

# Should Prone Positioning Be Routinely Used for Lung Protection During Mechanical Ventilation?

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## Introduction

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## Summary

**Prone positioning has been known for decades to improve oxygenation in animals with acute lung injury and in most patients with acute respiratory distress syndrome (ARDS). The mechanisms of this improvement include a more uniform pleural-pressure gradient, a smaller volume of lung compressed by the heart, and more uniform and better-matched ventilation and perfusion. Prone positioning has an established niche as an intervention to improve gas exchange in patients with severe hypoxemia refractory to standard ventilatory manipulations. Because the lung may be more uniformly recruited and the stress of mechanical ventilation better distributed, prone positioning has also been proposed as a form of lung-protective ventilation. However, several randomized trials have failed to show improvements in clinical outcomes of ARDS patients, other than consistently better oxygenation. Because each of these trials had design problems or early termination, prone positioning remains a rescue therapy for patients with acute lung injury or ARDS. Key words: prone position; oxygenation; acute lung injury; acute respiratory distress syndrome; ARDS; pleural pressure; ventilation; perfusion; gas exchange; hypoxemia; mechanical ventilation; lung-protective ventilation; rescue therapy. [Respir Care 2010;55(1):88–96. © 2010 Daedalus Enterprises]**

## Introduction

Lung protection is necessary during mechanical ventilation of patients with acute lung injury (ALI), because

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ventilation itself can perpetuate or exacerbate the underlying injury. This secondary injury is attributable largely to 2 mechanical stresses: excessive lung distention at peak inspiration, and repetitive opening and closure of lung units. The lung injury initiates an inflammatory response that can further injure the lung and injure distant organs.<sup>1,2</sup>

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There is wide agreement that lung-protective ventilation should be the primary goal of ventilatory support in ALI and acute respiratory distress syndrome (ARDS). However, there is less agreement on how this goal should be achieved.

The injury attributable to over-distention can be minimized by reducing tidal volume ( $V_T$ ) and limiting plateau pressure. This approach reduced ARDS mortality in a large multicenter randomized trial.<sup>3</sup> The second source of injury may be minimized by interventions that recruit the lungs to prevent cyclic alveolar closure, such as positive end-expiratory pressure (PEEP), lung-recruitment maneuvers, and alternative ventilation modes such as high-frequency oscillation. But the optimal way to set PEEP, and the utility of recruitment maneuvers and newer ventilation modes have yet to be established. The “dark side” of these interventions is that improved recruitment at end-expiration is difficult to uncouple from over-distention, so salubrious and lugubrious effects may cancel each other.

Prone positioning (also known as proning) is an adjunct to mechanical ventilation and holds promise as another pathway to lung protection. In the prone position, ventilation and perfusion of injured lungs are better matched,<sup>4,5</sup> and the gravitational gradient of pleural pressure is reduced.<sup>6</sup> Because transpulmonary pressures are more uniform, lung recruitment might be achieved in atelectatic regions without over-distending regions that were already recruited. The improved ventilation-perfusion matching also improves oxygenation. This benefit on gas exchange was the earliest justification for prone positioning,<sup>7</sup> suggested before ventilator-induced lung injury (VILI) was widely recognized. Reviews of the topic found improved oxygenation in about 70% of patients with ALI/ARDS when flipped from supine to prone, with consistent group mean improvements in oxygenation.<sup>8-12</sup>

However, experience with alternative approaches to lung-protective ventilation in the supine position has taught us that improved oxygenation may be an unreliable marker of reduced VILI or survival. Low- $V_T$  ventilation reduces mortality in ARDS but worsens gas exchange.<sup>3</sup> In most studies, higher PEEP reduced cyclic closure and improved oxygenation, but not survival.<sup>13-15</sup> The improved oxygenation seen in the prone position suggests lung recruitment but is not sufficient as a goal in itself. The effect of prone positioning on lung injury, although encouraging, has been less well studied.

The oxygenation response to prone positioning in patients with ARDS is itself quite variable. Although most patients improve, about a third do not, and there is a wide range of improvement in those who respond. Patient factors that correspond to improvement have not been well defined. They may include the stage of ARDS (early vs late), the cause (pulmonary vs extra-pulmonary), the radiologic pattern (patchy vs diffuse), the severity of hyp-

oxia, and the patient’s body habitus. This variability has contributed to controversy over broad application of proning. Indeed, if oxygenation is an unreliable marker of lung protection, it may also be a clinically inappropriate definition of a “response” to proning.

Several adverse effects associated with the prone position have been described, including facial edema, pressure ulcers, inadvertent extubation, main-bronchus intubation, and removal of vascular catheters.<sup>16-21</sup> Although some of these complications are rare, they are dramatic, disturbing, and potentially lethal. The patient harmed by such an event is vivid and specific, while the patients who might benefit from proning are hypothetical and ill-defined. This tempers enthusiasm for an intervention of uncertain benefit.

Finally, none of the several prospective randomized trials comparing supine to prone positioning has shown a definitively positive effect on survival.<sup>16-21</sup> As we will discuss, however, all of the trials have had deficiencies that confound their interpretation, such as “under-dosing” (ie, not enough hours per day in the prone position), diverse patient populations, and early trial closure due to low enrollment. The bedside clinician is challenged to interpret negative trials that are small or flawed.

Because of these ambiguities, the role of the prone position remains undefined. We believe it has a role as a life-saving intervention in patients with severe, life-threatening hypoxemia, but its *routine* use in patients with ALI and ARDS remains open to dispute. Additional trials may help establish, or finally doom, proning’s role as a standard intervention. In the absence of definitive data, we will present the polar views for the reader’s consideration.

### **Pro: Prone Positioning Should Be Routinely Used for Lung Protection During Mechanical Ventilation**

Prone positioning is an ideal approach to lung protection during mechanical ventilation for ALI/ARDS. It requires no special equipment. It is applicable to almost all patients, excluding only those with abdominal wounds, tenuous vascular or airway access, or similar conditions. In patients with cardiomegaly, it improves ventilation to dorsal lung regions without compensatory worsening of ventral ventilation,<sup>22</sup> reducing the local injurious stress and strain. In animal studies, proning reduced lung injury and inflammation.<sup>23-27</sup> Adverse effects have been rare and are largely avoidable. Prone positioning also improves oxygenation in most patients, allowing reduction in fraction of inspired oxygen or PEEP. Although definitive survival data from clinical trials are lacking, all of the studies published so far were too small or too flawed to determine bedside decisions. While awaiting more convincing proof, the pro position is that the default position should be prone.

### Effects of Prone Positioning on Distribution of Ventilation and Perfusion

Prone positioning was proposed over 30 years ago as a means to improve gas exchange in hypoxic respiratory failure.<sup>7,28</sup> Extensive physiologic investigation has explored the mechanisms of the observed improvements, which involve changes in the distribution of both ventilation and pulmonary blood flow. In any position in a gravitational field, pleural pressure increases from its most negative values in non-dependent regions to less negative values in dependent regions. In an upright normal subject the gradient is about 0.2–0.3 cm H<sub>2</sub>O per centimeter of vertical height.<sup>29</sup> It is attributable to several factors, including the weight of overlying lung and local mismatch between the resting shapes of the lung and overlying chest wall.

At any airway pressure, the gradient of pleural pressure means that the local transpulmonary pressure is higher in non-dependent regions. Alveoli there are more distended, but they also reside along the less compliant portion of their local pressure-volume relationship.<sup>30</sup> Therefore, for a given uniform change in transpulmonary pressure (caused by an increase in airway pressure or decrease in pleural pressure), the change in volume will be greater in dependent lung regions. Ventilation will flow preferentially to those regions.

In supine subjects, additional mechanical factors affect the distribution of ventilation, and the weight of the heart and pressure from the abdominal contents can compress the lung bases and decrease functional residual capacity.<sup>31</sup> Because the height of the lung in the gravitational axis is much less when the person is horizontal, gravitational effects on the pleural pressure gradient are reduced. In addition, the heart lies over the left lower lobe and can directly reduce ventilation to that lobe, especially in patients with cardiomegaly.<sup>22,32</sup>

In studies of animals with injured, flooded, and dense lungs, the gravitational gradient of pleural pressure is steeper in the supine than the prone position (Fig. 1).<sup>6</sup> Pleural pressure at the dependent dorsal regions can exceed zero, which leads to airway closure or atelectasis and contributes to hypoxemia. In the injured lung, ventilation of the flooded and atelectatic dependent regions is greatly reduced. Gas either does not enter those regions at all, or those lung zones open and close during the respiratory cycle. Non-dependent lung regions receive the bulk of the V<sub>T</sub>.<sup>33</sup> The compliance of the dependent, flooded regions is essentially zero, and atelectatic regions capable of opening will not open until they reach their airway-opening pressure, by which point the non-dependent regions may be at risk of over-distention during tidal breathing.

There is also a gravitational distribution of lung perfusion in the supine subject with normal lungs.<sup>34,35</sup> It remains controversial whether this distribution along the grav-

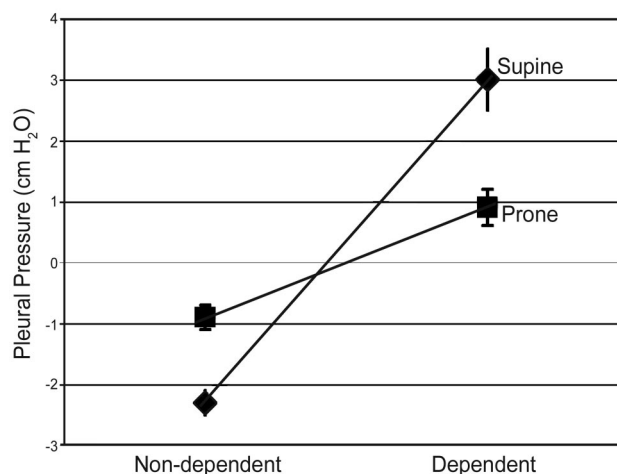


Fig. 1. Pleural pressure in dependent and non-dependent lung regions in supine and prone pigs after volume expansion. (Based on data in Reference 6.)

itational axis is entirely due to gravity.<sup>36</sup> There is substantial local flow heterogeneity within isogravitational planes, which follows fractal geometry, so other factors are clearly at play.<sup>37</sup> However, there is greater overall lung perfusion in the dependent, dorsal regions. This dorsal predominance persists in ALI.<sup>35,38</sup> Thus, in the supine patient with normal lungs, the spatial distribution of ventilation and perfusion match each other to optimize gas exchange. In the supine patient with lung injury, ventilation and perfusion are less well matched.

Many of these abnormalities in the injured lung are ameliorated by prone positioning. The gravitational gradient of pleural pressure becomes less steep.<sup>6</sup> Pressure in the dependent (ventral) regions becomes more negative (or less positive), and pressure in non-dependent regions becomes less negative, so the gravitational distribution of transpulmonary pressure is more uniform. In addition, ventilation of dorsal regions when they are non-dependent is improved, due in part to removal of the weight of the heart and abdominal contents from the large volume of lung that lie beneath them when supine, but not when prone (Fig. 2).<sup>22,32,39</sup> In patients with ALI the dorsal regions become more aerated in the prone position. Although ventral regions become less aerated, there may be less atelectasis added to the adverse effects of edema (Fig. 3). That is, the benefit is not just that the pleural pressure in dependent regions is less positive; it is also more uniform. Although chest wall compliance is reduced, the reduction is largely due to the constraint to the ventral chest wall. This makes chest wall compliance more uniform, and chest wall expansion in response to positive-pressure ventilation more uniform. The stress of a given V<sub>T</sub> is distributed more evenly, so efforts to recruit lung in the dependent, ventral regions will be less likely to over-distend the non-dependent dorsal regions. Thus, prone positioning is not only a

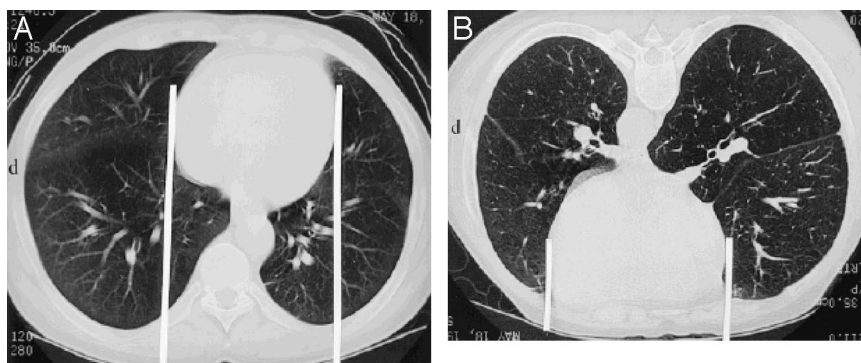


Fig. 2. Computed tomograms of a normal subject in the supine and prone positions. A greater area of the lung is beneath the heart in the supine position. (From Reference 39, with permission.)

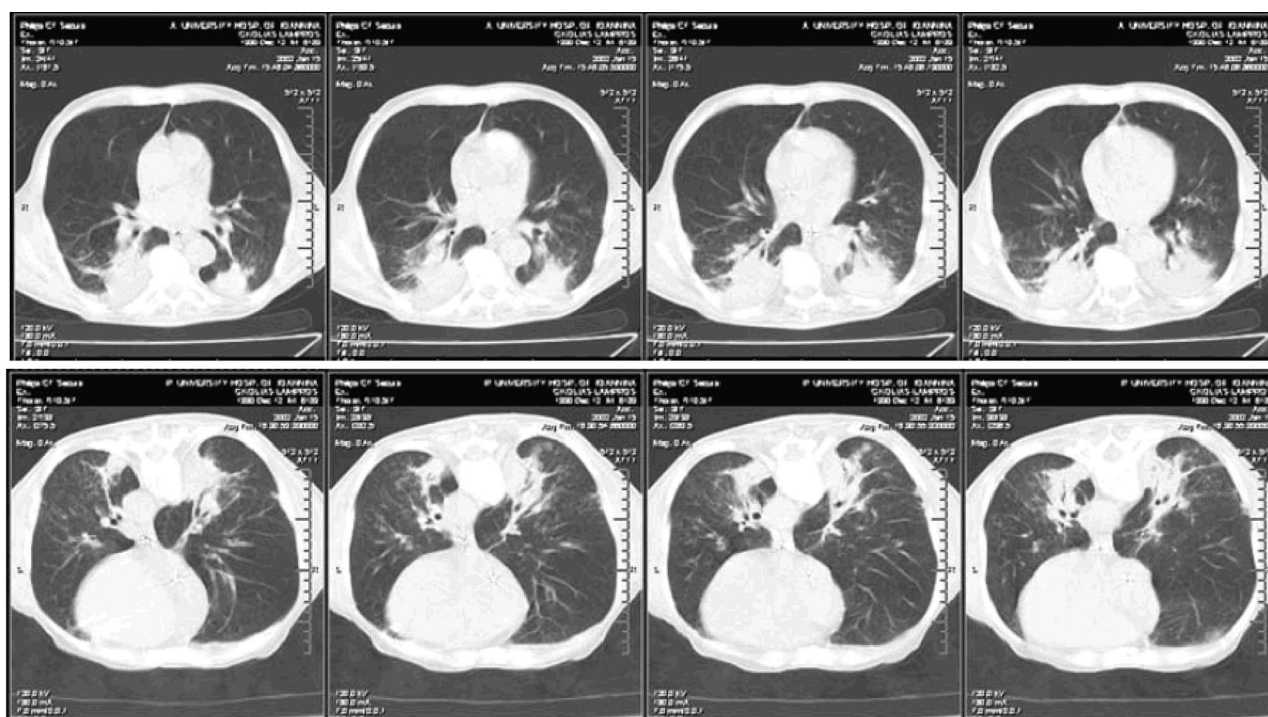


Fig. 3. Computed tomograms from a patient with acute respiratory distress syndrome in the supine and prone positions. Atelectatic dorsal lung regions are recruited in the prone position, without equivalent compression and derecruitment in ventral regions. (From Reference 40, with permission.)

means to recruit lung; it also makes lung recruitment safer and more effective.<sup>40,41</sup>

The gravitational distribution of perfusion is also more uniform in the prone position.<sup>34,35</sup> This suggests that local vascular resistance at any transmural vascular pressure is lower in basilar dorsal regions than in ventral regions.<sup>42</sup> Consequently, ventilation and perfusion are both more uniform and better matched in the prone position.<sup>4,43</sup> Venous admixture and arterial oxygenation can be improved, even in the absence of substantial net increased lung recruitment.<sup>41,44</sup>

### Effects of Position on Gas Exchange

Given that ventilation and perfusion are better matched, it follows that oxygenation is improved in the prone position. This has been demonstrated in numerous animal studies.<sup>5,6,23,38,45</sup> In smaller species, the effects of gravity are minimized by the small lungs; nevertheless, the development of VILI is delayed.<sup>27</sup>

In humans with ARDS, numerous case series have shown that about 70% of patients have improved oxygenation in the prone position.<sup>12</sup> It is not certain why some patients



fail to improve, or even worsen, but several causes have been proposed. Animals with abdominal distention are more likely to improve oxygenation when prone.<sup>46</sup> This may be because the deleterious effect of the supine position is greater in patients with abdominal distention. Patients may be more likely to respond early in the course of ARDS, when there is more atelectatic lung, than later, when the lung becomes more fibrotic.<sup>47</sup> Patients with lobar injury or direct lung causes of ARDS appear to respond more than do patients with diffuse ARDS.<sup>40</sup> Patients with more severe hypoxemia may respond more briskly.<sup>47</sup> Uncertainty about the value of prone positioning has probably been fueled by the heterogeneous oxygenation response and incomplete understanding of its mechanism.

However, oxygenation improvement is a poor surrogate outcome for VILI or survival. Oxygenation improvement can indicate better matching of ventilation and perfusion and reduced shunt, but with no lung recruitment whatsoever. It can also indicate lung recruitment that is accompanied by over-distention of previously recruited lung regions. If a better marker of “safe” ventilation existed, we might learn that some patients with a brisk oxygenation improvement are actually at greater risk from interventions that improve oxygenation, or that some patients with no change in oxygenation are nevertheless better protected.

Physiologic dead space ( $V_D$ ) represents lung regions that are ventilated but not perfused. In ARDS,  $V_D$  is increased and is an independent predictor of mortality.<sup>48</sup> This  $V_D$  may represent regions where the pulmonary capillaries are obliterated by inflammation or in-situ thrombosis. However, it may also reflect lung zones that are over-distended and thereby are in West zone 1. If  $V_D$  decreased in the prone position, it would suggest that the volume of ventilated but non-perfused lung decreased. Since prone positioning would not restore obliterated or thrombosed capillaries, a decrease in  $V_D$  suggests less over-distention.

Data on the effects of prone position on  $V_D$  are limited. Two studies with ARDS patients have attempted to measure the ratio of  $V_D$  to  $V_T$ . One found no change<sup>49</sup> and the other<sup>50</sup> found a significant decrease in the prone position. The immediate change in  $P_{aCO_2}$  was examined in a post-hoc analysis of the prone arm of a multicenter randomized trial of prone versus supine positioning.<sup>51</sup> The main trial was negative overall (discussed below), but patients whose  $P_{aCO_2}$  fell by more than 1 mm Hg when first turned prone had a lower mortality rate (35%) than those whose  $P_{aCO_2}$  did not fall (52%,  $P = .01$ ). Improvement in oxygenation upon proning did not predict survival. This suggests that reduction in  $V_D$  is a more clinically relevant and important marker of a response to prone position than is oxygenation.

## Effects of Position on Lung Injury

The logical intermediary between prone position and survival in ARDS is reduced lung injury. If the postulated benefit of decreased over-distention did not reduce VILI, improved survival would be unlikely. Animal studies of lung injury have used either injurious ventilation strategies (starting with normal lungs) or non-protective ventilation strategies combined with experimental lung injury. Although few in number, these studies have consistently found less lung edema, leak, histologic injury, or epithelial-cell apoptosis with proning than with supine positioning.<sup>23,24,26,27</sup>

In summary, despite the lack of supportive large randomized controlled trials, there is nevertheless strong evidence to support prone positioning in patients with ALI/ARDS.

### Con: Prone Positioning Should Not Be Routinely Used for Lung Protection During Mechanical Ventilation

There is little doubt that, as laid out above, prone positioning for ARDS has a solid physiologic foundation, ample preclinical evidence of benefit, and numerous case series showing oxygenation benefit in most patients with ARDS. As with any clinical intervention, these benefits must be proven in clinical trials by comparing them to existing standards of care. Once benefit is proven in clinical studies, the risks and benefits of a therapy may be weighed in any individual patient and therapy decisions made.

The observed preclinical benefits of prone positioning provided the basis for several randomized controlled trials of prone versus supine positioning in patients with ALI and ARDS. None of these trials has shown a mortality benefit, except one that did so after adjusting for baseline imbalances. The con side of this paper will emphasize that the studies were negative. However, it will also be emphasized that all of these trials were seriously flawed in design or execution.

The first trial, by the Prone-Supine Study Group, randomized 304 patients.<sup>18</sup> Subjects could have a wide range of ALI or ARDS severity, and there was no exclusion based on the duration of ALI/ARDS prior to enrollment. Other than positioning, mechanical ventilation was not controlled. Patients were kept prone only an average of  $7.0 \pm 1.8$  h/d, and the maximum days of proning allowed by the protocol was 10 days. The study was powered to detect a 20% absolute difference in mortality at day 10, an effect that seems unrealistically large at a time point that is clinically irrelevant. Even with those goals, the study stopped early, due to waning enrollment, when only about 70% complete. Twelve patients in the supine group crossed

over to the prone position, and 41 patients in the prone group missed periods of proning that they should have received. This was a negative study. However, it used a minimum “dose” (ie, hours per day) of prone positioning, did not control important confounders, was grossly underpowered, even for the chosen end point, and is therefore largely a lesson in how not to address the question.

A multicenter randomized trial by Guerin et al corrected only a few of those deficiencies.<sup>19</sup> The trial was larger (802 patients). It was powered to a more reasonable end point, a 10% reduction in 28-day mortality, and it met its recruitment goal. However, it also enrolled many patients with milder lung injury and was not limited to ALI/ARDS patients (only about half the subjects had either ALI or ARDS as the cause of respiratory failure). The study had no exclusion for duration of illness, did not control mechanical ventilation, and over 20% of supine patients were crossed over to the prone position due to hypoxemia. Although the planned (and median actual) duration of prone positioning was slightly greater (8 h/d), that is still only one third of the day. Proning sessions were continued until clinical criteria for improvement were met, which was after a median of only 4 days. Thus, while this study was larger, the exposure to prone positioning was still brief, and potential group differences were blurred by crossover. The subjects had a wide variety of causes of respiratory failure, only some of which might be expected to benefit from proning. For comparison, consider a well established therapy such as hypertension-control to reduce stroke risk. It is much less likely that the benefit would be discernable if half the subjects were normotensive, and participants took their anti-hypertensive medications only every third day.

Some adverse events were more frequent in the prone group: there were 6 excess incidents of selective intubation and 22 of tube obstruction. However, note that when such events occur in clinical practice, they are generally immediately apparent and easily corrected. There was no excess unplanned extubations. Pressure sores were somewhat more frequent (3.61 vs 3.03/100 patient days,  $P = .005$ ). The severity or clinical importance of these complications was not reported. On the other hand, the ventilator-associated pneumonia rate was lower in the prone group (1.66 vs 2.14/100 mechanical-ventilation patient-days,  $P = .045$ ).

Three other trials are quite small. A pediatric trial anticipated very large benefits on ventilator-free days and mortality.<sup>16</sup> Enrollment was stopped for futility after only 102 patients, the midpoint. Both study arms did much better than anticipated in the major outcomes. Two other studies stopped due to declining enrollment after only 40 patients. One was limited to trauma patients with ARDS, a group that typically has a low mortality compared to ARDS in other settings. Patients were prone an average

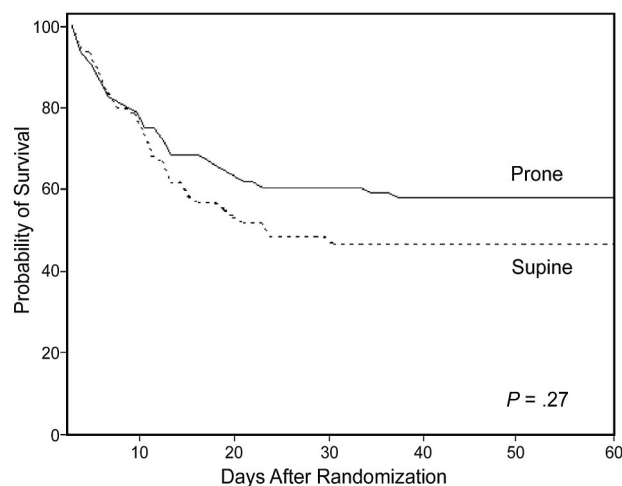


Fig. 4. Kaplan-Meier graph of intensive-care-unit survival of patients with acute respiratory distress syndrome randomized to supine or prone position. There was no significant difference between the groups. (From Reference 20, with permission.)

of just 11 h/d.<sup>52</sup> The other study extended the planned daily prone positioning to 20 h/d.<sup>17</sup> However, both studies are at least an order of magnitude too small to be conclusive.

A recent multicenter trial conducted in Spain and Mexico attempted to correct many of the shortcomings of earlier studies.<sup>20</sup> Subjects needed to have more severe gas exchange abnormalities (ARDS, not ALI) and had to be enrolled within 48 hours of meeting oxygenation criteria. If prone, they were kept prone most of the day (target 20 h, actual 17 h), and this was continued until recovery, an average of 10 days. There was little crossover between the groups. Unfortunately, mechanical ventilation was not closely controlled. For feasibility considerations, the study was powered to an unrealistic reduction of mortality from 50% to 30%. Because the study had minimal funding, recruitment diminished to a trickle and the study was halted after only 142 patients had been enrolled. Because of the small sample size and baseline differences between the arms, Mancebo et al adjusted the analysis for the duration of ARDS prior to inclusion and the baseline Simplified Acute Physiology Score, which was higher in the prone arm. After adjustment, the relative risk of death in the supine arm was 2.53 (95% confidence interval [CI] 1.09–5.89,  $P = .03$ ). While this finding may be considered hypothesis-generating, these methodological issues preclude drawing any definitive conclusions. However, it was the most rationally designed of the published studies, and the results arguably favor prone positioning (Fig. 4).

In November 2009 the results from a larger trial designed to build on the findings from that study were published.<sup>21</sup> This multicenter trial enrolled 344 patients with ARDS in 25 centers in Italy and Spain. Patients were

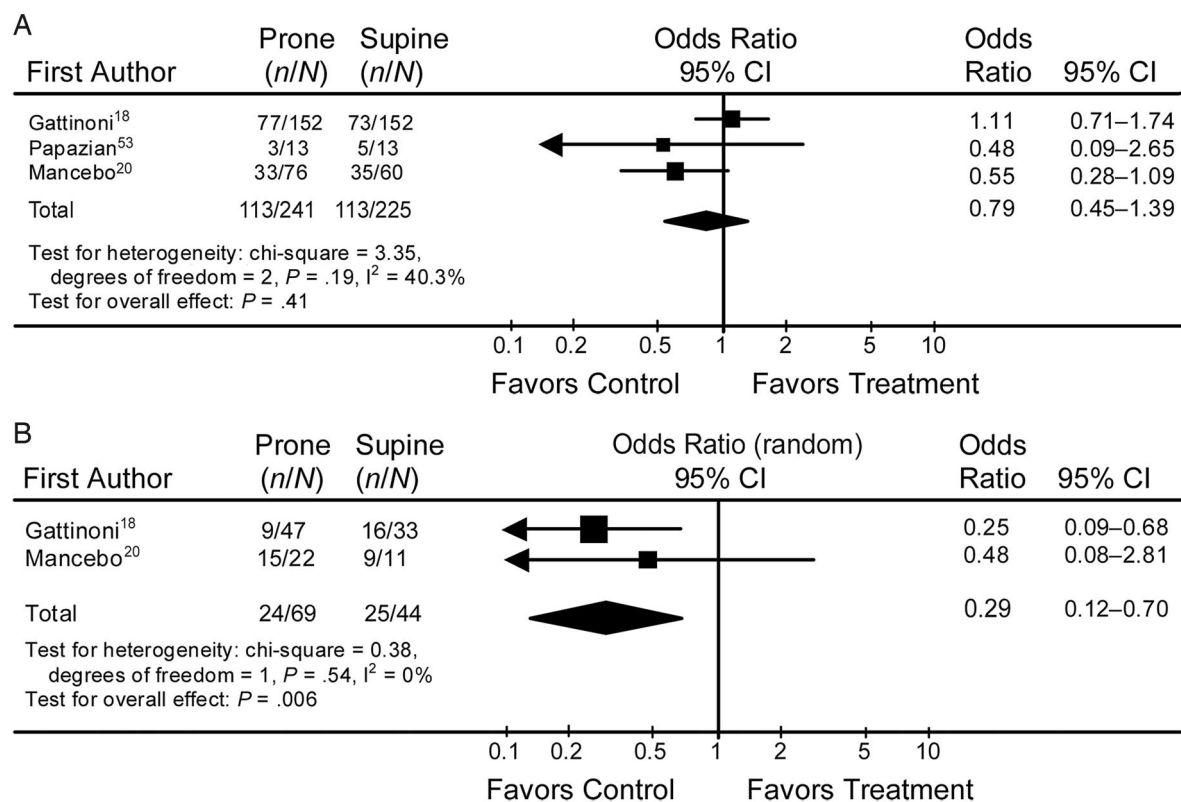


Fig. 5. A: Meta-analysis of effect of prone positioning on mortality, based on the 2 studies that reported a sub-group analysis of patients by Simplified Acute Physiology Score II (SAPS II) score. B: Effect of prone positioning on mortality in sicker patients (ie, SAPS II score > 50). (Adapted from Reference 9.)

stratified by ARDS severity (ratio of  $P_{aO_2}$  to fraction of inspired oxygen 100–200 mm Hg vs < 100 mm Hg) and were enrolled within 72 hours of meeting eligibility criteria. Patients were randomized to supine ventilation or prone ventilation, targeting 20 hours/day, and both groups received protocolized lung-protective ventilation with  $V_T$  of 8 mL/kg ideal body weight and plateau airway pressure < 30 cm  $H_2O$ . Prone positioning was maintained until physiologic lung recovery. The study was powered to detect a 15% absolute reduction in 28-day mortality. This is relatively optimistic, considering that small  $V_T$  only improved mortality by 9%.<sup>3</sup> Compliance with prone positioning was good, with a mean daily duration of  $18 \pm 4$  hours. Groups were similar at baseline in terms of severity of illness and gas exchange.

Over the entire cohort, gas exchange improved more quickly in the prone group. However, there was no difference in 28-day mortality (prone vs supine, 31% vs 33%, risk ratio 0.97, 95% CI 0.84–1.13,  $P = 0.72$ ), intensive care unit mortality (38% vs 42%, risk ratio 0.94, 95% CI 0.79–1.12,  $P = .47$ ), or 6-month mortality (47% vs 52%, risk ratio 0.90, 95% CI 0.73–1.11,  $P = .33$ ). Among the sub-group of patients with severe hypoxemia managed in

the prone position, the relative risk of death was lower, but the confidence intervals were wider, so the prone and supine mortality outcomes remained not significantly different: 28-day mortality risk ratio 0.87, 95% CI 0.66–1.14,  $P = .31$ ; intensive care unit mortality risk ratio 0.83, 95% CI 0.60–1.15,  $P = .25$ ; and 6-month mortality risk ratio 0.78, 95% CI 0.53–1.14,  $P = .19$ . Moreover, there were significantly more frequent adverse events in the patients managed prone, including airway obstruction, inadvertent extubation, hypotension, and vomiting. This large trial, designed based on everything that was learned from earlier trials, could detect only unfavorable effects of routine prone positioning in ARDS.

Four meta-analyses of proning studies were published in 2008.<sup>8–11</sup> Since all of the studies included in the analyses were negative, it is not surprising that the meta-analyses came to the same conclusion, that prone position had no effect on mortality (Fig. 5) or other clinical outcomes, but did improve oxygenation. Remember, however, that a meta-analysis cannot overcome the design deficiencies of the included trials. One interesting finding was that proning improved mortality in sicker patients, those with a Simplified Acute Physiology Score II > 50 (see Fig. 5). Until

this is prospectively confirmed, this finding should only be considered hypothesis-generating.

### Summary

The practicing clinician standing beside his or her patient with ARDS faces a dilemma. When high-quality, definitive clinical trial data support an intervention, the clinician has to decide if this patient resembles the patients in the trial, and whether this intensive care unit can carry out the interventions as safely and effectively as in the trial. This may be simple for a medication, but can be complicated for other interventions. If both conditions are met, however, then the risks and benefits to this patient should be similar to those in the trial's patients, and the principles of evidence-based medicine should guide action. Such is the state of the art with regards to setting  $V_T$ .

The situation with prone positioning is less certain. Prone positioning is certainly backed by a strong physiologic rationale and data. Adverse effects can be minimized if the clinician has experience with prone positioning and pays careful attention to patient pressure points.<sup>54</sup> There are, however, no definitive clinical trial data. Though one trial so far found a 2.5-fold greater risk of death with supine positioning, this was not confirmed in a more definitive study. There are important questions regarding the appropriate patients, "dose," and timing of proning in ALI/ARDS. Based on the results of trials and recent meta-analyses, it appears that in the sickest patients with ARDS there may indeed be physiologic or clinical benefit. Prone positioning is a rational approach for a patient whose hypoxemia appears urgently life-threatening, but its routine use is less defensible. Until more data are available, the prudent clinician will weigh the risks and potential benefits of proning with each patient.

### REFERENCES

- Imai Y, Nakagawa S, Ito Y, Kawano T, Slutsky AS, Miyasaka K. Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. *J Appl Physiol* 2001;91(4):1836-1844.
- Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;282(1):54-61.
- ARDS Network Investigators. 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(18):1301-1308.
- Pappert D, Rossaint R, Slama K, Gruning T, Falke KJ. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. *Chest* 1994;106(5):1511-1516.
- Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994;150(1):184-193.
- Mutoh T, Guest RJ, Lamm WJ, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. *Am Rev Respir Dis* 1992;146(2):300-306.
- Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976;4(1):13-14.
- Sud S, Sud M, Friedrich JO, Adhikari NK. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ* 2008;178(9):1153-1161.
- Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med* 2008;36(2):603-609.
- Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. *Intensive Care Medicine* 2008;34(6):1002-1011.
- Tiruvoipati R, Bangash M, Manktelow B, Peek GJ. Efficacy of prone ventilation in adult patients with acute respiratory failure: a meta-analysis. *J Crit Care* 2008;23(1):101-110.
- Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J* 2002;20(4):1017-1028.
- Mercat A, Richard JCM, Vieille B, Jaber S, Osman D, Diehl JL, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):646-655.
- Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al; ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351(4):327-336.
- Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299(6):637-645.
- Curley MA, Hibberd PL, Fineman LD, Wypij D, Shih MC, Thompson JE, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. *JAMA* 2005;294(2):229-237.
- Fernandez R, Trenchs X, Klamburg J, Castedo J, Serrano JM, Besso G, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008;34(8):1487-1491.
- Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345(8):568-573.
- Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004;292(19):2379-2387.
- Mancebo J, Fernandez R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173(11):1233-1239.
- Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, et al; Prone-Supine II Study Group. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009;302(18):1977-1984.



22. Wiener CM, McKenna WJ, Myers MJ, Lavender JP, Hughes JM. Left lower lobe ventilation is reduced in patients with cardiomegaly in the supine but not the prone position. *Am Rev Respir Dis* 1990; 141(1):150-155.
23. Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ. Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Crit Care Med* 2000;28(2):295-303.
24. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit Care Med* 1997;25(1):16-27.
25. Chan MC, Hsu JY, Liu HH, Lee YL, Pong SC, Chang LY, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community-acquired pneumonia. *J Formos Med Assoc* 2007;106(9):708-716.
26. Nakos G, Batistatou A, Galiatsou E, Konstanti E, Koulouras V, Kanavaros P, et al. Lung and end organ injury due to mechanical ventilation in animals: comparison between the prone and supine positions. *Crit Care* 2006;10(1):R38.
27. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, et al. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005;33(2):361-367.
28. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group: comments of a devil's advocate. *Am Rev Respir Dis* 1974;110(6 Pt 2):143-144.
29. Milic-Emili J, Mead J, Turner JM. Topography of esophageal pressure as a function of posture in man. *J Appl Physiol* 1964;19:212-216.
30. Glazier JB, Hughes JM, Maloney JE, West JB. Vertical gradient of alveolar size in lungs of dogs frozen intact. *J Appl Physiol* 1967; 23(5):694-705.
31. Moreno F, Lyons HA. Effect of body posture on lung volumes. *J Appl Physiol* 1961;16:27-29.
32. Alexander MSM, Peters AM, Cleland JP, Lavender JP. Impaired left lower lobe ventilation in patients with cardiomegaly. *Chest* 1992; 101(5):1189-1193.
33. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151(6):1807-1814.
34. Nyren S, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. *J Appl Physiol* 1999;86(4): 1135-1141.
35. Wiener CM, Kirk W, Albert RK. Prone position reverses gravitational distribution of perfusion in dog lungs with oleic acid-induced injury. *J Appl Physiol* 1990;68(4):1386-1392.
36. Hughes M, West JB. Point: Gravity is the major factor determining the distribution of blood flow in the human lung. *J Appl Physiol* 2008;104(5):1531-1533.
37. Glenny R. Counterpoint: Gravity is not the major factor determining the distribution of blood flow in the healthy human lung. *J Appl Physiol* 2008;104(5):1533-1535.
38. Richard JC, Bregeon F, Costes N, Bars DL, Tourvieille C, Lavenne F, et al. Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. *Crit Care Med* 2008;36(8): 2373-2380.
39. Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000; 161(5):1660-1665.
40. Galiatsou E, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efreimidis SC, Nakos G. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006;174(2):187-197.
41. Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, Gattinoni L. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998;157(2):387-393.
42. Beck KC, Rehder K. Differences in regional vascular conductances in isolated dog lungs. *J Appl Physiol* 1986;61(2):530-538.
43. Mure M, Domino KB, Lindahl SG, Hlastala MP, Altemeier WA, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. *J Appl Physiol* 2000;88(3):1076-1083.
44. Brazzi L, Pelosi P, Gattinoni L. Prone position in mechanically-ventilated patients. *Monaldi Arch Chest Dis* 1998;53(4):410-414.
45. Albert RK, Leasa D, Sanderson M, Robertson HT, Hlastala MP. The prone position improves arterial oxygenation and reduces shunt in oleic-acid-induced acute lung injury. *Am Rev Respir Dis* 1987; 135(3):628-633.
46. Mure M, Glenny RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998;157(6 Pt 1):1785-1790.
47. Blanch L, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, et al. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997;23(10): 1033-1039.
48. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay MA. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346(17):1281-1286.
49. Chiumello D, Cressoni M, Racagni M, Landi L, Li Bassi G, Polli F, et al. Effects of thoraco-pelvic supports during prone position in patients with acute lung injury/acute respiratory distress syndrome: a physiological study. *Crit Care* 2006;10(3):R87.
50. Mentzelopoulos SD, Roussos C, Zakyntinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. *Eur Respir J* 2005;25(3):534-544.
51. Gattinoni L, Vagginelli F, Carlesso E, Taccone P, Conte V, Chiumello D, et al. Decrease in  $P_{aCO_2}$  with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003;31(12):2727-2733.
52. Voggenteiter G, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, et al. Prone positioning improves oxygenation in post-traumatic lung injury: a prospective randomized trial. *J Trauma* 2005; 59(2):333-341.
53. Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, Roch A, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005;33(10):2162-2171.
54. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002; 165(10):1359-1363.

**Discussion**

**Moores:** I always thought intuitively or physiologically that maybe the pa-

tients who respond are those with non-pulmonary ARDS, and that pulmonary ARDS may have different physiology and a different kind of recruitment, so

you might not see the same outcomes. Is that reasonable, or is there something else that predicts which patients respond?

**Fessler:** Gattinoni did studies<sup>1,2</sup> that divided people by whether they had pulmonary or extra-pulmonary ARDS, but didn't specifically look at proning. One study<sup>3</sup> looked at proning and the radiologic distribution of ARDS, and the finding was somewhat counterintuitive in that patients with lobar infiltrates tended to improve their oxygenation more than those with diffuse infiltrates. I don't have a physiologic explanation for that.

1. Goodman LR, Fumagalli R, Tagliabue P, Tagliabue M, Tagliabue M, Ferrario M, et al. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. *Radiology* 1999;213(2):545-552.
2. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissan A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: different syndromes? *Am J Respir Crit Care Med* 1998; 158(1):3-11.
3. Galiatsou E, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006; 174(2):187-197.

**Talmor:** Gattinoni found a more equal distribution of the transpulmonary pressure in prone ARDS patients.<sup>1</sup> He also suggested that, since part of the benefit is due to redistribution of densities in the lung, there would be more benefit in patients with more recruitable lung. You would expect that might benefit patients with non-pulmonary ARDS more than patients with pulmonary ARDS.

1. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J* 2002;20(4):1017-1028.

**Moore:** I haven't listened to Gattinoni speak about it for a year or two, so I wasn't sure if that had been explored further or if they realized it was not as important and should be dropped.

**MacIntyre:** Is holding the abdomen in place important in proning? I'm intrigued that one effect of proning is that by stiffening up the chest wall it tends to equalize the distribution of gases in the lung and maybe perfusion as well. You mentioned a device that allows the belly to move freely, but maybe the belly should be on a flat surface to prevent a loss of this chest wall or thoracic stiffness.

**Fessler:** We use a rotisserie, Neil. There hasn't been a consistent finding that allowing the abdomen to hang free, versus having the patient lie on a mattress, changes the oxygenation response.

Animal studies have also had inconsistent findings: some better, some worse with abdominal support. In a study<sup>1</sup> with pigs they increased abdominal pressure by inflating a balloon in the abdominal cavity, and proning improved oxygenation more when the balloon was inflated.

1. Mure M, Glenn RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998; 157(6 Pt 1):1785-1790.

**MacIntyre:** So it had an effect, we're just not sure which way.

**Fessler:** It was either good or bad; I'm sure of that.

**Moore:** I thought that early on there was some thought that having the chest wall against something hard and flat was a good thing for chest compliance. However, another way you might recruit more lung is to allow the diaphragm to come down further, which could recruit more in the lower lungs. So if you let the abdomen hang free and get the abdominal contents away, you could let the diaphragm adjust its position more.

**Sessler:** Have investigators adhered to low-tidal-volume ventilation in the

more recent randomized controlled trials? And should that make much of a difference? Some of the earlier studies, including Gattinoni et al<sup>1</sup> in 2001, did not adhere to low-tidal-volume ventilation.

1. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345(8):568-573.

**Fessler:** The study by Mancebo et al<sup>1</sup> aimed for tidal volumes of less than 10 mL/kg. The average tidal volume in that study was maybe 500–600 mL. I don't know the details of the protocol that Gattinoni included in his current studies. But it is important to use state-of-the-art care in everything you're doing except the intervention you're studying. It might make proning look ineffective if all the benefit that can be achieved from a mechanical ventilator can be achieved by reducing tidal volume. Then you might not see any of the benefit of proning.

1. Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173(11): 1233-1239.

**MacIntyre:** Hank, from a practical perspective, if a patient failed to improve after so many hours in the prone position, would you just bag the idea?

**Fessler:** That has been my practice when I've used proning. I don't have a better marker to tell me that the patient who is not improving in oxygenation is improving in anything else.

**Talmor:** Both the Mancebo et al trial<sup>1</sup> and the Gattinoni et al<sup>2</sup> study used tidal volume of 10 mL/kg in both arms. The French trial<sup>3</sup> used around 8 mL/kg, so even that wasn't a low tidal volume by today's standard.

1. Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173(11):1233-1239.
2. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345(8):568-573.
3. Guerin C et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure. *JAMA* 2004;292(19):2379-2387.

**MacIntyre:** Dan, why would they use that injurious tidal volume in a clinical trial in 2009?

**Talmor:** I don't think you would if you were designing these trials now, but both the Gattinoni and the French trial started in the late 90s.

**MacIntyre:** Oh, I'm sorry, I thought you meant the current trials were doing that.

**Talmor:** No.

**Siobal:** You both mentioned the "dose" (ie, hours per day) of prone positioning. What is an adequate dose? We always run into that problem when we have a prone patient who appears to be responding but their oxygenation climbs when they're flipped supine. And how should we wean the proning dose? What do we wean first? Should we decrease the hours per day of prone positioning? Should we decrease the frequency of prone positioning by increasing the time of supine positioning? And when should we lower the PEEP?

**Fessler:** My prejudice is that the more time in the prone position, the more benefit the patient will have. When we've used proning, we've kept the patient prone for as much of the day as we can. So far there's no good indicator for when to stop using the prone position, but when the supplemental-oxygen requirement decreases to the point where you're thinking

about weaning, they probably don't need much more lung protection. We have not attempted to wean any patients prone. That would be an interesting trial.

**Moores:** The Shock Trauma Center at the University of Maryland has a lot of experience with this, but they publish little about it. They prone everybody, not just patients with ARDS. I'm not so sure why they do that, but all of their trauma patients are in Stryker frames, and they leave the patient prone unless there's a complication or problem, and as soon as they correct the problem, they flip the patient prone again. Their complication rate is fairly low, but, I think they're good at it because they do it all the time and they tend to keep people prone other than during nursing care.

**Siobal:** Dr Hibashi uses airway pressure-release ventilation and also publishes little about it, but I saw him present a photo of a patient in some type of bed or device standing up in a crucifix position, and I think that would be good for lung recruitment.

**Epstein:** Richard et al studied the physiology of upright positioning,<sup>1</sup> and I think there was some potential physiologic benefit, but nobody's done a clinical trial.

1. Richard JC, Maggiore SM, Mancebo J, Lemaire F, Jonson B, Brochard L. Effects of vertical positioning on gas exchange and lung volumes in acute respiratory distress syndrome. *Intensive Care Med* 2006; 32(10):1623-1626.

**Sessler:** One small study found an oxygenation benefit from some upright position, but I don't know if it was a standing position.

1. Hoste EA, Roosens CD, Bracke S, Decruyenaere JM, Benoit DD, Vandewoude KH, Colardyn FA. Acute effects of upright position on gas exchange in patients with acute respiratory distress syndrome. *J Intensive Care Med* 2005;20(1):43-49.

**Fessler:** Clearly, the only thing left to study is the inverted position.

**Sessler:** This strikes me as an area where translation from research to general practice is particularly important. As Lisa mentioned, there's a major difference between a "fine-tuned machine" such as the Maryland Shock and Trauma Center and a small hospital where a physician decides to try prone positioning with one nurse assisting; there is a high risk for misadventure. Has there been any research about broader application of proning in a non-research setting?

**Talmor:** I haven't seen any such studies. In a position piece<sup>1</sup> Rick Albert offered practical suggestions for how to avoid proning misadventures, but I don't think he said how many such events he'd seen.

1. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002;165(10):1359-1363.

**MacIntyre:** Are the sedation needs the same in the prone and the supine position?

**Moores:** The sedation requirement is greater.

**Sessler:** So is the requirement for neuromuscular blockade.

**Fessler:** One of the difficulties of interpreting these studies, particularly the physiologic studies, is that many of them routinely paralyzed the patients for the sake of the study. So the improvement in ventilation-perfusion ratio, for example, or oxygenation, may not apply to patients who are not paralyzed.

**Talmor:** I find prone positioning fascinating because it's one of those good ideas that's been disproved multiple times and it refuses to go away. There are 5 clinical trials at least (the relatively good ones) and multiple

meta-analyses. We've discarded a lot of interventions for much less than that. Can anybody who uses prone positioning routinely tell me why it refuses to go away?

**Epstein:** I think part of the problem is that all the studies have looked at routine use of proning, and I think most of us use it in patients we're having a hard time oxygenating; that's when I use it. I'd never prone a patient who is otherwise doing well. It's the patient

who is on 100% oxygen and a fairly high PEEP who we would put in the prone position.

I don't think the right population has been studied, because it's so difficult to do. You can't even enroll enough patients in routine applications, so it would be almost impossible to enroll large numbers who have profound hypoxemia.

**Gentile:** I think it's one of those applications that, despite what the clin-

ical trials say, people say, "We do it well, and we do it safely," but it certainly has risks, the smallest being a line pulled out, and the major one being cardiac arrest and you have to flip the patient back over. If you do proning, you have some complications and you learn from them. There are still people out there who really believe in it, they do it well, they have physiologic outcomes, I don't know what their other outcomes are, but they seem to do it a lot.



Photograph by David J Pierson