American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

International Consensus Conferences in Intensive Care Medicine: Ventilator-associated Lung Injury in ARDS

THIS OFFICIAL CONFERENCE REPORT WAS COSPONSORED BY THE AMERICAN THORACIC SOCIETY, THE EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE, AND THE SOCIETÉ DE RÉANIMATION DE LANGUE FRANÇAISE, AND WAS APPROVED BY THE ATS BOARD OF DIRECTORS, JULY 1999

This is the report of a consensus conference entitled "Ventilator-associated Lung Injury (VALI) in ARDS", which was held in Toronto, Canada in October 1998. The conference was sponsored by three societies: The American Thoracic Society (ATS), the European Society of Intensive Care Medicine (ES-ICM), and the Societé de Réanimation de Langue Française (SRLF). The methods of the consensus were originally established by the National Institutes of Health (NIH) (1) and were adapted in a previous consensus conference in critical care (2).

The process of the consensus conference had three phases. First, a comprehensive literature search was done and key articles were precirculated to a jury. Second, experts in VALI selected by the scientific advisors (F.L., J.M., and A.S.) delivered focused presentations at a 2-d symposium attended by about 500 individuals (October 29–30, 1998); there was ample debate and discussion. Third, the jury summarized the available evidence in response to five key questions over 2 days immediately after the conference. The jury was composed of 10 clinician-scientists not expert in the field of ventilator-associated lung injury. The jury's tasks were to review evidence and answer questions without the potential bias that could arise from experts in the field attempting to achieve consensus. Ventilator-associated lung injury in adult respiratory distress syndrome (ARDS) is a controversial topic, and information ranging from animal studies to multicenter randomized controlled trials was included. After this consensus report was first drafted, the results of a large multicenter trial conducted by the NIH directed at assessing the effect of low versus high tidal volume support of patients with ARDS were reported in preliminary fashion in April 1999; accordingly, the jury has modified the original report to reflect this important, albeit non-peer-reviewed, information.

For the purposes of this report, several terms need definition. Acute lung injury (ALI) and ARDS are defined using the American–European Consensus Conference definitions (3). Ventilator-induced lung injury (VILI) is defined as acute lung injury directly induced by mechanical ventilation in animal models. Since VILI is usually indistinguishable morphologically, physiologically, and radiologically from the diffuse alveolar damage of acute lung injury, it can only be discerned definitively in animal models. VALI is defined as lung injury that resembles ARDS and that occurs in patients receiving mechanical ventilation. VALI may be associated with preexisting lung pathology such as ARDS. However, unlike VILI,

one cannot be sure that VALI is caused by mechanical ventilation; rather, VALI is associated only with mechanical ventilation. For the purposes of this report barotrauma is defined as radiologic evidence of extraalveolar air. Five randomized controlled trials have compared low to higher tidal volume ventilation of patients with ALI/ARDS and are referred to as low/high tidal volume trials and arms. One of these trials compared a combined ventilator strategy with a high tidal volume strategy and is referred to as the combined strategy/high tidal volume trial and arms.

Extensive research on lung injury and ventilation has generated controversies regarding the pathophysiology, risk factors, incidence, outcome, clinical detection, monitoring, and prevention of VALI. The purposes of the Consensus Conference were to review, synthesize, and evaluate the literature, to hear and critique expert presentations, and to address five key questions regarding VALI.

Question 1: What are the Factors Identified by Experimental Studies Responsible for Ventilator-induced Lung Injury?

Investigators using many animal species and experimental designs have convincingly demonstrated that it is possible to induce alveolar and airway damage with mechanical ventilation. Before the publication of this body of literature, clinicians had largely assumed that ventilator-induced damage was confined to the development of air leaks, such as pneumothoraces. However, it is now recognized that more subtle morphologic, structural, and physiologic changes might develop with mechanical ventilation (4). The recognition that alveolar overdistention rather than high proximal airway pressure is the primary determinant of the injury (i.e., volutrauma rather than barotrauma) has constituted a substantial shift in clinicians' thinking about the pathogenesis of ventilator-induced complications. However, it is important to note that the alveolar overdistention is due to an increased transpulmonary pressure, so in truth the injury remains a form of barotrauma.

Mechanical ventilation with high pressure and volume can induce changes in endothelial and epithelial permeability that are indistinguishable from other forms of experimental lung injury. Light microscopy reveals severe alveolar damage, alveolar hemorrhage, and hyaline membranes in animals that die soon after the induction of overinflation injury, whereas collapsed alveolar spaces and proliferation of alveolar Type II cells are observed in animals that survive for a longer period after the inciting insult. Electron microscopy reveals endothelial abnormalities, with breaks and the formation of intracapillary blebs, and epithelial abnormalities, consisting of discontinuities and occasional complete destruction of Type I cells (5).

The most important factors that have been proposed as responsible for VALI are, first, high lung volume associated

with elevated transpulmonary pressure and alveolar overdistention, and, second, repeated alveolar collapse and reopening due to low end-expiratory volume; other factors that contribute to, or aggravate, injury include preexisting lung damage and/or inflammation, high inspired oxygen concentration, the level of blood flow, and the local production and systemic release of inflammatory mediators.

Excessive alveolar volume in conjunction with increased transalveolar pressure is important: isolated increase in airway pressure in the absence of a concomitant increase in alveolar volume is not deleterious (6). High pressure and volume during mechanical ventilation may increase both the lung permeability and the pulmonary vascular transmural pressures, and thereby induce lung edema or worsen preexisting edema. The avoidance of alveolar overdistention by limiting tidal volume and/or plateau pressure has been proposed as a method of minimizing this type of injury in patients (7).

Local inhomogeneities of ventilation, as could exist at low lung volume with lung injury, have been modeled to result in large shear forces applied to lung units undergoing cyclical opening and closing (8). The repeated collapse and reopening of lung units at low lung volumes may contribute to VALI by application of such shear forces (9). The addition of positive end-expiratory pressure to maintain alveolar recruitment throughout the respiratory cycle has been demonstrated to ameliorate lung injury in some models (10) and has been proposed as a means of minimizing VALI.

A different model of acute lung injury is the elevation of vascular transmural pressure in the isolated lung, which induces changes in the alveolocapillary barrier, visible by electron microscopy, that resemble the injuries induced by mechanical ventilation (11). In this model, the local or regional stress during lung inflation may increase microvascular transmural pressures and subsequent disruption of capillaries, so-called capillary stress failure.

Mechanical damage of lung tissue may activate inflammatory mediators. In animal models (12), the strategy of mechanical ventilation influences local release of inflammatory mediators from the lung: the prevention of repeated collapse and reopening and overdistention reduces the release of these mediators. These mediators may also be released to the systemic circulation (13). It is possible, although not confirmed, that these alterations in the inflammatory response may modify lung injury itself or conceivably lead to a systemic inflammatory response (13).

Major differences exist in the type of injury observed among different animal species. In small animals, mechanical ventilation can produce rapidly fatal severe pulmonary edema (5). This model represents an increase in lung permeability due to acute mechanical stretching of the lung. In larger animals, ventilator-induced pulmonary edema develops more slowly, and if death is sufficiently delayed, inflammatory cells, particularly neutrophils, infiltrate the interstitial and alveolar spaces and proliferation of fibroblasts and Type II pneumocytes may be observed (14). The effects of mechanical ventilation in acute experimental lung injury may also be markedly modified by the experimental design. For example, the injury seen in a closed-chest model may not be seen when the same ventilator settings are used when the chest is open owing in part to differences in hemodynamic and transpulmonary pressures (15). Likewise, in intact animals, manipulation of blood pressure and flow can influence the degree of injury (16). The modifying influence of perfusion is lacking in the *ex vivo*, isolated lung model. While many experimental models are based on a relatively large injury applied for a brief period of time, little is known about the "dose response" of lesser mechanical insults for longer periods of time, or the effects of frequency on repetitive insults during the respiratory cycle.

A major difference exists in the type of lesions induced by alveolar overdistention in distinction to capillary stress failure: endothelial blebbing, the hallmark ultrastructural lesion of alveolar overinflation (5), is not characteristic of capillary stress failure (11); epithelial cell swelling and hyaline membrane formation, as seen with prolonged ventilation, are not observed with capillary stress failure; and the duration of the challenge, an important factor with overinflation injury, does not increase the incidence of stress failure. In particular, studies have not been conducted in large animals receiving mechanical ventilation for days after an initial lung injury; such a model might provide useful insight into patients with ARDS.

Observations of patients with ARDS suggest that they may be at risk for VALI. Computed tomography (CT) scans reveal a decreased volume of aerated lung in patients with ARDS (17), supporting concern that the "baby lung" of ARDS could be readily overdistended with even modest tidal volumes. Pressure–volume relationships in many patients with ARDS exhibit upper and lower inflection points that parallel the findings in animal models and are taken to signal overdistension and recruitment–derecruitment, respectively. Moreover, many of the morphologic, structural, and physiologic abnormalities of acute lung injury and ARDS in patients also occur in experimental models. However, there are major differences between experimental models and patients. The time course of the injury in all current lung injury models is usually very brief, whereas the sequelae of acute lung injury in patients usually last days to weeks; moreover, the noxious stimuli are very different (e.g., depletion of surfactant by lavage as a model of lung injury). Most of the experimental models involve initially normal lungs, whereas patients at risk of VALI typically have an underlying lung disease and other comorbidities. Accordingly, extrapolation of the pathogenetic and pathophysiological mechanisms of experimental VILI to clinical ARDS must be done with caution. In biomedical research, a common sequence is to test a hypothesis in animals and to subsequently test a variant of that hypothesis in patients. This important translational step is missing in the studies of VILI.

Question 2: What is the Evidence for Ventilator-associated Lung Injury in Patients with ARDS?

The lungs of mechanically ventilated patients with ARDS have physiological, radiological, and histopathological features that resemble VILI in experimental animals. These features include interstitial and alveolar edema, hemorrhage, hyaline membranes, neutrophilic alveolitis, and diffuse alveolar damage. Furthermore, as injury and duration of mechanical ventilation progress there is profound remodeling of lung structure manifested as fibroproliferation, regional loss of lobular and alveolar architecture, cyst formation, and local emphysema. Because insults leading to ARDS generally precede the institution of ventilatory support in humans these changes in lung structure could be due either to progression of ARDS or to VALI, or both.

Barotrauma occurs in patients with ARDS who are mechanically ventilated. Barotrauma occurs because the lung injury is severe and/or because the injured lung is being overdistended by mechanical ventilation. Since overdistension may play a role in the pathogenesis of more subtle forms of VALI (e.g., pulmonary edema), more overt forms of VALI (e.g., barotrauma) have been used as a surrogate marker of VALI. However, mechanisms of VALI are complex and probably require repeated mechanical insults, while barotrauma may result from a single overinflation of the lungs. Therefore, baro-

trauma may be a relatively insensitive and nonspecific marker of more subtle forms of VALI.

Several observations have suggested that VALI may occur in patients with ARDS. First, a steady decline in mortality from ARDS, observed in some studies, was associated with the use of lower tidal volumes and inflation pressures (18, 19). Second, patients with ARDS who were mechanically ventilated and died had extensive consolidation, emphysema, and multiple cysts on CT scan before death and evidence of marked tissue remodeling and lung destruction on autopsy (20). Randomized prospective clinical trials of patients with ARDS may be more persuasive. For example, one such trial suggests that compared with a ventilator strategy of high tidal volume and low positive end expiratory pressure (PEEP), a strategy combining recruitment maneuvers, low tidal volume (adjusted to maintain the pressure–volume curve below the upper inflection point), and higher PEEP (adjusted to maintain the pressure–volume curve above the lower inflection point) improves survival and decreases the incidence of barotrauma (7). Importantly, the NIH completed a multicenter trial that enrolled 861 patients, comparing higher tidal volume (12 cm^3/kg) with lower tidal volume (6 cm^3/kg) ventilation for ARDS (NIH ARDS Trials Network, as reported on the World Wide Web [WWW] and at the International Meeting of the ATS, San Diego, April 1999). The targeted tidal volumes were based on ideal body weight, not actual body weight (the latter was approximately 20% greater). At interim analysis, mortality had been significantly reduced in patients receiving the low tidal volume ventilator strategy, from about 39% to about 31%. In another study (21), the ventilation of patients with ARDS, using lower tidal volumes and higher PEEP levels set according to the lower and upper inflection points of the respiratory system pressure–volume (PV) curve, produced lower concentrations of inflammatory mediators in bronchoalveolar lavage fluid and blood, as compared with patients ventilated with higher tidal volume and lower PEEP levels set by more conventional criteria.

It is clear that clinical observations can only infer that VALI occurs in humans. A definitive trial to prove that mechanical ventilation per se causes lung injury in humans cannot be designed. However, modifications of ventilator strategy based on growing understandings of mechanisms of lung injury have been, and should continue to be, assessed in outcome studies.

Question 3: What are the Risk Factors, Incidence, and Effects on Outcome of VALI?

Patients without readily apparent lung injury (e.g., neuromuscular disease with respiratory failure) have been treated with positive pressure ventilation for protracted periods of time without clinically discernible VALI. Patients with ALI/ARDS, on the other hand, have a number of conditions that potentially predispose them to this complication of mechanical ventilation: the injured lung may be inherently at risk for further injury; the lung injury is often nonhomogeneous and the resulting reduced volume of aeratable lung ("baby lung") is at risk for overdistension with conventional ventilator settings; and the interaction of cyclical ventilation and lung injury causes recruitment–derecruitment with consequent mechanical stress. Thus, ALI/ARDS may be considered the most important and readily identified risk factor for VALI (22). Whether specific subsets of ALI/ARDS are at greater risk seems conceivable but poorly defined at present.

Because VALI may not be readily defined nor detected, our ability to determine its independent risk factors, incidence, and effects on outcome is inherently hampered (23,

24). Even large observational studies cannot clarify these issues, since correlation of ventilator parameters to outcome cannot discern between adverse or beneficial effects of mechanical ventilation strategies and the changing requirements for such support dictated by worsening underlying lung disease. Barotrauma has been employed in a number of these studies as a surrogate measure of VALI. While barotrauma has a specific radiologic and clinical definition, its relationship to the microstructural lesions of VALI is unknown. The use of barotrauma as a surrogate measure of VALI is also confounded because it may be caused by pleural injury secondary to central venous catheterization. The timing of barotrauma has varied in reported series, with some investigators reporting that it is more common early in the course of mechanical ventilation (< 6 d) (23, 25), whereas others report a predominance of late (> 7 d) (24) appearance.

The incidence of barotrauma in patients with ALI/ARDS varies widely, from approximately 5 to 50% (Table 1) (26–31). In most recent series the incidence ranges from 5 to 15% and the higher incidence reported in earlier studies may relate to highly selected patient groups or different ventilator strategies. Clinicians have sensed a decline in the incidence of barotrauma, perhaps related to reduction of tidal volume and limitation of distending lung pressure during mechanical ventilation. On the basis of the results of multiple reports, a plot of the incidence of barotrauma versus the mean plateau airway pressure of patient groups shows that lower airway pressure is associated with a lower incidence of barotrauma. There appears to be a threshold of 35 cm H_2O, above which incidence rises dramatically. The mortality attributable to barotrauma events such as pneumothorax is not well known, although the mortality directly attributable to barotrauma seems low (23–27).

Other common cointerventions for mechanical ventilatory support of patients with acute lung injury may very well contribute to VALI. The roles of cointerventions such as fraction of inspired oxygen, vascular filling pressure, and ventilator frequency in either preventing or promoting VALI have yet to be defined.

In patients dying of ARDS, lung histopathology revealed a greater than 85% incidence of cysts, bronchiolar dilatation, or alveolar overdistension (20). More severe lesions were seen in patients receiving higher airway pressures, tidal volumes, and

TABLE 1

INCIDENCE OF BAROTRAUMA IN PATIENTS WITH ARDS

Reference	No. of Patients	Population and Study Design	Barotrauma (%)
20	30	Case series, patients dying of ARDS	36
28	84	Case series, ARDS with extracorporeal support	49
23	41	Case series, medical	40
24	100	Case series, medical	13
27	41	Case series, surgical	17
26	725	Exosurf trial	7
7	HTV, 24	RCT, medical	HTV, 42
	CS, 29	RCT, medical	CS, 7
29	HTV, 60	RCT, medical–surgical	HTV, 7
	LTV, 60		LTV, 10
30	HTV, 58	RCT, medical–surgical	HTV, 12
	LTV, 58		LTV, 14
31	HTV, 26	RCT, medical–surgical	HTV, 4
	LTV, 26		LTV, 8

Definition of abbreviations: CS = combined strategy; HTV = higher tidal volume; LTV = lower tidal volume; RCT = randomized control trial.

concentrations of oxygen. However, these studies have not analyzed risk factors prospectively or evaluated lesions as predictors of outcome, nor have they separated the potential contributions of VALI and the underlying lung disease. In addition, similar lesions were reported anecdotally as present in patients dying of acute lung injury before the routine use of mechanical ventilatory support (32).

Lung CT of patients with ALI/ARDS may reveal macroscopic air collections that are not readily detected by routine chest radiography (28). There are no prospective clinical studies that have determined risk factors for, incidence of, or outcome resulting from macroscopic air collections on lung CT.

Finally, the incidence of barotrauma with different ventilator strategies in the treatment of ALI/ARDS has been reported in recent prospective randomized control clinical trials (*see* Table 1 and QUESTION 5).

Question 4: What is the Best Approach to Detect and Monitor VALI in the Clinical Setting?

There are no clinical symptoms, signs, changes in physiological variables, or bedside investigations that are specific to detect VALI. The microscopic manifestations of VALI cannot be detected clinically. While macroscopic air leaks can be detected clinically or radiographically, these may or may not be caused by VALI. Cost, logistic problems associated with patient transport, and lack of evidence of improved patient outcome related to repeated scanning mean that chest CT scanning cannot be recommended as a routine method for the detection or monitoring of VALI. Nevertheless, lesions, including pneumothorax, intraparenchymal cysts, or evidence of areas of lung hyperinflation can be seen on high-resolution CT scan when not evident from clinical examination or routine chest X-ray. CT scans performed with increased PEEP can show evidence of lung recruitment.

Technical difficulties, anteroposterior films, and supine positioning reduce the sensitivity of chest X-rays taken in the intensive care unit compared with films taken under ideal conditions. Interobserver variability in detection of pulmonary interstitial emphysema is high because the chest X-ray signs are nonspecific (22).

VALI should always be considered as part of the differential diagnosis of a deterioration in respiratory function in a patient with ALI/ARDS undergoing mechanical ventilation. Other causes are progression of ARDS related to the underlying disease process, pulmonary or extrapulmonary infection, fluid overload, and absorption atelectasis.

ARDS is a heterogeneous and dynamic disorder with morphology and pulmonary mechanics changing over time (28). The early phase of the syndrome is often characterized by predominance of lung edema, whereas the later or proliferative phase of ARDS is characterized by inflammation, fibrosis, and disordered healing. The relationship of VALI to these phases of ARDS—either in terms of susceptibility of the lung to injury or of VALI as a contributor to the various findings over time—is not understood. Pulmonary mechanics may also vary with the etiology and particularly between pulmonary and extrapulmonary causes of ARDS (33). Frequent patient evaluation is therefore essential during mechanical ventilation, so as to monitor the occurrence of potential risk factors for VALI and assess the response to changes in ventilator settings.

Both experimental studies of VILI and clinical trials to minimize the potential impact of VALI have used the PV curve of the respiratory system to assess mechanics and titrate ventilator settings. PEEP set above the lower inflection point and plateau pressure lower than the upper inflection point of the PV curve have been suggested as necessary to maintain recruitment and avoid overdistention, respectively (7, 34, 35). The PV curve inflection points can be difficult to identify and they are also affected by chest wall compliance (not just lung compliance), causing some uncertainty as to whether these points truly reflect lung recruitment and lung overdistention in clinical practice; this concern may be most important in patients with surgical conditions causing increased abdominal pressure and coincident acute lung injury, in whom PV curve inflection points have been shown to reflect chest wall rather than lung mechanics (34, 35). A number of methods of performing PV curves are available (36) but there is no consensus on the best way to obtain such a curve during patient care. Some methods of performing PV curves carry a risk of adverse effects, including hypoxemia at low lung volumes and derecruitment at low levels of PEEP. Other problems that can arise with PV curve determination include circulatory changes (e.g., diminished venous return) or complications of sedation and paralysis, which are usually required for the thorough characterization of passive mechanics of the respiratory system. For all these reasons, and because of a lack of general familiarity with methodology and interpretation, PV curves are not usually obtained as part of routine clinical assessment. Nevertheless, research using PV curves has provided the conceptual framework on which routine ventilator settings and associated monitoring are based. The variables that are important include peak inspiratory, transpulmonary, and plateau pressures, tidal volume, PEEP, and auto-PEEP.

Increases in peak inspiratory and plateau pressures during volume-controlled ventilation, or a decrease in tidal volume during pressure controlled ventilation, may indicate deterioration in lung mechanics, potentially related to VALI. Likewise, a decrease in Pa_{O_2} (or $Pa_{O_2}/F_{I_{O_2}}$) and/or increase in Pa_{CO_2}, alone or combined with ventilator changes, may be the result of VALI. Such changes, however, virtually always have other potential explanations.

Question 5: What Nonpharmacological Approaches are Currently Available for Prevention of VALI?

Ventilatory strategies aimed at preventing or attenuating VALI have been tested in five randomized clinical trials in adults with, or at risk of, ARDS (7, 29–31) (NIH ARDS Trials Network) (Table 2). Four trials have compared the effect of ventilation with lower versus higher tidal volume, without use of PV curves to set PEEP or tidal volume. As a consequence of the study design of these four trials, PEEP levels were similar between the patient groups studied, while Pa_{CO_2} levels were higher and plateau airway pressures lower in patients receiving a lower tidal volume strategy. Three of these trials (29–31) did not show any difference in mortality between low and high tidal volume ventilation. However, the largest of the trials (NIH ARDS Trials Network, preliminary and non-peer-reviewed results as reported on the WWW and at the International Meeting of the ATS, San Diego, April 1999), which enrolled 861 patients, demonstrated an ∼ 20% reduction in mortality (from 39 to 31%) associated with a lower tidal volume ventilation strategy. Reconciling the different conclusions of these studies is not straightforward; a detailed analysis of the NIH trial will be required once it is published. The larger size of the NIH trial may have provided power to detect differences not seen in the smaller trials of Brochard and coworkers (108 patients), Brower and coworkers (52 patients), and Stewart and coworkers (120 patients) (*see* Table 2). It is conceivable that a wider difference in delivered tidal volumes was achieved in the NIH study, thus accentuating differences in lung injury and outcome; preliminary analysis of the absolute

difference in tidal volumes across the studies suggests this may be the case (*see* Table 2), although significant overlap in plateau airway pressures exists across the four studies. Pooled analysis of data may yield improved insight into the different outcome observations among these studies.

One of these trials (7) compared the effect of a combined strategy, composed of a low tidal volume, relatively high PEEP titrated according to the PV curve, plus an intermittent continuous positive airway pressure (CPAP) recruitment maneuver, versus ventilator settings aimed at normalizing P_{CO_2} without limitation in peak inspiratory pressure (Table 2). The combined strategy achieved a significant reduction in mortality at 28 d (but not at hospital discharge), associated with improved oxygenation, a decreased incidence of barotrauma, and increased rate of weaning from mechanical ventilation. Comparison of this trial with the others is difficult, given the many differences in ventilator strategy.

In summary, these results suggest that (*1*) use of high tidal volumes (12 ml/kg), resulting in high transpulmonary pressure and plateau airway pressure (Pplateau) in excess of 30–35 cm H_2O, is potentially hazardous, since it may increase the risk of barotrauma and mortality; (*2*) a relatively simple strategy of reducing tidal volume to 6 ml/kg, or lower if necessary to reduce the plateau airway pressure to less than 30 cm H_2O, appears safe and associated with improved outcome; and (*3*) an increase in PEEP, titrated to the PV curve, may have a protective effect against VALI, but this warrants further testing and is not recommended for routine clinical management. Moreover, the independent contribution of each component in this combined strategy is not currently understood. In one sense, the clinical studies to date may not have specified a lung-protective strategy derived from low tidal volume ventilation so much as they have identified risks associated with higher tidal volume ventilation, with the threshold level yet to be defined.

TABLE 2
SUMMARY OF RANDOMIZED TRIALS OF VENTILATORY STRATEGIES IN TREATMENT OF ADULT PATIENTS WITH ALI/ARDS

	Study (Reference No.)				
	Amato and coworkers (7)	Brochard and coworkers (30)	Brower and coworkers (31)	Stewart and coworkers (29)	NIH[‡]
Population					
Entry criteria	LIS > 2.5, Ppa,we < 16, MV < 7 d	LIS > 2.5, MV < 3 d	$Pa_{O_2}/F_{I_{O_2}}$ < 200, MV < 1 d	$Pa_{O_2}/F_{I_{O_2}}$ < 250, MV < 1 d	$Pa_{O_2}/F_{I_{O_2}}$ < 300, MV < 36 h
Exclusion criteria	Coronary insufficiency, prior lung disease, barotrauma, uncontrolled acidosis, intracranial hypertension, terminal disease	Left heart failure, acute or chronic organ failure, chest wall abnormality, intracranial hypertension, head injury, terminal disease	Age < 18, left heart failure, acute neurologic disease, chronic lung disease, thoracic surgery	Age < 18, left heart failure, myocardial ischemia, acute or chronic neurologic disease, PIP > 30 for 2 h, terminal disease	Age < 18, left heart failure, acute neurologic disease, life expectancy < 6 mo, hepatic failure
Characteristics at inclusion					
APACHE II	28 versus 27	18 versus 17	90 versus 85 (APACHE III)	22 versus 21	
$Pa_{O_2}/F_{I_{O_2}}$	112 versus 134	144 versus 155	129 versus 150	123 versus 145	
LIS	3.4 versus 3.2	3.0 versus 3.0	2.7 versus 2.8	—	
Targeted settings					
Intervention	V_T < 6 ml/kg, PIP < 40 cm H_2O, Pdriving < 20 cm H_2O, CPAP recruiting	Pplateau ≤ 25–30 cm H_2O, V_T = 6–10 ml/kg	Pplateau ≤ 30 cm H_2O, V_T ≤ 8 ml/kg IBW	PIP < 30 cm H_2O, V_T ≤ 8 ml/kg IBW	V_T ≤ 6 ml/kg IBW, reduce V_T if Pplateau > 30 cm H_2O
Control	V_T = 12 ml/kg, Pa_{CO_2} 35–38 mm Hg, PIP unlimited	V_T = 10–15 ml/kg, PIP < 60 cm H_2O	Pplateau ≤ 45–55 cm H_2O, V_T = 10–12 ml/kg IBW	PIP ≤ 50 cm H_2O, V_T = 10–15 ml/kg IBW	V_T = 12 ml/kg IBW, reduce V_T if Pplateau > 50 cm H_2O
PEEP, cm H_2O					
Intervention	2 above Pflex	0–15, titrated to best P/F ratio	5–20, titrated to best P/F ratio	5–20, titrated to best P/F ratio	Titrated to gas exchange
Control	Titrated to P/F ratio	Same	Same	Same	Titrated to gas exchange
Resulting settings*					
Pplateau, cm H_2O	30 versus 37	26 versus 32	25 versus 32	22 versus 28	25 versus 32–34
PEEP, cm H_2O	16 versus 7	11 versus 11	10 versus 9	9 versus 7	8–9, both groups
V_T, ml or ml/kg	350 versus 770 ml	7 versus 10 ml/kg	7 versus 10 ml/kg	7 versus 11 ml/kg	6.2 versus 11.8 ml/kg
Pa_{CO_2}, mm Hg	55 versus 32	60 versus 41	50 versus 40	54 versus 46	
Outcomes					
Mortality	13/29 (45%) versus 17/24 (71%)	47% versus 38%	13/26 (50%) versus 12/26 (46%)	30/60 (50%) versus 28/60 (47%)	31 versus 39%
Barotauma[†]	2 (7%) versus 10 (42%)	8 (14%) versus 7 (12%)	1 (4%) versus 2 (8%)	6 (10%) versus 4 (7%)	No difference

Definition of abbreviations: CPAP = continuous positive airway pressure; IBW = ideal body weight (*note*: the formulas used for calculation of IBW were not uniform across studies; Brochard and coworkers used "dry weight" to determine tidal volume); LIS = lung injury score; MV = mechanical ventilation; Pdriving = driving pressure; Pflex = pressure at lower inflection point of pressure–volume curve; PIP = peak inspiratory pressure; Ppa,we = pulmonary artery wedge pressure; Pplateau = plateau pressure; V_T = tidal volume.

* Precise comparison of resulting settings across the studies is difficult, since there is variation in the schedule of reporting; we have attempted here to compare mean values on Days 1–3.

† Barotrauma was defined by Amato and coworkers as "clinical barotauma," by Brower and colleagues as pneumothorax, by Stewart and coworkers as pneumothorax, pneumomediastinum, subcutaneous emphysema, and lung cysts on chest radiograph, and by Brochard and colleagues as pneumothorax requiring a chest tube.

‡ NIH ARDS Trials Network, as reported on NIH website (www.nih.gov).

When the full details of the NIH study become available, one approach pending further investigation of these mechanisms would be to employ the full protocol of this study, which demonstrated improved survival.

Tidal volume limitation may result in severe hypercapnia, which appears to be well tolerated. Further delineation of patient groups in whom hypercapnia is poorly tolerated will be important in the formulation of general recommendations regarding the use of these ventilator strategies. The use of bicarbonate infusions in the treatment of hypercapneic acidosis may result in adverse consequences, such as reduced hypoxic pulmonary vasoconstriction and reduced myocardial contractility.

Alternative ventilatory modes associated with low tidal volumes and driving pressure that are designed to avoid both overdistention and alveolar collapse have been evaluated in randomized trials in neonates and adults. High-frequency oscillation (HFO) (37–42) and high-frequency jet ventilation (HFJV) (43, 44) have been compared with conventional ventilation in neonates with respiratory distress syndrome. The results of these trials have been inconsistent, partly because of the substantial impact of concomitant surfactant therapy. Before surfactant was in widespread use, neither HFO (37, 40) nor HFJV (43, 44) were associated with a lower mortality, requirement for oxygen at 30 d, or incidence of bronchopulmonary dysplasia. Since the introduction of surfactant into routine therapeutic use, these ventilatory modes appear to be associated with improved pulmonary outcomes. Two randomized trials of HFJV in adults (45, 46) showed no difference in mortality.

Prone positioning may also contribute to prevention of VALI. In animal experiments, VALI appears to be more severe in the supine than in the prone position. In case series reports, some patients managed in the prone position had improved oxygenation and decreased shunt without an increase in distending pressures (47). Safety concerns, including accidental extubation and catheter removal, hemodynamic instability, and pressure necrosis could limit applicability of the prone position. Recommendations about the use of prone positioning will be better informed by randomized trials that carefully evaluate its short- and long-term risks and benefits.

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