airway and alveolar epithelium and alveolar macrophages), may be activated and release cytokines and mediators in response to mechanical stress[28,29] and thus contribute to VILI.

There is intense research into the role of the many, and varied, cytokines and mediator (e.g. cyclo/lipo-oxygenase, nitric oxide) pathways in VILI. Pioneering work by Tremblay *et al*,[30] showed that injurious ventilatory strategies (e.g. high $V_T \pm$ low PEEP) resulted in a sixfold increase in lung lavage cytokines in an isolated perfused rat lung model. Recently, Ranieri *et al*,[31] demonstrated that the concentrations of pro-inflammatory cytokines in both bronchoalveolar lavage fluid and plasma were decreased in patients ventilated with a low V_T, high PEEP strategy. The presence of these mediators in increased amounts in the systemic circulation leads onto the hypothesis that spillover of mediators associated with VILI may cause, or perpetuate, distant organ dysfunction.[32] It has also been shown that endotoxin translocation from the lungs to the systemic circulation may occur as a result of mechanical ventilation, and bacteraemia can be reduced with protective ventilatory strategies.[33,34] Bacteria may have easier access to the bloodstream in the presence of severe bronchial and alveolar epithelial damage.

Mechanotransduction or conversion of mechanical stimuli (e.g. cell deformation) into a biochemical response is possible via stimulation of stretch-sensitive ion channels and direct cell membrane molecular conformational change or damage. Parker *et al*,[35] prevented the increase in pulmonary capillary filtration coefficient in rat lungs subjected to high-pressure ventilation, by using gadolinium, a blocker of stretch-activated cation channels. Expression of early response genes/transcription factors can be induced by stretch. Current research suggests that the shear stress responsive transcription factor, Nuclear Factor κβ (NF-κβ), is possibly responsible for the generation and propagation of the cytokine response in VILI, as it has been demonstrated in ARDS and the sepsis syndrome.[36]

Increased vascular transmural pressure

Outward radial traction on extra-alveolar vessels during lung inflation increases transmural pressure, which in turn favors fluid filtration.[37] When there are non-uniformities in lung aeration (i.e. atelectasis), distending pressures across adjacent alveoli can be great (interdependence phenomenon).[16] These increased forces not only exert a shearing effect on alveoli adjacent to collapsed areas, but also increase transmural pressure in extra-alveolar vessels. Increased alveolar surface tension, due to surfactant loss or inactivation with mechanical ventilation, may result in negative interstitial pressure surrounding alveolar vessels, again favoring fluid filtration.[38] The effect is reversible with PEEP.

Effects of underlying lung injury

The effects of VILI and prior lung injury are synergistic. Dreyfuss *et al*,[39] showed that rat lungs injured by α-naphthyl-thiourea (ANTU) had greater lung injury at a given level of ventilation than predicted by ANTU or ventilation alone (Figure 3).

Heterogeneous lungs and reduced surfactant activity with any lung injury increases the likelihood of regional overdistension and cyclical opening and closing of distal lung units.

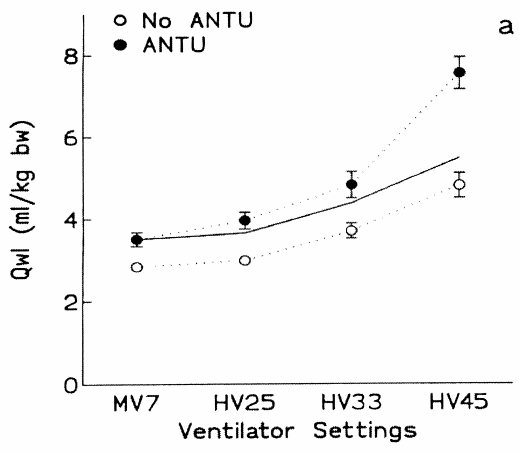

Figure 3. Interaction between previous lung alterations and mechanical ventilation on pulmonary oedema: (*a*) Effect of previous toxic lung injury. Extravascular lung water (Qwl) after mechanical ventilation in normal rats (*open circles*) and in rats with mild lung injury produced by α-naphthylthiourea (ANTU) (*closed circles*). Tidal volume (V_T) varied from 7 to 45 ml/kg. The *solid line* represents the Qwl value expected for the aggravating effect of ANTU on ventilation oedema assuming additivity. ANTU did not potentiate the effect of ventilation with V_T up to 33 ml/kg. In contrast, ventilation at 45 ml/kg resulted in an increase in oedema that greatly exceeded additivity, indicating synergy between the two insults.

CLINICAL PERSPECTIVES

The NIH ARDSnet study[10] demonstrated that ventilator-induced lung injury is a clinically relevant entity in humans. Current preventative ventilatory strategies and their efficacy will be described below.

Tidal volume reduction

Tidal volume reduction reduces end-inspiratory stretch in a heterogeneous lung (i.e. 'baby-lung'). The American-European Consensus conference on ARDS recommends arbitrarily limiting plateau pressure < 35cm H_2O, based on the normal transpulmonary pressure seen at total lung capacity in normal lungs.[40] This does not have great clinical utility, as the resulting V_T will vary greatly depending upon set PEEP level and chest wall compliance. However, it is probably prudent to limit plateau pressure to < 35cm H_2O with any combination of PEEP and V_T in those who have normal chest wall compliance. Five recent trials, with varying results, have been conducted using a V_T lowering strategy.[10,41-44] One study used the static PV curve to titrate PEEP or V_T (see Table 1).[44]

Table 1. Clinical studies using tidal volume reduction

	Tidal Volume Study vs. Control (mL/kg)	PEEP Study vs. Control (cmH_2O)	Mortality Study vs. Control %	Clinical Barotrauma %
Brochard[42]	7 vs 10	0 - 15**	47 vs 38†	14 vs 12†
Brower[43]	7 vs 10	5 - 20**	50 vs 46†	4 vs 8†
Amato[41]	6 vs.12	> 2cm above LIP vs. titrated to DO_2	38 vs 71‡	7 vs 42‡
Stewart[44]	7 vs 11	5 - 20**	50 vs 47†	10 vs 7†
NIH Ardsnet[10]	6 vs 12*	5 - 25**	31 vs 39‡	Nil diff

Definition of abbreviations: LIP= lower inflection point; DO_2= oxygen delivery;
Barotrauma defined as pneumothorax, pneumomediastinum and pneumatocoeles.
* Predicted body weight calculated from formula.
** PEEP titrated to best PaO_2/FiO_2 ratio.
† Non significant difference.
‡ Significant difference.

The largest of these studies, the NIH ARDSnet study, included over 800 patients with acute lung injury (ALI). Tidal volume reduction based on a predicted weight algorithm and the use of prespecified combinations of inspired oxygen fraction (F_IO_2) and PEEP resulted in a reduction in mortality from 39 to 31%. In addition, the incidence of breathing without assistance at day 28 and the number of days without organ failure were more frequent in the study group compared with the control group. The Amato study,[44] which included a PEEP titration strategy in the study group, resulted in a striking difference in mortality but not at hospital discharge. However, the 70% control mortality is at odds with currently reported figures in ARDS and thus this study must be viewed with caution. The other studies did not show significant mortality differences, which may be explained by the smaller differences between delivered tidal volumes in the study and control groups and the small patient numbers. Most of these strategies result in hypercapnia, the adverse effects of which are a matter of considerable debate. In at least three of the above trials, hypercapnic acidosis was buffered with bicarbonate. There is experimental evidence to suggest that acidosis, especially hypercapnic acidosis, may exert protective organ system effects and that buffering this may worsen

lung injury.[45]

A recent epidemiological study in Australia found that average tidal volumes and inspired oxygen fraction (F_IO_2) were higher and PEEP levels were lower than those found to be beneficial in the recent NIH ARDSnet study.[46]

High PEEP strategies.

PEEP stabilises terminal airway units, preventing cyclic opening and closing and the resultant shear force injury. It reduces effective capillary filtration as a result of increased intrathoracic pressure and preserves surfactant function by avoiding surface film collapse and loss into the airways. The use of higher PEEP levels, especially in those with extrapulmonary ARDS may help lessen VILI.[47] In order to prevent tidal recruitment, a static total respiratory PV curve is constructed and PEEP is set to a level above the lower inflection point (LIP). Although Amato[44] used a high PEEP strategy using this technique, it is impossible to determine the individual effect of the PEEP strategy as a concurrent V_T reduction was employed. The practical issues that limit widespread adoption of the recently recommended 'PEEP titration' techniques include:

a) PV curve titration is cumbersome
b) The lower inflection point may not be present
c) The PV curve only provides a snapshot of the mechanical properties of the respiratory system, which vary over time and with body position.

Titrating PEEP to 'best oxygenation' instead of the LIP, may not always correlate with maximal recruitment, as PEEP may alter the ventilation/perfusion relationships within the lung, and hence oxygenation, by redistributing pulmonary blood flow. We await further studies in this area.

Recruitment manoeuvres

Recruitment manoeuvres (RM) or sustained inflations or sighs between 40 - 60cm H_2O immediately improve compliance and oxygenation in anaesthetised subjects with a low V_T.[48] Progressive atelectasis may occur despite the use of high levels of PEEP in ARDS patients, possibly due to resorption in areas of low V/Q ratio.[49] High pressures are required to re-open these units after which they require less pressure to maintain their patency, especially in surfactant depleted lungs.[50] Pelosi *et al* used a strategy of 3 sighs per minute at 45 cm H_2O in ARDS patients, which significantly improved the PaO_2, shunt fraction, end-expiratory lung volume and lung elastance.[48] These variables returned to baseline 1 hour after the sighs were stopped.

Extrapulmonary ARDS responds better to RM than pulmonary causes of ARDS.[48,49] The magnitude and duration of the best recruitment manoeuvre is not known. It has been suggested that a single RM of approximately 60 cm H_2O would be sufficient to inflate the majority of recruitable lung.[49]

Other techniques

High frequency techniques (HF)

In theory, high frequency jet ventilation (HFJV) and high frequency oscillation (HFO) can simultaneously prevent alveolar collapse and overdistension. Indeed, animal studies have shown better lung compliance and oxygenation and lower indices of lung oedema using HFO.[51] HFO appears to be associated with improved pulmonary outcomes in neonates with hyaline membrane disease[52] and paediatric ARDS,[53] however, its use in adults has failed to develop. Previous studies using high frequency techniques in adults with ARDS have shown no mortality benefit over conventional ventilation.[54-57]

These studies must be viewed with caution as a number of factors may have masked any benefits. They were performed in the 1980's when potentially injurious low volume / low pressure strategies were used. In addition patient numbers were small, and in two of the trials, high frequency techniques were instituted only after conventional ventilation had failed. No study showed HF to be worse than conventional ventilation. We await further large studies of early application of HF techniques aimed at maximising lung recruitment with ventilators custom-built for adult use.

Extracorporeal techniques

Extracorporeal membrane oxygenation (ECMO) is an invasive technique which is not associated with an overall survival benefit.[58] Extracorporeal CO_2 removal ($ECCO_2R$), while maintaining lung inflation with a continuous distending pressure interrupted by a few breaths, reduces PCO_2 during V_T limitation and improves PO_2.[59] In the absence of proven adverse effects of hypercapnia, the invasive nature of this technique, and a large single centre trial that was not associated with improved survival,[60] use of $ECCO_2R$ is not recommended.

Tracheal gas insufflation

Tracheal gas insufflation increases CO_2 elimination. Fresh gas flow varying between 6 - 10 L/min via a catheter, washes out the CO_2 that remains in the dead space proximal to the catheter tip. It can be delivered continuously or during inspiration or expiration, the former being associated with greater CO_2 clearance. Auto-PEEP generation (especially during expiratory pathway obstruction or occlusion) and the inability to compensate for the additional gas delivered during

expiration with pressure controlled ventilation are major drawbacks that currently outweigh its benefits, particularly when data highlighting the adverse effects of hypercapnia are lacking.

Inspiratory flow pattern and I:E ratio

Given the heterogeneity of lung unit time constants in ALI, a change in flow pattern or I:E ratio may alter distribution of ventilation during ventilation. Ludwigs and co-workers, using inverse ratio ventilation (IRV) in a computerised lung model with varying time constants, showed that overdistension was greatest in lung units with both high compliance and high resistance. The effect was greater with pressure controlled IRV than volume controlled IRV.[61] Kacmarek and co-workers, using a four unit physical lung model, found that auto-PEEP was associated with a greater maldistribution of local lung unit end-expiratory pressure and volume compared with similar levels of extrinsic PEEP.[62] Thus, induction of intrinsic PEEP occurs non-uniformly throughout the diseased lung and may lead to regional differences in aeration, which contrasts with the uniform distribution produced by equal levels of extrinsic PEEP.[63,64] Neumann and co-workers have subsequently confirmed these findings, showing better matching of ventilation-perfusion distribution and more uniform aeration on CT scan with applied PEEP than with intrinsic PEEP, in an animal model of lung injury.[65] In patients with ARDS ventilated at constant V_T, respiratory rate and total PEEP, using multiple linear regression analysis of pressure and flow waveforms, we have shown that pressure controlled ventilation is associated with potentially less regional overdistension compared to volume controlled ventilation. This benefit was negated when pressure controlled IRV was used.[66]

Prone positioning

Prone positioning may reduce VILI. Multiple case series have demonstrated rapid and sustained improvement in oxygenation without an increase in distending pressures.[67] Two randomised controlled trials using early prone positioning are underway to assess this.

Surfactant replacement therapy

This is clearly beneficial in neonates but a large trial has not shown it to be beneficial in adults.[68] The optimal components in surfactant, and the method and adequacy of delivery, are issues that must be confirmed before one can draw conclusions about the efficacy of this treatment.

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