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Improving Outcomes in Critically Ill Patients

The Seduction of Physiology

Arthur S. Slutsky, MD

THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS), the most severe form of acute lung injury, is a deadly condition characterized by infiltrates on chest radiography and severe hypoxemia not secondary to left heart failure. The syndrome affects approximately 200 000 adults in the United States annually and has a mortality of 35% to 45%.¹ Ironically, mechanical ventilation—a therapy that is initially lifesaving—has contributed to the subsequent high mortality. In clinicians' previous zeal to maintain relatively normal blood gas values, they ventilated patients using relatively large tidal volumes. This approach changed with greater insight into the pathophysiology of ARDS, better understanding of the importance of ventilator-induced lung injury,² and a large-scale clinical trial demonstrating that a ventilatory strategy using smaller tidal volumes decreased mortality from 40% to 31%.³ However, mortality in patients with ARDS remains high, and in some patients the current lung-protective strategy is not lung-protective enough. This has led to ongoing research into better methods of applying mechanical ventilation.

One such method is to ventilate patients in the prone position, a concept first suggested 35 years ago by Bryan as a method to expand collapsed lung units.⁴ This was the approach evaluated by Taccone et al in their randomized trial reported in this issue of JAMA.⁵ The investigators enrolled 342 patients with ARDS, stratified by degree of hypoxemia, and ventilated the intervention group in the prone position for more than 18 hours per day for longer than 8 days.

Similar to most other studies,⁶ the authors observed an increase in oxygenation in the prone group, but mortality was not statistically different from that of the control group. Prone ventilation was associated with a nonsignificant decrease (37.8% vs 46.1%) in 28-day mortality in the subgroup of patients with severe hypoxemia, but given the small numbers, definitive conclusions cannot be drawn regarding the effect on mortality in this subgroup.

Based on the findings from the trial by Taccone et al⁵ combined with data from previous published reports,⁶⁻⁹ prone

ventilation should not be used routinely in all patients with ARDS. However, for a patient at imminent risk of death from hypoxemia, it makes sense to try prone ventilation, because multiple studies have demonstrated that it can increase oxygenation.¹⁰ A more difficult question is how to manage patients who have severe (ratio of PaO₂ to fraction of inspired oxygen [FIO₂] <100), but not life-threatening, hypoxemia. Evidence from 4 trials (admittedly post hoc and each statistically nonsignificant) demonstrates a nonsignificant reduction in mortality in this subgroup of patients (J. Mancebo, MD, written communication, October 21, 2009¹¹; C. Guérin, MD, written communication, October 21, 2009¹²).^{5,13} This, along with a biologically plausible mechanism—less oxygen toxicity attributable to lower FIO₂ during prone positioning, which is likely to be more important at higher FIO₂ levels (ie, in patients with severe hypoxemia)—suggests that prone ventilation is a reasonable treatment option for these patients. Ideally, prone ventilation should be performed only in centers with expertise in this modality, because multiple issues must be considered in implementing prone ventilation,¹⁴ and it can be associated with serious complications.⁵

Today, 35 years after prone ventilation was suggested and after hundreds of articles have been published, including more than 150 review articles and more than 10 meta-analyses, why are more definitive conclusions about prone ventilation not available? In this regard, prone ventilation is similar to other physiologically based interventions (eg, higher positive end-expiratory pressure [PEEP] levels, high-frequency ventilation) for which the effect on important clinical outcomes has not been conclusively proven. Given the current interest in physiologically based randomized controlled trials, several important aspects of this category of trials deserve careful consideration.

Physiology is seductive, especially to physicians who care for critically ill patients. In many respects, the intensive care

See also p 1977.

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unit is a physiology laboratory in which patients' vital signs and other functions are monitored and treated around the clock, 7 days a week. By explaining why a patient has a physiological abnormality such as a decrease in oxygenation or worsening renal function, these measurements can suggest therapies to correct the abnormal "physiology." But these physiological "fixes" do not always work as planned. Interventions that improve one physiological value may worsen another. For example, increasing PEEP may increase a surrogate end point such as oxygenation and decrease certain aspects of ventilator-induced lung injury but may worsen hemodynamic function and increase overdistension-induced lung injury. Surrogate end points are particularly seductive in physiologically based studies because of the immediate feedback the clinician receives after the intervention is implemented; normalization of the abnormality brings hope that the patient's overall clinical condition will improve. However, caution is required; surrogate end points can be misleading as predictors of clinically important outcomes.^{3,15}

The appeal of physiological interventions is not just that they can be quickly instituted and monitored at the bedside. Physiological interventions such as placing a patient in the prone position or increasing PEEP are relatively inexpensive or even "free." As such, the clinical implications from such trials are important globally. However, very few large companies have a commercial interest in the results, making it difficult to obtain funding for these studies. This may partly explain why such trials are often underpowered and why definitive answers to guide use of physiological interventions are often lacking.

Several key issues must be considered for future physiologically based trials. First, many challenges relevant to other trials (eg, clear definitions, ensuring homogeneous study populations, appropriate surrogate end points, ethical issues) are relevant to physiological trials and must be addressed.¹⁶ Second, physiologically based trials should be based on interventions that directly validate the study's underlying hypothesis. For example, the study by Taccone et al addressed the hypothesis that prone positioning for ventilation would decrease ventilator-induced lung injury, but no measurements were made to determine whether lung stress in the prone position was actually decreased in any specific patient. This is similar to how many physiologically based intervention trials (eg, most high-PEEP trials) have been conducted. Unfortunately, there are no well-accepted ways of monitoring lung stress, but accelerated development of novel physiological therapies will require better proof-of-concept studies. Novel imaging approaches currently being developed may help in this regard.

Third, many physiologically based studies have control groups treated with approaches that have not been rigorously evaluated in clinical trials, eg, supine positioning for ventilation. As such, it is challenging to interpret a trial that demonstrates a strong but statistically nonsignificant improvement in important outcomes in the intervention group.

The conventional approach is to conclude that the trial is negative and to continue treating patients in the same way as prior to the trial. However, does it make sense not to use a novel (or not so novel) therapeutic strategy that has a strong physiological rationale, demonstrates a strong positive trend in an important clinical outcome, has an acceptable adverse-effect profile, and is inexpensive? Perhaps it is time to reconsider how evidence from these trials is evaluated and incorporated into practice.

Fourth, the sample-size issue that limited inferences that could be drawn from the severely hypoxic subgroup of the trial by Taccone et al is an important and often daunting challenge in the critical care setting, where mortality is frequently the primary end point. Clearly mortality is important and clinically relevant, but using dichotomous variables requires relatively large sample sizes, which may be problematic in uncommon disease states, when patients have multiple comorbid disorders, and when informed consent is difficult to obtain. Use of novel clinical trial designs¹⁷ and surrogate end points are potential solutions. One interesting approach is to conduct very large, "simple" trials, using a clinically important primary end point (eg, mortality) but collecting a minimal data set. Major proponents of this approach argue that "many trials still collect ten or a hundred times too much information per patient. . . ."¹⁸ This concept, already used in some acute care trials,¹⁹ reduces the cost per patient, and the large sample size may help to overcome some patient heterogeneity issues and small treatment effects—but the concept does have inherent problems, especially with ensuring quality control. However, this does not mean that smaller studies should not be conducted. On the contrary, there should be more smaller studies, but they should focus on mechanisms, dose response, proof-of-concept, and feasibility of interventions. What should be eliminated are underpowered, mid-sized studies addressing clinical outcomes.

The key to having large, simple, generalizable trials is to develop a large global network of investigators. This is not straightforward, but the time may be opportune, because the world's critical care community is coalescing around an initiative to perform large-scale clinical trials to rapidly address the potential H1N1 pandemic.²⁰

A deep understanding of physiological principles is essential in the care of critically ill patients. Although physiological insights developed at the bedside have led to important, lifesaving therapies, obtaining convincing proof of improved clinical outcomes for many physiological interventions has proved surprisingly elusive. More large-scale, well-conducted randomized controlled trials assessing these interventions are necessary to separate fact from seduction.

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The Purpose and Limits to Professional Self-regulation

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TRUST ME, I'M A DOCTOR." IN THE UNITED STATES AND United Kingdom, a recent survey reports, more than 80% of the public does.¹ According to the Cambridge moral philosopher O'Neill, "Each of us and every profession and every institution needs to be trusted."² She questioned whether the new climate of accountability and regulation in society was improving trust in physicians. She suggested that new systems of accountability cannot only change but also distort the proper aims of professional practice; if society wants a culture of public service then professionals and public servants must in the end be free to serve the public rather than their paymasters.² However, if physicians are to be trusted by the public they serve, they have to deserve to be trusted, and that is why medical professionalism matters.

A report on Doctors in Society prepared by the Royal College of Physicians of London in 2005 suggested that professionalism lies at the heart of being a good doctor.³ This report defined medical professionalism as a set of values,

behaviors, and relationships that underpins the trust the public has in physicians.

Following this report a series of consultation events across England and Wales took place to debate the issue of medical professionalism with physicians and medical students, nurses, allied health professionals, and managers as well as patients and families. At all these events there was support for regular and robust testing of fitness to practice.⁴ This is also the subject of the article by Shaw and colleagues from the United States, United Kingdom, and Canada in this issue of *JAMA*.⁵ While comparing recertification in these countries, the authors ask whether physician self-regulation can survive under the increasing pressure for accountability and transparency in the regulation of the medical profession.

Others have suggested a need to redefine medical professionalism given the changing roles of physicians and the increasing expectations of the public, and this in turn will have an effect on regulation. New ways of practice have developed including more team and multidisciplinary work and diversification of medical roles to include academic, managerial, strategic, and advisory functions that raise questions for the profession.⁶ Can or should professional self-regulation cover all roles of a physician in the delivery of

See also p 2008.

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