

# Ventilatory Management of Acute Lung Injury and Acute Respiratory Distress Syndrome

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FOR NEARLY 4 DECADES SINCE THE acute respiratory distress syndrome (ARDS) was first described,<sup>1</sup> research has been ongoing in an effort to improve the outcome of this critical illness. Acute respiratory distress syndrome is characterized by the acute onset of hypoxemia and bilateral infiltrates on chest radiography in the absence of left atrial hypertension. Various pulmonary (eg, pneumonia) and nonpulmonary (eg, pancreatitis) risk factors are associated with ARDS.<sup>2</sup> Mortality rates range from 26% to 74%, with most deaths attributed to associated conditions, such as sepsis and multisystem organ failure, rather than hypoxemia alone.<sup>2-6</sup> Some survivors of ARDS have reduced quality of life with physical, neurocognitive, and emotional morbidity.<sup>7-10</sup>

The original ARDS case series<sup>1</sup> outlined a number of clinical features that were later incorporated into more formal definitions of this syndrome (TABLE 1).<sup>11-13</sup> In 1994, the American-European Consensus Conference (AECC) definition was developed and is used widely by clinicians and researchers.<sup>13</sup> Under this definition, acute lung injury (ALI) is designated for patients with significant hypoxemia (partial pressure of arterial oxygen to fraction of inspired oxygen [ $\text{PaO}_2/\text{FiO}_2$ ] ratio

**Context** The acute lung injury and acute respiratory distress syndrome are critical illnesses associated with significant morbidity and mortality. Mechanical ventilation is the cornerstone of supportive therapy. However, despite several important advances, the optimal strategy for ventilation and adjunctive therapies for patients with acute lung injury and acute respiratory distress syndrome is still evolving.

**Evidence Acquisition** To identify reports of invasive ventilatory and adjunctive therapies in adult patients with acute lung injury and acute respiratory distress syndrome, we performed a systematic English-language literature search of MEDLINE (1966-2005) using the Medical Subject Heading *respiratory distress syndrome, adult*, and related text words, with emphasis on randomized controlled trials and meta-analyses. EMBASE and the Cochrane Central Register of Controlled Trials were similarly searched. The search yielded 1357 potential articles of which 53 were relevant to the study objectives and considered in this review.

**Evidence Synthesis** There is strong evidence to support the use of volume- and pressure-limited lung-protective ventilation in adult patients with acute lung injury and acute respiratory distress syndrome. The benefit of increased levels of positive end-expiratory pressure and recruitment maneuvers is uncertain and is being further evaluated in ongoing trials. Existing randomized controlled trials of alternative ventilation modes, such as high-frequency oscillation and adjunctive therapies, including inhaled nitric oxide and prone positioning demonstrate no significant survival advantage. However, they may have a role as rescue therapy for patients with acute respiratory distress syndrome with refractory life-threatening hypoxemia.

**Conclusions** Volume- and pressure-limited ventilation strategies should be used in managing adult acute lung injury and acute respiratory distress syndrome patients. Further research is needed to identify barriers to widespread adoption of this strategy, as well as the role of alternative ventilation modes and adjunctive therapies.

JAMA. 2005;294:2889-2896

www.jama.com

<300), while ARDS represents the subset of ALI patients with the most severe lung injury ( $\text{PaO}_2/\text{FiO}_2$  ratio <200). Using these definitions, ALI and ARDS are relatively common with annual incidences estimated at 20 to 50 and 15 to 30 cases per 100 000 persons, respectively.<sup>2,3</sup>

No specific pharmacologic therapy has proved effective for ALI or ARDS, and therapy is largely supportive with the use of mechanical ventilation.<sup>11</sup> Perhaps the most important advance in ALI and ARDS research has been the recognition that mechanical ventilation, al-

though necessary to preserve life, can potentiate or directly injure the lungs through a variety of mechanisms col-

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lectively referred to as ventilator-associated lung injury.<sup>14-16</sup> These mechanisms include exposure to high inflation pressures or overdistention (barotrauma or volutrauma),<sup>17</sup> repetitive opening and closing of alveoli (atelectrauma),<sup>18</sup> and mechanotransduction resulting in up-regulated cytokine release and a systemic inflammatory response (biotrauma).<sup>19</sup> The lungs of patients with ALI or ARDS are particularly prone to ventilator-associated lung injury because they are heterogeneously affected, as demonstrated in computed

tomography studies (FIGURE).<sup>20</sup> As a result, some areas of the lung (often dependent regions) are atelectatic, consolidated, less compliant, and thus less available for ventilation while other areas (usually nondependent regions) appear and behave normally. Understanding this heterogeneity has led to the "baby lung" concept, which suggests that, overall, a markedly reduced volume of lung is available for ventilation in ALI or ARDS, effectively, a functionally baby-sized lung within an adult-sized body.<sup>21,22</sup> Conse-

quently, mechanical ventilation can result in barotrauma or volutrauma when volumes and pressures meant for the entire lung are forced into only a small portion of functional lung. In addition, shear forces at the interface between the open and closed lung units result in atelectrauma. Both of these types of injury also can lead to release of cytokines from the lung and have adverse systemic effects, contributing to the development of multisystem organ failure.<sup>18,19</sup>

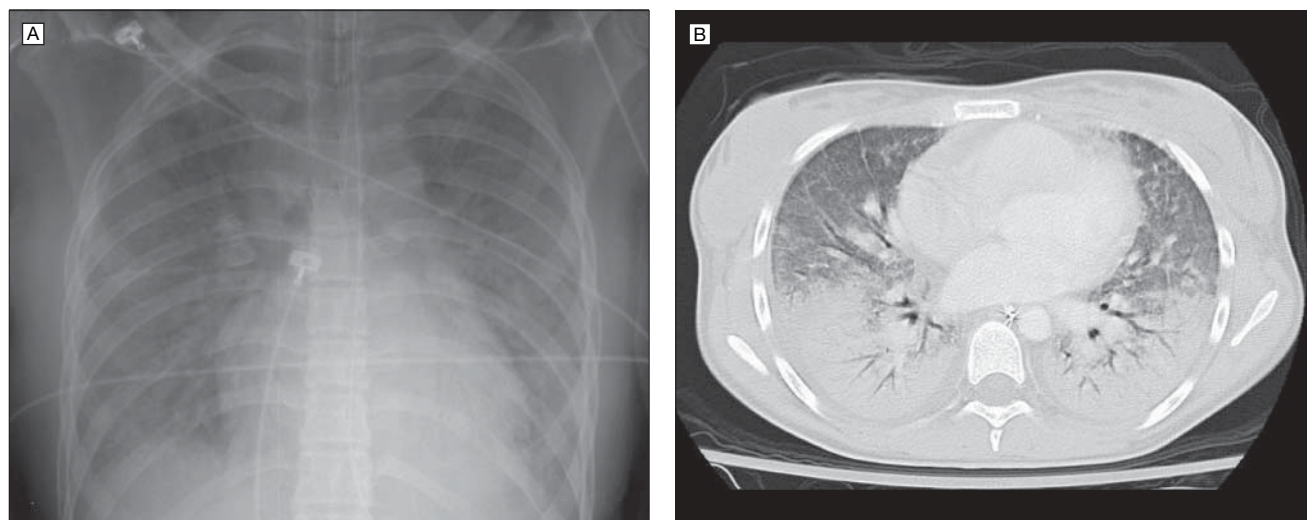
This improved understanding of ALI and ARDS and ventilator-associated lung injury has been important in designing lung protective mechanical ventilation strategies aimed at attenuating ventilator-associated lung injury and improving outcomes. Such strategies for the invasive ventilatory management of adult ALI and ARDS have recently been tested in a number of important clinical trials, which we review in this article. In addition, we discuss alternative invasive ventilatory modes and adjunctive therapies, with a focus on those that we believe are widely available for clinical use in adults at the present time. We also highlight recent controversies and suggest areas for future research.

**Table 1.** Diagnostic Criteria for ARDS

Source	Oxygenation	Chest Radiograph	Other Criteria
Petty and Ashbaugh, <sup>11</sup> 1971	Cyanosis refractory to oxygen therapy	Diffuse alveolar infiltrates on frontal chest radiograph	Impaired pulmonary compliance Marked difference in inspired vs arterial oxygen tensions
Murray et al, <sup>12</sup> 1988	Hypoxemia ( $\text{PaO}_2/\text{FiO}_2$ ), by quintiles	No. of quadrants of alveolar consolidation on frontal chest radiograph	PEEP and respiratory system compliance (by quintiles) Preexisting direct or indirect lung injury Nonpulmonary organ dysfunction
Bernard et al, <sup>13</sup> 1994	ALI, $\text{PaO}_2/\text{FiO}_2 \leq 300$ , regardless of PEEP level ARDS, $\text{PaO}_2/\text{FiO}_2 \leq 200$ , regardless of PEEP level	Bilateral infiltrates on frontal chest radiography	PCWP $\leq 18$ mm Hg if measured or no clinical evidence of left atrial hypertension

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome;  $\text{PaO}_2/\text{FiO}_2$ , ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PCWP, pulmonary capillary wedge pressure; PEEP, positive end-expiratory pressure.

**Figure.** Typical Chest Radiograph and Computed Tomographic Scan of a Patient With Acute Respiratory Distress Syndrome



A, The chest radiograph shows bilateral pulmonary infiltrates that appear to be diffuse. B, A computed tomographic scan of the thorax from the same patient demonstrates that the distribution of the bilateral infiltrates is predominantly in dependent regions with more normal-appearing lung in nondependent regions.

## EVIDENCE ACQUISITION

To assist with this review, we systematically searched MEDLINE (1966 to September 2005), using the Medical Subject Heading *respiratory distress syndrome, adult*, and related text words (*acute respiratory distress syndrome, acute lung injury, respiratory distress syndrome, adult respiratory distress syndrome, ALI, or ARDS*). The search results were limited to English language, human subjects, randomized controlled trials, and meta-analyses. EMBASE and the Cochrane Central Register of Controlled Trials were also similarly searched. This strategy resulted in 1357 potentially relevant articles for which citations, abstracts, or both were reviewed. Bibliographies of all selected articles and review articles were hand searched for additional relevant articles. Studies evaluating non-invasive ventilation, pharmacologic therapies (not part of a mechanical ventilation strategy), and small, exploratory randomized trials (<50 patients) were excluded. To provide a focused and pragmatic review, we also excluded studies of therapies that we believed were not widely available for clinical use in adults at the present time (eg, exogenous surfactant and extra-

corporeal membrane oxygenation). A total of 53 articles met our criteria and were considered in this review.

## EVIDENCE SYNTHESIS

### Conventional Lung Protective-Ventilation

Conventional lung-protective ventilation involves strategies designed to mitigate further lung injury in patients with ALI or ARDS using a standard mechanical ventilator. Five randomized controlled trials<sup>23-27</sup> and 3 meta-analyses<sup>28-30</sup> have evaluated lung-protective ventilation compared with conventional approaches, using a variety of volume- and pressure-limited strategies (TABLE 2). Three of the randomized trials, with sample sizes of 52 to 120 patients, did not find a difference in mortality between the treatment and control arms.<sup>24-26</sup> One study by Amato et al<sup>23</sup> used higher positive end-expiratory pressure (PEEP) and recruitment maneuvers in conjunction with pressure- and volume-limited ventilation in the intervention group. This study was stopped early, enrolling 53 of 58 patients, after demonstrating a significant reduction in 28-day mortality. However, there was no significant difference in mortality at hospital dis-

charge, and a high mortality rate (71%) in the control group may have accounted for the survival difference. Nevertheless, this trial strongly suggested that ventilatory strategies could impact mortality, and the results in the intervention group generated interesting hypotheses that have been pursued in subsequent studies. The largest trial of volume- and pressure-limited ventilation was conducted by the ARDS Network (ARDSNet).<sup>27</sup> This trial of 861 patients demonstrated a 9% absolute decrease in mortality (31% vs 40%;  $P=.007$ ) when patients with ALI or ARDS receiving mechanical ventilation have reduced tidal volumes (target of 6 mL/kg of predicted body weight with a range of 4-8 mL/kg depending on plateau pressure and pH) and reduced pressures (plateau pressure, measured after a 0.5-second end-inspiratory pause,  $\leq 30$  cm H<sub>2</sub>O).

Three meta-analyses<sup>28-30</sup> of these 5 clinical trials have been performed.<sup>23-27</sup> The first meta-analysis concluded that the control groups of the 2 trials, which demonstrated a survival advantage,<sup>23,27</sup> did not reflect the "standard of care" and were likely responsible for the mortality difference.<sup>28</sup> In addition, the authors suggested that the low tidal

**Table 2.** Trials of Volume- and Pressure-Limited Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome

Study Participants	Source				
	ARDS Network, <sup>27</sup> 2000	Amato et al, <sup>23</sup> 1998	Brochard et al, <sup>24</sup> 1998	Stewart et al, <sup>25</sup> 1998	Brower et al, <sup>26</sup> 1999
No.	861	53	116	120	52
Mean age, y	52	35	57	59	49
Target intervention					
Tidal volume, mL/kg	6 vs 12 PBW	$\leq 6$ vs 12 ABW	6-10 vs 10-15 DBW	$\leq 8$ vs 10-15 IBW	$\leq 8$ vs 10-12 PBW
Plateau pressure, cm H <sub>2</sub> O	$\leq 30$ vs $\leq 50$	$<20$ vs unlimited	25-30 vs $\leq 60$	$\leq 30$ vs $\leq 50^*$	$\leq 30$ vs $\leq 45$ -55
Actual intervention†					
Tidal volume, mL/kg	6.2 vs 11.8	384 vs 768‡	7.1 vs 10.3	7.0 vs 10.7	7.3 vs 10.2
Plateau pressure, cm H <sub>2</sub> O	25 vs 33	30 vs 37	26 vs 32	22 vs 27	25 vs 31
Outcomes mortality, %	31 vs 40§	38 vs 71	47 vs 38¶	50 vs 47#	50 vs 46#
P value	.007	.001	.38	.72	.61

Abbreviations: ABW, actual body weight; DBW, dry body weight; IBW, ideal body weight, calculated as 25 m<sup>2</sup>; PBW, predicted body weight, calculated as 50 plus 0.91 (height in centimeters minus 152.4) for men or 45.5 plus 0.91 (height in centimeters minus 152.4) for women.

\*Represents peak inspiratory pressure rather than plateau pressure.

†Mean values at earliest recorded time point are reported and represent lung-protective vs control ventilation groups.

‡Tidal volume available in milliliters only.

§Mortality at hospital discharge or at 180 days.

||28-Day mortality.

¶60-Day mortality.

#In-hospital mortality.

volumes used in the intervention group of the ARDSNet trial may be harmful.<sup>28</sup> This meta-analysis has been criticized as having important methodological flaws, such as inappropriately grouping the individual trial results.<sup>29-31</sup> In addition, its findings are contradicted by 2 subsequent meta-analyses,<sup>29,30</sup> which suggested that volume-limited ventilation, particularly in the setting of elevated plateau pressure ( $>30$  cm H<sub>2</sub>O), has a short-term survival benefit. One meta-analysis also concluded that decreased tidal volumes may be advantageous below a threshold level ( $<7.7$  mL/kg predicted body weight).<sup>30</sup>

In many instances, lung-protective ventilation may lead to an elevation of arterial carbon dioxide, referred to as *permissive hypercapnia*. Although acute hypercapnic respiratory acidosis has many potential adverse effects, the extent to which a more controlled subacute elevation of carbon dioxide is harmful remains uncertain.<sup>32</sup> In fact, some evidence indicates that permissive hypercapnia is relatively benign.<sup>32</sup> At present, there are few data to inform physicians on a clinically relevant threshold of hypercapnia, acidosis, or both that require specific interventions, such as increasing effective ventilation, decreasing carbon dioxide production, or using buffer therapy (eg, bicarbonate). Of note, the ARDSNet study<sup>27</sup> investigators used a stepwise approach of increasing respiratory rates (to a maximum of 35 breaths/min), allowing bicarbonate infusions (at the physicians' discretion), and increasing tidal volumes for the management of acidosis.

Other important consequences of lung-protective ventilation possibly include worsened oxygenation and the need for increased sedation or analgesia compared with patients receiving conventional ventilation. Of note, patients in the intervention arm of the ARDSNet study had reduced oxygenation in the first few days but improved survival.<sup>27</sup> Furthermore, a recent analysis of a subset of the ARDSNet study revealed no significant differ-

ences in sedation or analgesia use between lung-protective and conventional mechanical ventilation groups.<sup>33</sup> However, the effect of any potential increase in sedation or analgesia use in patients receiving lung-protective ventilation requires further study.

In addition to pressure and volume limitation, higher PEEP and the use of recruitment maneuvers may be important components of a lung-protective ventilation strategy. Recruitment refers to the dynamic process of reopening collapsed alveoli through an intentional increase in transpulmonary pressure, which may be achieved through a variety of mechanisms, such as a transient high continuous positive airway pressure (eg, 40 cm H<sub>2</sub>O for 40 seconds).<sup>34</sup> Human studies evaluating recruitment maneuvers have yielded variable results.<sup>35-39</sup> Such factors as the type (eg, primary vs secondary) and stage (eg, early vs late) of ALI or ARDS and recruitment technique used may be important determinants of response.<sup>40-42</sup> The optimal pressure, duration, and frequency of recruitment maneuvers has not been defined and tested in clinical trials. Of note, the safety of recruitment maneuvers also requires careful evaluation. Although transient oxygen desaturation and hypotension are the most common adverse effects, other clinically significant events, such as barotrauma (eg, pneumothorax), arrhythmia, and bacterial translocation, may occur.<sup>38,43</sup>

The isolated effect of higher PEEP and recruitment maneuvers could not be determined in the small trial by Amato et al.<sup>23</sup> A much larger study, known as the ALVEOLI trial,<sup>44</sup> was conducted by ARDSNet to investigate this issue. This study provided volume- and pressure-limited lung-protective ventilation to all study patients and evaluated the effect on mortality of higher PEEP (12-24 cm vs 5-24 cm H<sub>2</sub>O) in the treatment group. In addition, recruitment maneuvers were conducted in patients randomized to the higher PEEP group by applying a pressure of 35 to 40 cm H<sub>2</sub>O for 30 seconds to assess the effect

on oxygenation. After evaluating the first 80 patients, recruitment maneuvers demonstrated only a modest effect on oxygenation with no difference in the requirement for oxygenation support (ie, PEEP or FIO<sub>2</sub>) and were not continued for the remainder of the study.<sup>39</sup> The study was stopped early, due to futility, after enrollment of 549 of 750 patients. There was no significant difference in in-hospital mortality, even after adjusting for important imbalances in baseline characteristics between the study groups (higher, 25.1% vs lower, 27.5% PEEP; 95% confidence interval [CI], -3.6% to 8.4%;  $P=.47$ ). However, some have suggested that a true effect may have been missed due to stopping the study early.<sup>45</sup> Alternatively, a beneficial effect of higher PEEP in some (recruitable) patients may have been negated by a detrimental effect in other (nonrecruitable) patients. These issues require further investigation.

### Alternative Ventilatory Approaches to Lung Protection

The precise role of alternative methods of ventilation, such as high-frequency ventilation (ie, jet, oscillation, and percussive ventilation) and airway pressure release ventilation, has not been established. High-frequency ventilation allows for higher mean airway pressures that may be advantageous for lung recruitment. In addition, it also allows for markedly reduced tidal volumes (1-3 mL/kg) compared with conventional ventilation, which may further reduce ventilator-associated lung injury.<sup>46,47</sup> Airway pressure release ventilation not only provides higher mean airway pressures but also allows for spontaneous breathing, which may be associated with better gas exchange, hemodynamics, and reduced sedation requirements.<sup>48</sup>

Of these alternative ventilatory modes, only high-frequency oscillatory ventilation (HFOV) has been studied in moderately sized randomized trials.<sup>49</sup> In a trial of 148 patients comparing HFOV with conventional mechanical ventilation with respect to key



adverse outcomes (eg, new airleak, intractable hypotension), there were no significant differences between groups. Mortality was examined as a secondary outcome, with a nonsignificant lower 30-day mortality in the HFOV group (37% vs 52%,  $P = .10$ ). This finding must be interpreted with caution because the conventional ventilation protocol did not use the current standard for volume- and pressure-limited lung protective ventilation and the study was not powered to assess mortality. A second trial of 61 ARDS patients comparing HFOV with conventional mechanical ventilation also revealed no significant differences in survival without supplemental oxygen or ventilatory support (HFOV vs conventional ventilation 32% vs 38%; adjusted odds ratio, 0.80; 95% CI, 0.22-2.97;  $P = .79$ ), or other secondary end points.<sup>50</sup> However, a post hoc analysis revealed that patients with the most severe hypoxemia had a trend toward a benefit from HFOV.

#### **Adjunctive Therapies to Lung-Protective Ventilation**

Adjunctive therapies are cointerventions that may result in improved outcomes when combined with lung-protective ventilatory strategies. Prone positioning and inhaled nitric oxide are 2 adjunctive therapies that are currently widely available and have been studied in large randomized trials of adult patients with ALI or ARDS.

The use of prone positioning with mechanical ventilation was first described in 1974.<sup>51</sup> Placing the patient in a prone position has potential physiological benefits, including the recruitment of dorsal (nondependent) atelectatic lung units, improved respiratory mechanics, decreased ventilation-perfusion mismatch, increased secretion drainage, reduced and improved distribution of injurious mechanical forces, and improved fit of the lungs within the thorax.<sup>52</sup>

There are 3 randomized trials of prone positioning in adults with ALI or ARDS.<sup>53-55</sup> In the first study, 304 patients were randomly assigned either to

the supine or the prone position for at least 6 hours per day over a 10-day period.<sup>53</sup> Although oxygenation significantly improved in the prone group, there was no significant difference in mortality or any secondary outcome. A post hoc analysis of the most severely ill patients revealed decreased mortality for patients randomly assigned to the prone position (relative risk [RR, 0.54; 95% CI, 0.32-0.90] at day 10, but this benefit did not persist beyond intensive care unit discharge. The second study randomized 791 patients (48% with ALI or ARDS) to supine or prone positioning for at least 8 hours per day and also demonstrated improved oxygenation without a survival benefit at 28 days (supine, 31.5% vs prone 32.4%; RR, 0.97; 95% CI, 0.79-1.19;  $P = .77$ ).<sup>54</sup> This second trial revealed a significantly higher rate of adverse events in the prone group, including selective (right or left mainstem bronchus) intubation, endotracheal tube obstruction, and pressure sores. The third study of prone positioning in ARDS, was stopped early (133 of 200 patients) due to problems with enrolment. It revealed a large, but statistically insignificant, difference in intensive care unit mortality between the 2 groups (supine, 58.6% vs prone, 44.4%,  $P = .43$ ).<sup>55</sup>

Inhaled nitric oxide provides selective vasodilation in ventilated lung units thus improving ventilation-perfusion mismatch, hypoxemia, and pulmonary hypertension.<sup>56</sup> This therapy has been studied in 6 randomized, placebo-controlled trials of adults with ALI or ARDS.<sup>57-62</sup> None of these studies demonstrated a sustained benefit. A Cochrane meta-analysis of more than 500 patients (80% adults) concluded that inhaled nitric oxide led to a transient improvement in oxygenation for up to 72 hours but no survival benefit (RR, 0.98; 95% CI, 0.66-1.44).<sup>63</sup> After this meta-analysis was completed, the largest trial of inhaled nitric oxide was published.<sup>62</sup> This study randomly assigned 385 nonseptic patients with ALI or ARDS to receive either continuous low-dose inhaled nitric oxide at 5 ppm or placebo. The results of this trial were

consistent with earlier studies in demonstrating only transient improvements in oxygenation without a significant mortality benefit (nitric oxide, 23% vs placebo 20%,  $P = .54$ ).

#### **CURRENT UNRESOLVED QUESTIONS AND PERSONAL PERSPECTIVE**

##### **Current ALI and ARDS Definition and Clinical Trials**

Despite a strong physiological rationale, many therapies for ALI and ARDS have not led to a significant survival benefit when tested in large clinical trials. It is possible that the case definition of ALI and ARDS may have contributed to this. The current American-European Consensus Conference definition has important limitations in its reliability and validity. First, the  $\text{PaO}_2/\text{FIO}_2$  ratio that defines hypoxemia does not consider the effect of ventilatory settings (eg, PEEP) or adjunctive therapies (eg, inhaled nitric oxide), which can have an important acute influence on  $\text{PaO}_2$ , nor does it consider whether a patient meets ALI or ARDS criteria.<sup>64-66</sup> Thus, variation in ventilation practices across institutions may lead to systematic differences in defining this disease entity for clinical studies and patient management. Second, there is only moderate interobserver agreement in interpreting the chest radiograph for ARDS, and ventilator settings also can influence the degree of infiltrates appearing on the radiograph.<sup>13,67</sup> Finally, in comparison to autopsy findings of nonsurvivors, a single-center study demonstrated only moderate accuracy of the ARDS definition.<sup>68</sup> Refinement of the current definition of ALI and ARDS to achieve more homogeneous patient populations may be beneficial in order to detect a significant treatment effect in clinical trials of ALI and ARDS therapies. However, a more restrictive definition also may exclude patients who may potentially benefit from a particular intervention. Further consideration of the current ALI and ARDS definitions are necessary before potentially important therapies are rejected as nonbeneficial.

### Widespread Adoption of the ARDSNet Ventilation Protocol

Given that the ARDSNet study<sup>27</sup> provided the only ventilation protocol that had a significant and sustained short-term mortality benefit, we believe patients with ALI or ARDS would benefit if all institutions used a lung-protective ventilation protocol based on this volume- and pressure-limited strategy. Although the ARDSNet protocol can be successfully implemented in clinical practice,<sup>69</sup> widespread adoption has not rapidly occurred.<sup>70-73</sup> One possible explanation for this finding is a perception by caregivers that implementation could be harmful to patients,<sup>73</sup> despite the lack of evidence to support this notion.

Some argue that adoption of the exact ARDSNet protocol (available at [www.ardsnet.org](http://www.ardsnet.org)) may be unnecessary and use of other modes of ventilation, which achieve similar volume and pressure limitations (ie, tidal volume 4-8 mL/kg predicted body weight and pressure <30 cm H<sub>2</sub>O), may be equally beneficial.<sup>74</sup> Such alternate volume- and pressure-limited protocols may be easier to implement and follow, especially if they are already consistent with local practice patterns. However, the use of custom-made protocols, which may seem logical, should be approached with caution, for it remains unclear what specific aspect of the ARDSNet protocol confers the survival advantage. For instance, a secondary analysis of the ARDSNet data<sup>75</sup> suggested that tidal volume reduction even benefited patients with safe plateau pressures of 31 cm H<sub>2</sub>O or less of water, meaning that pressure-limited ventilation, without concomitant volume-limitation, may be detrimental. Irrespective of this controversy as to whether the exact ARDSNet protocol should be adopted, the existing evidence (including 2 meta-analyses of all trials) supports that clinicians should change their practice and adopt volume- and pressure-limited ventilation for patients with ALI or ARDS. As additional evidence emerges, ongoing reassessment and evolution of these protocols will be necessary.

### Role for Rescue Therapy

There are many alternative ventilatory approaches and adjunctive therapies that have some evidence of short-term physiological benefit, but no consistent evidence for a survival advantage when studied with large randomized trials. Consequently, deciding the exact role of such therapies in managing individual patients is difficult. One approach is to completely avoid all of these therapies outside of clinical trials until their efficacy has been adequately demonstrated. Assuming their physiological benefit and safety have been appropriately evaluated in prior human studies, another approach is to limit use of these therapies to well-defined rescue situations in which a patient is deemed to be failing, or at risk of harm, from conventional ventilation. In these instances, rescue therapy may be considered to potentially avoid significant morbidity or mortality. However, the controversy lies in determining which rescue therapies should be used (either alone or in combination) and at what point they should be initiated and terminated. For example, preliminary data suggest that earlier institution of HFOV may portend a better prognosis<sup>76</sup> and that there may be synergistic benefits of combining different rescue modalities for ARDS patients with severe, life-threatening hypoxemia.<sup>77,78</sup> Although some protocols have been reported,<sup>79</sup> there is insufficient evidence to support the superiority of any particular approach to rescue therapy. Whenever possible, such patients should be considered for transfer to institutions with significant experience in ALI and ARDS management to allow further expert evaluation and treatment. Additional research is needed to build on the anecdotal evidence supporting the benefit of rescue therapies for the most severely ill patients with ALI or ARDS.

### Conclusions and Future Considerations

Recognition that mechanical ventilation, although life-saving, can contribute to patient morbidity and mortality

has been the most important advance in the management of patients with ALI and ARDS. Volume- and pressure-limited ventilation clearly leads to improved patient survival. The role of recruitment maneuvers, higher levels of PEEP, or both remain controversial and are the subject of 2 ongoing multicenter clinical trials (ExPress trial [France], LOVS trial [Canada, Australia, and Saudi Arabia]). At this time, use of alternative modes of ventilation (eg, HFOV) and adjunctive therapies (eg, inhaled nitric oxide and prone positioning) should be limited to future clinical trials and rescue therapy for patients with ALI or ARDS with life-threatening hypoxemia failing maximal conventional lung-protective ventilation.

Although agreement on the current definition of ALI and ARDS has been a fundamental step forward in research and clinical practice, further refinement is required to ensure that the efficacy of new and existing therapies are evaluated in the most appropriate patient population.

Finally, after decades of ALI and ARDS research, it is important to ensure widespread uptake of efficacious volume- and pressure-limited mechanical ventilation. It is critical that clinicians who treat patients with ALI or ARDS reassess their current ventilation strategies, assimilate the available evidence, and modify their practices to ensure the highest quality of care and best outcomes for their patients. Understanding the existing barriers to use of lung-protective ventilation and methods for increasing implementation of current research findings are important opportunities for future study.

**Financial Disclosures:** None reported.

**Funding/Support:** Dr Needham is supported by the Canadian Institutes of Health Research (Clinician-Scientist Award), Royal College of Physicians and Surgeons of Canada (Detweiler Fellowship), and grant P050 HL 73994-01 from the National Institutes of Health.

**Role of the Sponsor:** None of the funding organizations or sponsors had any role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

**Acknowledgment:** We thank A. Slutsky, MD, Interdepartmental Division of Critical Care Medicine and Department of Medicine, and A. Detsky, MD, PhD, Department of Medicine, both at the University of Toronto, Toronto, Ontario, and C. Soong, MD, De-

partment of Medicine, William Osler Health Center, Etobicoke, Ontario, for their review of early drafts of this article.

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Art may be served by morality: it can never be its servant. For the principles of art are eternal, while the principles of morality fluctuate with the spiritual ebb and flow of the ages.

—Arthur Symons (1865-1945)