In Prone Ventilation, One Good Turn Deserves Another  
Guy W. Soo Hoo, M.D., M.P.H.

The management of the acute respiratory distress syndrome (ARDS) remains daunting as we approach a half century since its description. Both direct and indirect insults produce acute lung injury, diffuse alveolar damage, and increased vascular permeability, with more severe involvement classified as ARDS. Although this suggests homogeneous injury, computed tomography clearly shows heterogeneous disease. Treatment with positive end-expiratory pressure (PEEP) and prone positioning improves oxygenation by increasing functional lung. Both increase functional residual capacity and decrease atelectasis, with improved ventilation–perfusion relationships with prone ventilation.

Both interventions were in use within a decade after the description of ARDS. When patients are in the prone rather than the supine position, oxygenation increases in at least 60% of patients, with oxygenation ratios 34% higher. Clearance of secretions is improved and ventilator-associated pneumonia may decrease with prone ventilation. Although several randomized trials have examined prone ventilation, there have been no randomized trials of PEEP (no PEEP vs. PEEP) involving patients with ARDS; yet, PEEP has become ingrained in ARDS management, with prone ventilation often relegated to second-tier status.

This is probably due to clinical trials that have failed to show a reduction in mortality with prone positioning, despite consistent improvement in oxygenation. The failure of physiological benefit to translate into decreased mortality has several explanations. Death in ARDS may be more often due to late complications (sepsis) than the initial respiratory insult. Treatment with prone ventilation may have been insufficient, with not enough time spent in the prone position. This, and probably other reasons, contributed to the perception that prone ventilation was not beneficial.

Guérin and colleagues now report in the Journal the results of the Proning Severe ARDS Patients (PROSEVA) trial, a multicenter trial of prone ventilation focusing on patients with severe ARDS. The 28-day mortality with prone ventilation was halved (16.0% vs. 32.8% with supine ventilation, P<0.001), a treatment effect virtually unprecedented in modern medicine. Several caveats are worth noting.

The importance of prior experience with prone ventilation by study-site staff cannot be underestimated. The trial involved a highly select group of patients, who represent a minority of those with ARDS who presented to study sites. Less than 15% of all patients with ARDS and one third of screened patients with ARDS underwent randomization, with almost 60% ineligible on the basis of exclusion criteria. A stabilization period of 12 to 24 hours eliminated patients with rapid improvement.

Nevertheless, these results will change the approach to patients with severe ARDS. Treatment focused on patients with the most severe hypoxemia (with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <150 mm Hg). Prone ventilation was initiated within an hour after randomization and was applied for 73% of the available time, and patients were returned to the supine position at least once daily. This contrasts with trials in which prone ventilation was applied for about 30% of the day. Ventilator care, including low-tidal-volume ventilation and PEEP, was standardized, with a systematic approach to weaning...
and extubation. The survival curves separated within a few days after study entry, and the mortality benefit persisted after adjustment for severity of illness and other characteristics at study inclusion. As compared with supine ventilation, prone ventilation produced better oxygenation, lower oxygen requirements, and more ventilation-free days. The mortality among controls (32.8%) was similar to the mortality of 25 to 40% observed in various trials.2

The results are compelling, but are they compelling enough to change practice patterns? Prone ventilation has been an option for about four decades, with supportive evidence similar to that of PEEP, but it is used far less often than is PEEP. This was probably also influenced by the logistics of prone ventilation. Prone ventilation is a conceptually simple intervention but can seem technically challenging. Being prone may seem like an unnatural patient position, and turning an intubated patient prone requires teamwork and additional personnel. There is a risk of kinking and dislodgment of not only the endotracheal or tracheostomy tube, but also intravascular lines, body-cavity drains, and feeding tubes. Electrocardiographic leads are repositioned on the back, suctioning can be a challenge, and some complications are unique to prone ventilation.

The experience of other centers will facilitate adoption of prone ventilation for treatment of severe ARDS.10 A video accompanies the report of Guérin et al. (available at NEJM.org) that illustrates movement of a patient to prone ventilation. The move is quick and smooth but does require a small cadre of personnel. There is a learning curve, but staff will become more facile with each patient. There can no longer be any doubt. Prone ventilation in selected patients with severe ARDS has arrived and is ready for its turn in the management of the disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Pulmonary and Critical Care Section (111Q), West Los Angeles Veterans Affairs Healthcare Center, Veterans Affairs Greater Los Angeles Healthcare System, and the David Geffen School of Medicine, University of California, Los Angeles — both in Los Angeles.

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**Bedside to Gene and Back in Idiopathic Pulmonary Fibrosis**


Idiopathic pulmonary fibrosis is a syndrome of chronic, progressive fibrosing interstitial pneumonia of unknown cause.¹ The prevalence of this disorder, which is associated with a rate of death similar to that of lung cancer, is increasing.² The only consistent clues to its cause have been that it occurs primarily in older adults, many of whom have been smokers.

As has been the case for other mysterious illnesses, genetic studies have resulted in an improved understanding of this disorder. Mutations in genes encoding surfactant proteins C and A2 (SFTPC and SFTPA2, respectively), telomerase reverse transcriptase (TERT), and telomerase RNA component (TERC) were initially discovered in cases of rare familial idiopathic pulmonary fibrosis.³ Two years ago, Seibold et al.⁴ identified a genetic linkage and association with a cluster of gel-forming mucin genes on chromosome 11p. Their finding of a strong association with a sin-