Management of patients with adult respiratory distress syndrome (ARDS) has been a therapeutic challenge for years. Despite scientific interest, there has been a lack of high quality clinical studies demonstrating a mortality benefit. In 2000 a large trial funded by the US National Institutes of Health (NIH) [1] demonstrated a 9% reduction in absolute mortality in patients ventilated with a low tidal volume strategy (6 ml/kg versus 12 ml/kg). This clinical finding is supported by many animal experiments that have also shown that mechanical ventilation, in particular with smaller tidal volumes, can prevent or minimize lung injury.

Although the mechanisms of ventilator-induced lung injury remain incompletely understood, over-distention and repeated opening and collapse of alveoli can damage the alveolar–capillary barrier and initiate or amplify a local and systemic inflammation. Data presented by Frank and Matthay in their review [2] (this issue) also provide strong evidence from experimental models that limiting alveolar stretch is associated with a significant decline in inflammatory cytokine release. This decline in release of cytokines has also recently been shown to occur not only in animal models but also in humans. In a study conducted by Ranieri and coworkers [3], 44 patients with ARDS treated with lung protective strategies were found to exhibit a decline in inflammatory cytokines in lung lavage fluid. Damage to the alveolar–capillary barrier in combination with release of inflammatory cytokines is theorized to be a major contributor to the development of the multiorgan dysfunction that leads to death in patients with ARDS [4].

Lung protective strategies are considered by many to be standard of care, although clinicians may have modified the ARDS Network protocol [1]. The ARDS Network protocol was complex, and differences in management between the experimental and control groups were not limited to changes in the volume of tidal breaths or in plateau pressures. Therefore, many interventions other than the lower tidal volume may well have contributed to the mortality benefit. For example, it may be very tempting for clinicians to adopt a ventilator strategy that minimizes tidal volume, as was employed in the ARDS Network protocol, but to permit much higher arterial carbon dioxide tensions than were allowed in that protocol. After all, there is good experimental evidence...
that permissive hypercapnia not only may protect the lung but also may even have its own therapeutic benefit [5]. However, failure to increase the respiratory rate as dictated by the ARDS Network protocol may negate other potentially beneficial effects of the protocol. Indeed, a follow-up study of some patients ventilated according to the ARDS Network protocol [6] provided evidence that the more rapid respiratory rate led to the development of intrinsic positive end-expiratory pressure (PEEP). Did the higher total PEEP in the experimental group contribute to the reduction in mortality?

In recent weeks the ARDS Network protocol has come under much scrutiny. A meta-analysis sponsored by the NIH suggests that adopting a ventilation strategy with low tidal volumes may not reduce mortality [7]. In that study, the five trials testing mechanical ventilation with low tidal volumes [1,8–11] were classified into two groups: two ‘beneficial’ trials, which showed an improvement in survival; and three ‘nonbeneficial’ trials, which showed no survival benefits. The authors of the report observed that plateau pressures in the control groups of the two beneficial trials were larger than those used in the control groups of the nonbeneficial trials. Furthermore, no difference was observed in the plateau pressures between the beneficial and nonbeneficial trials. They concluded that the greater survival of the experimental groups in the two beneficial studies was not related to an experimental ventilation strategy with low tidal volumes. Rather, it was ascribed to the deleterious consequences of adopting a control strategy with higher tidal volumes resulting in excessive plateau pressures. In our opinion, such conclusions may be premature and unfounded. Indeed, the plateau pressure was not the only variable that differed between the control groups of the beneficial and nonbeneficial trials. The ARDS Network as well as the other study protocols documented in the literature involved a complex interplay of many physiologic parameters. To attempt to reduce them to a single factor – the plateau pressure – may be overly simplistic. Before attributing the survival benefits solely to differences in plateau pressure, one would also have to account for all other clinical and protocol variables that may have differed between the control groups of the beneficial and nonbeneficial trials. It is also difficult to understand why we should ascribe the mortality benefit seen in the ARDS Network experimental group to the suboptimal treatment of the control arm, given that this control arm experienced one of the lowest mortality rates documented in the literature to date. Should clinicians adopt a strategy that only limits tidal volume or should they adopt the NIH protocol in its entirety?

Considering the methodological shortcomings of NIH meta-analysis and the absence of other large clinical trials showing a reduction in mortality, we believe that the optimal decision remains to use the ARDS Network protocol in its entirety. Even slight alterations in the protocol may have consequences that simply cannot be appreciated, given the complexity of the treatment and of the body’s response. There remain many outstanding clinical questions in ARDS. The transition of physiologic concepts derived from basic science research into management strategies has already significantly impacted on the care of patients with ARDS. Standard of care will continue to evolve as the answers to outstanding questions concerning the exact role of alternate therapies (e.g. high frequency oscillation ventilation, recombinant surfactant, open-lung strategies, prone positioning, steroids, and ideal PEEP) become better defined. Because of the large number of possible therapeutic options and the innate difficulty in performing high quality clinical trials in the critically ill, it becomes impossible to test all possible therapeutic options in the clinical arena.

Therefore, it is only through a greater understanding of basic scientific concepts that researchers will become able to identify the few questions that are most likely to be of clinical benefit and that should be systematically tested in large, high quality epidemiological studies with sufficient power to demonstrate clinically significant differences. Until more data become available, we believe that clinicians should adhere to the ARDS Network protocol in its entirety, because this is the only evidence available that shows that lives can be saved.

Competing interests
None declared.

References
1. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000, 342:1301-1308.
2. Frank JA, Matthay MA: Science review: Mechanisms of ventilator-induced injury. Crit Care 2003, 7:233-241.
3. Ranieri VM, Suter PM, Tortorella C, De Tulio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 1999, 282:54-61.
4. Slutsky AS, Tremblay LN: Multiple system organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998, 157:1733-1743.
5. Laffey JG, Tanaka M, Engelberts D, Luo X, Yuan S, Tansewell AK, Post M, Lindsay T, Kavanagh BP: Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med 2000, 162:2287-2294.
6. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, Slutsky AS, Ranieri VM: ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2002, 165:1271-1274.
7. Eichacker P, Gerstenberger E, Banks S, Cui X, et al.: A meta-analysis of ALL and ARDS trials testing low tidal volumes. Am J Respir Crit Care Med 2003; in press.
8. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kaiallra RA, Deheinzelin D, Munoz C, Oliveira R, Takakgi TY, Carvalho CR: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998, 338:347-354.
9. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS: Evaluation of a ventilation strategy to prevent barotraumas in patients at high risk for acute respiratory distress syndrome. N Engl J Med 1998, 338:355-361.
10. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clemente E, Mancebo J, Factor P, Matamis
D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F: *Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume Reduction in ARDS*. *Am J Respir Crit Care Med* 1998, **158**:1831-1838.

11. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Plantadosi S: *Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome in patients*. *Crit Care Med* 1999, **27**:1492-1498.