Commentary

Mechanical ventilation: lessons from the ARDSNet trial

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Abstract

The acute respiratory distress syndrome (ARDS) is an inflammatory disease of the lungs characterized clinically by bilateral pulmonary infiltrates, decreased pulmonary compliance and hypoxemia. Although supportive care for ARDS seems to have improved over the past few decades, few studies have shown that any treatment can decrease mortality for this deadly syndrome. In the 4 May 2000 issue of *New England Journal of Medicine*, the results of an NIH-sponsored trial were presented; they demonstrated that the use of a ventilatory strategy that minimizes ventilator-induced lung injury leads to a 22% decrease in mortality. The implications of this study with respect to clinical practice, further ARDS studies and clinical research in the critical care setting are discussed.

Keywords: acute lung injury, artificial respiration, barotrauma, biotrauma, iatrogenic, respiratory failure

Introduction

ARDS is an inflammatory disease of the lungs characterized clinically by bilateral pulmonary infiltrates, decreased pulmonary compliance and hypoxemia [1,2]. Despite intense research for decades, the mortality rate in patients with ARDS remains very high, although there is some evidence that these rates might be decreasing [3]. Interestingly, although the major initial physiological abnormalities are often pulmonary in origin, patients who go on to die of their acute illness usually die of multiple system organ failure (MSOF) rather than a respiratory death (ie hypoxemia). Virtually all patients with ARDS require mechanical ventilation to provide adequate oxygenation; this therapy is supportive, providing time for the lungs to heal.

As with any therapy, there are side effects of mechanical ventilation; for decades our understanding of these complications was largely limited to the gross air leaks induced by the large transpulmonary pressures – so-called barotrauma. Over the past decade we have learned about more subtle detrimental sequelae of mechanical ventilation, based largely on basic studies on mechanisms of injury [4]. These studies have demonstrated that mechanical ventilation can induce injury manifested as increased alveolar-capillary permeability due to overdistension of the lung (volutrauma) [5], can worsen lung injury by the stresses produced as lung units collapse and re-open (atelectrauma) [6,7], and can lead to even more subtle injury manifested by the release of various mediators

ARDS = acute respiratory distress syndrome; HFV = high-frequency ventilation; ICU = intensive care unit; MSOF = multiple system organ failure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; VILI = ventilator-induced lung injury; V_t = tidal volume.

(biotrauma) [8,9]. The latter provides a putative mechanism to explain the high mortality rate in patients with ARDS: if the mediators released by the lung owing to the increased pulmonary stresses enter the circulation it could lead to distal organ dysfunction, and ultimately organ failure [10]. Ironically, although mechanical ventilation is life-saving, a logical conclusion of the large body of data on ventilator-induced lung injury (VILI) is that it might be causing or perpetuating the pulmonary inflammation, preventing or delaying the recovery process. This reasoning led to a recommendation to limit end-inspiratory lung stretch in mechanically ventilated patients [11], and led to a number of randomized clinical trials of 'lung protective strategies'. The results of the most recently completed trial were presented in the 4 May 2000 issue of *New England Journal of Medicine* [12]. This landmark paper answers a key question in relation to the supportive therapy of patients with ARDS but, as with any exciting research, raises a number of interesting questions, which will be addressed in this Commentary.

Brief review of ARDSNet study

The study was a multi-centered randomized controlled trial performed by a group called the ARDSNet who were funded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) to conduct clinical trials in patients with ARDS. Ten academic centers with 75 intensive care units (ICUs) enrolled patients with acute lung injury or ARDS into the trial, which compared a control ventilatory strategy with a tidal volume (V_t) of 12 ml/kg [based on predicted body weight (PBW)] to a lung protective strategy using a V_t of 6 ml/kg PBW [12]. The study set out to enroll up to 1000 patients but accrual was stopped at 861 patients when an interim analysis revealed that the mortality rate in the lung protective group was 22% lower than in the control group. These beneficial results seemed to hold across a wide spectrum of patients, including septic and non-septic patients, and also those with different degrees of lung dysfunction as assessed by respiratory system compliances. The study is very important from a clinical perspective, but also raises a large number of questions on the mechanisms underlying the decreased mortality, on the optimal way to ventilate patients with ARDS, and more broadly on the conduct of clinical trials in the critical care setting.

Why was this trial positive when three previous trials were negative?

This was not the first trial to assess a lung protective strategy in patients with acute lung injury or ARDS; in fact there were three previous negative trials [13–15], but this was the first large trial that showed a decrease in mortality by simply addressing the injury imposed by overstretching the lung. Why was this trial positive when other similar trials were negative?

One possible reason could be the relative power of the various studies; the ARDSNet trial enrolled 861 patients compared with the 288 patients enrolled in the three previous studies. This seems unlikely to be the major factor for the difference in results, because in each of the three negative trials the trend was for the high-V_t groups to have a lower mortality rate than the protective arms; combining all three studies the mortality rate was 44% in the control arm and 48% in the lung protective arm. Another possible explanation for the lack of efficacy in the previous trials might be related to the different approaches used to control respiratory acidosis. All the trials applied the concept of 'permissive hypercapnia' [16], ie allowing the P_aCO_2 to increase if necessary, rather than increasing V_t (or pressure). However, the approach to increases in P_aCO_2 differed substantially between studies. Specifically, the ARDSNet study was the most aggressive in terms of trying to maintain P_aCO_2 relatively close to the normal range, employing higher respiratory rates as well as more liberal use of bicarbonate than the other studies. There are reasons to believe that hypercapnia might actually be beneficial in the context of VILI [17,18]; for example, acidosis attenuates a number of inflammatory processes, inhibits xanthine oxidase (a key component in reperfusion injury), and attenuates the production of free radicals [18]. However, there are also potential detrimental effects such as increased catecholamine release [19] that might mitigate the potential beneficial effects of hypercapnia on lung injury.

The higher respiratory rate that was used in the low-V_t arm of the ARDSNet study to minimize hypercapnia might have had a fortuitous benefit, by leading to the development of auto-positive end-expiratory pressure (auto-PEEP). Increased end-expiratory lung volume has been shown to be protective in terms of VILI by minimizing the injury due to recruitment and de-recruitment of lung units (atelectrauma). No results have yet been presented on the degree of auto-PEEP in the ARDSNet patients, but minute ventilation was virtually identical between the low-V_t and high-V_t groups, making this explanation less likely because, for any given respiratory mechanics, minute ventilation is the major determinant of auto-PEEP. Furthermore, one could argue that the low-V_t group might have been subject to more atelectrauma because the smaller V_t would probably lead to reduced recruitment with each tidal cycle.

Another explanation for the positive ARDSNet trial might be related to the greater spread in V_t and plateau pressure (P_{plat}) between the control arm and the protective strategy. For example, the difference between the P_{plat} (on day 1) in this study was 8 cmH_2O, compared with 4.5 [13], 5.7 [15] and 6.0 [14] ml/kg in other studies; similarly there was a greater difference in V_t between the control and intervention arms in the ARDSNet trial. Clearly, the greater the difference in the independent variable, the greater the

signal:noise ratio, and the greater the likelihood of a positive finding (if the therapy is efficacious).

Finally, there might be a threshold in P_{plat} (as a surrogate for overdistension) above which injury due to mechanical ventilation might increase markedly. This was one of the explanations put forward in the *New England Journal of Medicine* editorial by Dr MJ Tobin that accompanied the ARDSNet publication [20]. On the basis of the data from the trials, he suggested that values of P_{plat} less than 32 cmH_2O would be fairly protective; because the three negative trials had had average P_{plat} values (in both groups) that were less than 32 cmH_2O, one would not expect any change in mortality between groups because both were receiving 'protective' strategies. In contrast, the ARDSNet trial had an average P_{plat} in the control arm of 33 cmH_2O, a value greater than the threshold value. This suggestion could also explain the results of Amato *et al* [21] in which the P_{plat} over the first 36 h averaged 46.0 cmH_2O in the control arm, and 30.5 in the protective arm. We do not know what the shape of a 'lung injury versus V_t' curve would be and whether there is some magical V_t or P_{plat} above which ventilation is 'unsafe' and below which ventilation is 'safe'. It seems highly unlikely that there is a specific break point for every patient, especially when one considers the spatial heterogeneity in injury and the difficulty in interpreting a high P_{plat} in the context of a stiff chest wall.

This latter possibility brings up the issue of whether the intervention arm was really protective or whether the control arm was injurious because the V_t used was too large. The implication of this question is that the ARDSNet used a V_t in the control arm that would not be considered to be 'conventional' (at the time). In addressing this issue it is important to point out that the ARDSNet calculated V_t on PBW, not measured body weight. The latter was approx. 20% greater in the study than PBW. Thus, on the basis of measured body weight, the V_t used in the control arm was approx. 10 ml/kg. This is certainly a value that would have been considered 'conventional'.

Implications of the ARDSNet trial

What are the messages from this landmark paper? From an ARDS research perspective, there is no question that a V_t of 6 ml/kg as implemented in the ARDSNet trial is, for now, the gold standard against which all other ventilation studies in ARDS will be judged. From a clinical perspective there are a number of issues and still many unanswered questions. In applying the results of this study at the bedside, it is important to re-emphasize the fact that V_t was calculated on the basis of predicted body weight; this must also be borne in mind when comparing the V_t values used in the various ventilation trials, which used different definitions for calculating V_t.

Must one use volume controlled ventilation with a V_t of 6 ml/kg (as was used in the ARDSNet trial), or can one use pressure controlled ventilation (PCV) with relatively low pressures that are in the range of those found in the lung protective arm (ie less than 30 cmH_2O)? This question is difficult to answer given the results available. From a physiological standpoint, it seems reasonable to suggest that PCV with relatively low values of pressure is acceptable; however, from an evidence-based medicine perspective one could argue that this is not the strategy that the ARDSNet investigators used and thus PCV might not be appropriate. There are cogent arguments on both sides. Physiologically, lung distension is minimized if P_{plat} is kept reasonably low – arguing that a pressure limited strategy should be as good as a volume limited strategy. However, we have to acknowledge that there might be something specific to the ARDSNet strategy not incorporated by using pressure limitation. Although this suggestion is somewhat unappealing, it might have some merit; for example, in a patient with a very stiff chest wall, limiting the P_{plat} to 30 cmH_2O might limit V_t more than is necessary to minimize overdistension, and in fact might lead to underrecruitment of the lung, poor oxygenation and further derecruitment. This might not have occurred if the hypothetical patient had been treated exactly as in the ARDSNet protocol.

The other important issue not addressed in the published ARDSNet trial is the following: What is the importance of recruitment maneuvers, and how does one set the appropriate PEEP level in patients with ARDS? This question is a central one because preventing recruitment and derecruitment seems to be crucial in animal studies of VILI. The ARDSNet is currently evaluating this question in a large trial in which they are using recruitment maneuvers and higher PEEP levels than in their previous study. Similarly, the large body of literature on VILI suggests that high-frequency ventilation (HFV) may be an ideal way of ventilating patents with ARDS because it can provide adequate gas exchange, while minimizing both overdistension and the recruitment and de-recruitment of the lung. A number of studies are currently re-evaluating this approach in the context of VILI.

The study also raises broader questions with regard to clinical trials in the context of the ICU setting. For many years there has been an uneasy feeling in the critical care community that perhaps it would not be possible to prove that any therapy is beneficial in patients with ARDS or sepsis. This pessimism was based on the large number of negative phase III type (randomized, large *n*, multicentered) clinical trials in the treatment of these diseases. There are a number of possible reasons for the large number of negative trials, including of course the possibility that the tested therapy was indeed not effective. However, the major concern was that we might never

obtain a positive trial even if a therapy was effective, because of the tremendous heterogeneity in the patient population, multiple co-morbidities, widely differing underlying diseases, difficulty in controlling co-interventions, and so on. The ARDSNet trial has partially put these concerns to rest: it is the first large-scale trial to show that a particular therapy is effective in patients with ARDS, and in some sense it can be considered a 'proof of concept' that the obstacles to successful trials in patients with ARDS and, it is hoped, in patients with sepsis are surmountable.

The trial is a role model of the way in which clinical trials should be conducted in the ICU; however, it required a large number of patients, took a long time to complete, and was extremely expensive. If studies this large, long, and costly are to be performed to evaluate all changes in management of our patients with or without ARDS, it will be extremely difficult to prove almost anything definitively in the ICU setting, other than interventions that are extremely effective. How, then, will it be possible to evaluate the use of inhaled nitric oxide, HFV, the prone position, less restrictive V_t values, optimal PEEP levels and a whole host of changes in management? We do not have any definitive answers to these questions; ideally other networks such as the ARDSNet should be set up to answer some of these questions with large-scale trials. In addition, it would be wonderful if a reasonably robust, yet less expensive (both in monetary terms and in the numbers of patients required) study designs could be developed. Perhaps for some questions we should accept less stringent *P* values when assessing a mortality endpoint. After all, a *P* value of less than 0.05 is arbitrary, and for studies that make physiological sense and have other physiological endpoints that seem to be improving, a less stringent statistical hurdle might be appropriate. This is particularly true for therapies for which there is no physiological or biological concern a priori concerning the toxicity of the intervention.

In this regard, it has been argued that physiological (also called intermediate) endpoints might be useless, and even grossly misleading. For example, in the ARDSNet study the P_aO_2:inspired fractional concentration of O_2 (F_IO_2) ratio was higher in the 12 ml/kg group for the first couple of days and yet mortality also ended being higher in this group. Results such as this have been used to suggest that studies that use physiological endpoints should not be used to change clinical practice. We would argue that physiological endpoints might be useful but should be used advisedly. Intermediate endpoints that are immediately 'downstream' from a specific intervention might not be useful. By 'downstream' we mean physiological events that are a direct consequence of the intervention. For example, we know that higher mean airway pressures, as would be observed with higher V_t values, usually lead directly to higher P_aO_2 values; the use of inhaled nitric oxide also leads directly to increases in P_aO_2. Because these endpoints are a direct consequence of the intervention, they might not give us clues to potential detrimental effects of the interventions and hence might not be ideal endpoints for outcome studies. However, endpoints that are further downstream and are correlated with mortality might be suitable; an example of such an endpoint within the context of ventilation trials might be changes in inflammatory cytokines with different ventilatory strategies.

Finally, what are the mechanisms that led to the lower mortality in the 6 ml/kg group? It was certainly not due to a decrease in barotrauma, as the incidence of barotrauma was virtually identical in the two groups (10% versus 11%). It is tempting to speculate that it might have been related to the greater decrease in serum cytokines (interleukin-6 was measured in the present study). As discussed above, it had previously been suggested that injurious forms of mechanical ventilation could lead to an increase in various mediators in the lung (biotrauma) and, owing to the increased alveolar-capillary permeability, that these mediators might enter the circulation and cause organ dysfunction. This hypothesis is attractive and has some indirect experimental support data [22], but it is extremely difficult to prove – at the moment all we have is tantalizing correlative results, but a definitive answer to this question might require a study that specifically targets these mediators and examines changes in outcome.

Indeed, if this hypothesis is correct, it would suggest possible novel approaches to the assessment and treatment of patients at risk for VILI. Ideally, one should apply ventilatory strategies that are relatively non-injurious, but in patients with severe ARDS this might be extremely difficult, if not impossible, because of the spatial heterogeneity of their lung disease [23]. A strategy that maintains a given lung unit open might lead to the overdistension of other units. In situations such as this, anti-inflammatory therapies (such as anti-cytokine therapies) might prove to be useful adjuncts to lung protective strategies [24,25], possibly by preventing distal organ injury. Admittedly this approach is purely conjectural at the moment, but if it turns out to be correct, how might we decide which patients would benefit from these therapies? A number of studies have now shown that septic patients who are homozygous for a specific polymorphism in the tumor necrosis factor-α (TNF-α) gene have increased TNF-α levels and have an increased risk of death. If similar polymorphisms turn out to be important in the context of the biotrauma induced during mechanical ventilation, then a ventilated patient's therapy in future might depend on their particular genotype, an approach that might be known as 'ventilogenomics', indicating the interplay between the patient's genetic predisposition to biotrauma and ventilatory strategy. Perhaps patients with a genetic predisposition to the development of high levels of pro-inflammatory mediators would be those who require these novel adjunctive anti-inflammatory therapies.

Summary

These are exciting times for basic scientists, clinical researchers and physicians caring for patients with ARDS. Basic discoveries in the laboratory have been translated into randomized controlled trials, demonstrating decreases in mortality in patients with ARDS by changes in ventilatory strategy that are relatively easy to implement in all ICUs. Furthermore, there is now the hope that a number of other ventilatory and non-ventilatory interventions that are currently under intense study (recruitment maneuvers, higher PEEP levels, prone positioning, high-frequency ventilation, liquid ventilation) will be found to decrease mortality further in ARDS patients. Finally, as our understanding of the molecular consequences of VILI increases, and as our understanding of genetic DNA-sequence variants increases, novel approaches to anti-inflammatory therapies of VILI will certainly emerge.

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