

## Prone Positioning Beyond Physiology

**I**N the current issue of ANESTHESIOLOGY, Petersson *et al.* provides us with a physiologic study describing, in anesthetized human volunteers, the effects of prone positioning and the application of 10 cm H<sub>2</sub>O positive end-expiratory pressure (PEEP) on the regional distribution of pulmonary ventilation and perfusion.<sup>1</sup> This article creates a complete formulation of the pulmonary ventilation and perfusion in the prone position.

In the supine position, at 0 cm H<sub>2</sub>O PEEP, the size of the alveolar units decreases exponentially from ventral (nondependent) to dorsal (dependent) lung regions.<sup>2</sup> This indicates that the distending forces of the lung (*i.e.*, the difference between the alveolar and the pleural pressure) decreases along the ventral-to-dorsal axis. The increase of pleural pressure close to the dependent lung regions is commonly considered the result of the push of the abdominal organs towards the lungs, which increases from the ventral to the dorsal regions.

In spontaneously breathing subjects, the engine of ventilation is the diaphragm, which displaces a huge amount in its dorsal (dependent) portion. This action is associated with a more favorable position of the dependent alveolar units along their pressure-volume curves<sup>3</sup> and accounts for the greater ventilation observed in the most dependent lung regions. During anesthesia and paralysis, however, the diaphragm acts as a passive flaccid membrane. The insufflated gas is then preferentially distributed towards the ventral and nondependent lung areas.<sup>4</sup> Because the regional distribution of lung perfusion is greater in the dependent lung regions, the final result is that mechanical ventilation, at 0 cm H<sub>2</sub>O PEEP, is associated with some degree of ventilation-to-perfusion ( $V_A/Q$ ) mismatch. This result is consistent with both the gravitational (West *et al.*<sup>5</sup>) or fractal distribution (Glenny *et al.*<sup>6</sup>) theories of lung ventilation/perfusion. The addition of PEEP partially corrects this mismatch because it progressively moves ventilation towards the dependent lung regions (as previously shown by computed tomography scanning<sup>7</sup> and in the current study<sup>1</sup>), whereas perfusion is further increased in the dependent lung regions.

In the prone position, at 0 cm H<sub>2</sub>O PEEP, the size of

alveolar units decreases with an exponential decay from dorsal (now nondependent) to ventral (now dependent) lung regions. This occurs to a much lower extent than that observed in the supine position. As a result, alveolar ventilation is more homogeneously distributed in the prone than in the supine position.<sup>2</sup> Because lung perfusion redistributes towards the dependent regions, this results in a more homogeneous  $V_A/Q$  matching at 0 cm H<sub>2</sub>O PEEP, such as shown by Petersson *et al.*<sup>1</sup> and others.<sup>8,9</sup> Surprisingly, after the addition of PEEP, Petersson *et al.* found that perfusion increased in the ventral lung regions (now dependent), whereas the distribution of alveolar ventilation remained unchanged. Consequently, the authors claimed that  $V_A/Q$  matching was decreased by the addition of PEEP in the prone position and suggested that lower PEEP levels might be preferred in the prone position compared with the levels of PEEP used in the supine position.

This conclusion may be incorrect when a patient has underlying acute lung injury. Because patients with acute lung injury often have severe hypoxemia resistant to typical therapies, Bryan<sup>10</sup> suggested that prone positioning might lead to improved oxygenation. His prediction was fully confirmed in most of the studies subsequently published, which undoubtedly showed that in approximately 70% of patients with acute respiratory distress syndrome (ARDS), prone position—always applied in association with some degree of PEEP—improves oxygenation. Therefore, there is clearly a difference between normal lungs; for example, a deterioration of  $V_A/Q$  was observed by the current authors after 10 cm H<sub>2</sub>O PEEP was added to the patients in the prone position.<sup>1</sup>

The explanation for the improvement of  $V_A/Q$  in patients with ARDS in the prone position involves understanding the distribution of edema in the diseased lungs. In patients with ARDS, the mass of the lung with the edema may be increased to 300% of that of normal lungs.<sup>11</sup> Therefore, the dependent lung regions in ARDS patients are compressed from the abnormal weight of the lung tissue above (nondependent) in the supine position.<sup>12</sup> When the ARDS patient is prone,

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the mass of the dorsal lung, which reinflates (*i.e.*, dorsal becomes the nondependent lung regions), is greater than the potential mass of the ventral (now dependent) lung regions, which may collapse.<sup>13</sup> When lung perfusion is substantially unmodified, the overall  $V_A/Q$  matching improves as new pulmonary units are recruited for more effective gas exchange.

This is probably the primary mechanism for the improvement in oxygenation in the prone ARDS patient, although other mechanisms (including a different shape of the diaphragm, changes of hypoxic pulmonary vasoconstriction, and a differential production of nitric oxide in different lung regions) may play a role. Sadly, there can be negative consequences to prone positioning, including a possible increase in chest wall stiffness.<sup>2</sup> The reduced chest wall compliance leads, in the case of pressure-controlled ventilation, to an initial reduction in transpulmonary pressure (*i.e.*, decreased tidal volume) or, in the case of volume-controlled ventilation, to an increase in plateau airway pressure. The overall balance of the positive and negative effects of the prone position can be observed by looking at the variation in arterial carbon dioxide. Independent of oxygenation changes, a decrease in arterial carbon dioxide indicates a recruitment of lung parenchyma, whereas an increase in arterial carbon dioxide may indicate a large increase in chest wall stiffness.

We believe that the most recent clinical trial of prone ARDS patients may provide some insights about the relationship between PEEP and the prone position.<sup>14</sup> In that study, the patients that had been randomized to the prone arm were allowed to undergo a variation in the ventilator settings aimed towards a less dangerous ventilation, if the oxygenation improved. Two maneuvers were allowed: first, a reduction of inspired oxygen fraction, and second, a reduction of PEEP, with a target arterial partial pressure of oxygen between 70–90 mmHg. The results clearly showed an identical level of PEEP between the two arms, suggesting that a decrease in PEEP was not possible in the prone ARDS patients.

These data from prone ARDS patients, contrast with the findings observed by Petersson *et al.* in normal patients.<sup>1</sup> The comparison of the results suggest that in ARDS patients, reductions of PEEP are inappropriate, at least when  $V_A/Q$  matching and systemic oxygenation are being evaluated.

Finally, although the article by Petersson *et al.*, as well as our comments, have focused on gas exchange, there may be an effect from prone positioning in ARDS patients on their survival. The survival benefit of prone positioning during ARDS is probably a result of a decrease in the harmful effects of mechanical ventilation. The prone position leads to more homogeneous lung inflation and more homogeneous alveolar ventilation, suggesting that the strain applied to the lung parenchyma and its associated stress are more homogeneously distributed than in the supine position.<sup>15</sup> This should decrease ventilator-induced lung injury. As a matter

of fact, all the meta-analyses performed on prone positioning of ARDS patients, so far, agree with two major points: (1) In all patients, a systemic oxygenation improvement is observed, and this is obviously greater in the most hypoxemic patients; and (2) in the most severe ARDS patients, when lung dishomogeneity is the greatest, prone positioning appears to provide about a 10% survival benefit.<sup>16,17</sup>

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#### References

- Petersson J, Ax M, Frey J, Sánchez-Crespo A, Lindahl SGE, Mure M: Positive end-expiratory pressure redistributes regional blood flow and ventilation differently in supine and prone humans. *ANESTHESIOLOGY* 2010; 113:1361–9
- Gattinoni L, Pelosi P, Valenza F, Mascheroni D: Patient positioning in acute respiratory failure, Principles and practice of mechanical ventilation. Edited by Tobin M. New York, McGraw Hill, 2004, pp 1067–76
- Otis AB, McKerrow CB, Bartlett RA, Mead J, McIlroy MB, Selver-Stone NJ, Radford EP Jr: Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol* 1956; 8:427–43
- Froese AB, Bryan AC: Effects of anesthesia and paralysis on diaphragmatic mechanics in man. *ANESTHESIOLOGY* 1974; 41:242–55
- West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol* 1964; 19:713–24
- Glenny RW, Robertson HT: A computer simulation of pulmonary perfusion in three dimensions. *J Appl Physiol* 1995; 79:357–69
- 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; 151:1807–14
- Mure M, Domino KB, Lindahl SG, Hlastala MP, Altmeier WA, Glenny RW: Regional ventilation-perfusion distribution is more uniform in the prone position. *J Appl Physiol* 2000; 88:1076–83
- Richter T, Bellani G, Scott Harris R, Vidal Melo MF, Winkler T, Venegas JG, Musch G: Effect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. *Am J Respir Crit Care Med* 2005; 172:480–7
- 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; 110:143–4
- Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–86
- Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L: Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149:8–13
- Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D: Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *ANESTHESIOLOGY* 1991; 74:15–23

14. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, Caspani L, Raimondi F, Bordone G, Iapichino G, Mancebo J, Guérin C, Ayzac L, Blanch L, Fumagalli R, Tognoni G, Gattinoni L, Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977-84
15. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, Aletti G, Porro GA, Irace M, Carlesso E, Carboni N, Lazzarini M, Gattinoni L: Prone position delays the progression of ventilator-induced lung injury in rats: Does lung strain distribution play a role? *Crit Care Med* 2005; 33:361-7
16. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guérin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. *Intensive Care Med* 2010; 36:585-99
17. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J: Prone positioning improves survival in severe ARDS: A pathophysiologic review and individual patient meta-analysis. *Minerva Anesthesiol* 2010; 76:448-54

# Positive End-expiratory Pressure Redistributes Regional Blood Flow and Ventilation Differently in Supine and Prone Humans

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## ABSTRACT

**Background:** Animal studies have demonstrated an interaction between posture and the effect of positive end-expiratory pressure (PEEP) on regional ventilation and lung blood flow. The aim of this study was to explore this interaction in humans.

**Methods:** Regional lung blood flow and ventilation were compared between mechanical ventilation with and without PEEP in the supine and prone postures. Six normal subjects were studied in each posture. Regional lung blood flow was marked with  $^{113\text{m}}\text{In}$ -labeled macroaggregates and ventilation with Technegas ( $^{99\text{m}}\text{Tc}$ ). Radiotracer distributions were mapped using quantitative single-photon emission computed tomography.

**Results:** In supine subjects, PEEP caused a similar redistribution of both ventilation and blood flow toward dependent

(dorsal) lung regions, resulting in little change in the V/Q correlation. In contrast, in prone subjects, the redistribution toward dependent (ventral) regions was much greater for blood flow than for ventilation, causing increased V/Q mismatch. Without PEEP, the vertical ventilation-to-perfusion gradient was less in prone postures than in supine, but with PEEP, the gradient was similar.

**Conclusions:** During mechanical ventilation of healthy volunteers, the addition of PEEP, 10 cm H<sub>2</sub>O, causes redistribution of both lung blood flow and ventilation, and the effect is different between the supine and prone postures. Our results suggest that the addition of PEEP in prone might be less beneficial than in supine and that optimal use of the prone posture requires reevaluation of the applied PEEP.

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## What We Already Know about This Topic

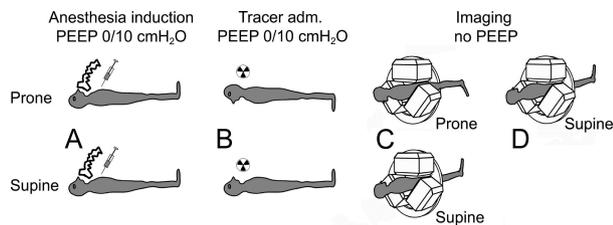
- ❖ Prone positioning improves oxygenation in hypoxemic patients with acute respiratory distress syndrome.

## What This Article Tells Us That Is New

- ❖ In healthy anesthetized, mechanically ventilated volunteers, a high-resolution imaging method documented that positive end-expiratory pressure caused a redistribution of blood flow and ventilation that is different between the supine and prone positions, leading to increased ventilation-to-perfusion mismatch in prone normals.

**M**ECHANICAL ventilation with positive end-expiratory pressure (PEEP) is an important intervention employed to counteract arterial hypoxemia in patients with acute respiratory failure. Large clinical trials have confirmed that prone positioning improves oxygenation in the majority of these patients.<sup>1-4</sup> Both interventions are widely used clinically, although clinical trials have failed at showing a survival benefit of prone positioning or using high *versus*

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**Fig. 1.** The figure outlines the experimental protocol. (A) Anesthesia induction, (B) administration of inhaled Technegas via the ventilator and IV injection of  $^{113m}\text{In}$ -labeled macroaggregates, (C) SPECT imaging in the same posture as during tracer administration, and (D) repeated imaging in supine for subjects where tracers were administered in prone. Six subjects were studied in each posture, and each subject was studied twice, once during ventilation with PEEP, 10 cm  $\text{H}_2\text{O}$ , during tracer administration and once without. All images were obtained during ventilation without PEEP. PEEP = positive end-expiratory pressure; SPECT = single-photon emission computed tomography.

low PEEP.<sup>1-3,5-7</sup> However, a recent meta-analysis suggests that prone positioning is associated with improved survival in patients with severe acute respiratory distress syndrome.<sup>8</sup> One reason for the negative clinical trials might be an incomplete understanding of the physiology of these interventions, precluding optimal clinical use. With both treatment modalities, arterial oxygenation is improved through redistribution of either regional lung blood flow, ventilation, or both. Prior studies have shown that lower PEEP is needed to maintain oxygenation in the prone posture than in the supine.<sup>9,10</sup> These results suggest that optimal PEEP might be lower in the prone posture than in the supine, possibly adding to the lung protective effect of prone positioning demonstrated in animal experiments.<sup>11,12</sup> Recent animal experiments have shown an interaction between PEEP and posture and its effect on regional lung blood flow and ventilation.<sup>13-17</sup> For example, Walther *et al.* showed that PEEP redistributed both blood flow and ventilation differently in the supine and prone postures.<sup>14,15</sup> In this study of mechanically ventilated healthy volunteers, our aim was to test the hypothesis that the effect of PEEP on regional lung blood flow and ventilation also differ between supine and prone normal subjects. A novel quantitative single-photon emission computed tomography (SPECT) method was used to map regional blood flow and ventilation simultaneously during mechanical ventilation with and without PEEP in the supine and prone postures.

## Materials and Methods

### Subjects

Twelve healthy volunteers (3 men and 9 women), age 20–52 yr, were studied. For six subjects, radiotracers were administered in the supine posture, and for six other subjects, radiotracers were administered in the prone posture. All subjects were of normal weight and height. None of the subjects had any underlying lung disease, all were nonsmokers, and all had

normal spirometry and lung volumes. The subjects received written information about the procedure, and written consent was obtained. The local committees for research ethics (Stockholm, Sweden) and radiation safety (Stockholm, Sweden) approved the study.

### Experimental Protocol

An outline of the experimental protocol is provided in figure 1. Induction of general anesthesia and intubation and insertion of an arterial catheter were done with subjects supine. For six subjects, the protocol was continued in the supine posture, and six subjects were turned to the prone posture. Stabilization was followed by a recruitment maneuver and 15 min of unaltered conditions. Regional lung blood flow and ventilation were then marked using radiotracers, as described below, followed by computed tomography and SPECT imaging. Gas exchange efficiency at the time of radiotracer administration was assessed by measurements of arterial blood gases and end-tidal concentration of carbon dioxide. After image acquisition, subjects studied in the prone posture were turned to the supine posture. Imaging was then repeated in this posture after a new recruitment maneuver and 15 min of stabilization. Each subject was studied twice, once ventilated with a PEEP of 10 cm  $\text{H}_2\text{O}$  before and during radiotracer administration and once ventilated without PEEP in randomized order. Thus, when radiotracers were administered supine, the protocol yielded two sets of images, both sets obtained in supine, representing regional ventilation and blood flow during ventilation with and without PEEP.

An interval of at least 48 h was required between the two occasions. The sequence of the two conditions was randomized. All images were obtained during ventilation without PEEP to ensure identical lung tissue distribution during imaging, and 10 min without PEEP was allowed for stabilization before imaging, if PEEP had been applied during radiotracer administration.

### Anesthesia

Monitoring included electrocardiogram, blood pressure, pulse oximetry, airway pressures, respiratory rate, tidal volume, and concentration of oxygen and carbon dioxide in inhaled and exhaled gases. General anesthesia was induced by IV administration of alfentanil 0.5–1.0 mg and propofol 1–3 mg/kg, and induction was preceded by preoxygenation using 60% oxygen. Muscle paralysis was established with rocuronium 0.5 mg/kg, and subjects were intubated orally. Anesthesia was maintained by infusion of propofol 4–10 mg/kg/h and alfentanil 0.5 mg as needed. Repeated doses of rocuronium were administered when more than one twitch occurred at train-of-four stimulation.

### Mechanical Ventilation

Subjects were ventilated with a Siemens Servo 900D ventilator (Siemens, Solna, Sweden) using volume control with a tidal volume of 8 ml/kg throughout the experiment. Respiratory rate was adjusted to maintain an end-tidal carbon

dioxide concentration of 4.5–5.5 kPa. The inspiratory oxygen concentration was initially 30% and increased if pulse oximetry readings decreased below 95%. Lung recruitment was performed by changing the ventilator setting to continuous positive airway pressure and applying a pressure of 40 cm H<sub>2</sub>O for 20 s.

### Radiotracers

Regional ventilation was marked using inhaled Technegas, microscopic graphite particles labeled with radioactive Technetium (<sup>99m</sup>Tc),<sup>18</sup> approximately 100 MBq. Subjects were connected to the inspiratory port of the ventilator *via* two parallel circuits, one incorporating the Technegas generator (Tetley Manufacturing Ltd., Sydney, Australia). During Technegas administration, a valve was turned that allowed a variable fraction of the flow from the ventilator to pass through the generator. Administration was done during close monitoring of inspiratory oxygen concentration (maintained above 21%) and pulse oximetry because Technegas initially consists of 100% argon. Immediately after Technegas administration, regional lung blood flow was marked by the use of 50 MBq <sup>113m</sup>In-labeled macroaggregates of albumin administered *via* a peripheral venous catheter. The subjects were estimated to receive a total effective dose of radioactivity of about 8 mSv.

### SPECT

The employed dual-isotope SPECT method is a development of a previously reported technique.<sup>19,20</sup> Images were obtained using a combined computed tomography-SPECT system (Millenium VG; General Electric Medical Systems, Milwaukee, WI). Image acquisition required 30 min. The two sets of projected images, one for each principal photon energy (140 and 392 keV), were corrected for photon scattering and attenuation as well as for the contribution of high-energy photons in the lower photon energy window and the radioactive decay before image reconstruction. Computed tomography images were used for the attenuation correction routine and for delineation of the lungs. Spatial coordinates and number of events per voxel (size 4.42<sup>3</sup> mm<sup>3</sup>) were extracted from the reconstructed <sup>113m</sup>In-LyoMAA and <sup>99m</sup>Tc-Technegas images. Counts per voxel were normalized to the mean number of counts for all voxels. The final data represent blood flow or ventilation for each voxel relative to the mean for all voxels. These data were also used to calculate ventilation-to-perfusion ratios for each voxel.

### Data Analysis

In the following, dependent and nondependent always refer to the conditions during radiotracer administration, regardless of posture during imaging. The lung was divided into segments, each representing 10% of the total distance from the most dependent to the most nondependent lung regions. Distributions of blood flow, ventilation, and ventilation-to-perfusion ratios were visualized using plots of mean values for all voxels within each segment. Ventral-to-dorsal gradients

were estimated as the regression coefficients from linear regressions of regional blood flow, ventilation, and ventilation-to-perfusion ratio on the dependent-to-nondependent distance. Gradients are thus quantified as the change in normalized flow, ventilation, and ventilation-to-perfusion ratio per cm. The PEEP-induced redistributions were estimated from (1) comparison of plots from ventilation with and without PEEP and (2) by subtracting the gradient during ventilation with PEEP from the gradient without PEEP for each posture. A difference in gradient more than 0 means a PEEP-induced redistribution from dependent to nondependent regions, a difference less than 0 means a shift in the opposite direction, and a difference of 0 means that the addition of PEEP did not change the gradient.

Interpretation of images of regional lung blood flow and ventilation is complicated because the amount of tissue per unit lung volume varies between regions in a posture-dependent manner.<sup>21,22</sup> Differences between images of, for example, regional blood flow in two postures can therefore be caused by either different distribution of lung tissue within the thorax or different distribution of blood flow within the vasculature. We used radiotracers that remain fixed in the lung parenchyma after administration. Thus, regardless of any change in posture before imaging, the distribution of radioactivity within the tissue represents the distribution of blood flow and ventilation at the time of administration. The effect of posture on the distributions of blood flow or ventilation within the lung tissue can be estimated if radiotracer administration in different postures is followed by imaging in one posture. Differences between images can then only be explained by different distribution of blood flow or ventilation within the lung vasculature and airways, respectively, at the time of radiotracer administration. Recently, we used this to demonstrate that the redistribution of lung tissue is responsible for most of the differences between images of regional blood flow and ventilation obtained in the supine and prone postures during spontaneous breathing.<sup>22</sup> In the current study, we therefore used images obtained in supine after radiotracer administration in prone posture to compare the PEEP-induced redistribution of blood flow and ventilation between the two postures. Likewise, we also used these images to compare the distribution of blood flow and ventilation between the two postures. Reporting prior studies, we have been asked about the spatial distributions while being in the prone posture for comparison with previous data. Imaging prone, after radiotracer administration prone, was therefore included in the study protocol. Also PEEP might shift the distribution of lung tissue, confounding the comparison of regional blood flow or ventilation during ventilation with and without PEEP. All images were therefore obtained during ventilation without PEEP.

### Statistics

Paired two-tailed *t* tests were used for statistical comparisons of physiologic parameters and gradients during ventilation with and without PEEP. Unpaired two-tailed *t* tests were

**Table 1.** Measurements of Gas Exchange and Airway Pressure

	Supine		Prone	
	No PEEP	PEEP 10 cm H <sub>2</sub> O	No PEEP	PEEP 10 cm H <sub>2</sub> O
Pao <sub>2</sub> mmHg	206 ± 53	211 ± 55	274 ± 20	242 ± 5
Pao <sub>2</sub> /Fio <sub>2</sub> mmHg	526 ± 117	522 ± 140	611 ± 40	592 ± 23
Paco <sub>2</sub> mmHg	39 ± 2	39 ± 2	38 ± 2	39 ± 2
Paco <sub>2</sub> -ETCO <sub>2</sub> mmHg	3 ± 1	3 ± 2	2 ± 2	4 ± 2
Pplat cm H <sub>2</sub> O	9.9 ± 1.6	16.1 ± 1.2	9.8 ± 1.5	18.2 ± 1.0*

Values are mean ± SD and refer to measurements at the time of radiotracer administration.

\*  $P < 0.01$  versus supine with PEEP.

ETCO<sub>2</sub> = end-tidal carbon dioxide partial pressure; Paco<sub>2</sub> = arterial carbon dioxide partial pressure; Paco<sub>2</sub>-ETCO<sub>2</sub> = difference between arterial carbon dioxide partial pressure and end-tidal carbon dioxide partial pressure; Pao<sub>2</sub> = arterial oxygen partial pressure; PEEP = positive end-expiratory pressure; Pplat = inspiratory plateau pressure.

used to compare physiologic parameters, gradients, and PEEP-induced redistribution between the two administration postures. Gradients and PEEP-induced redistributions were tested for equality with zero using two-tailed one-sample  $t$  test. A  $P$  value less than 0.05 was considered significant. All analyses were done using Statistica 7.0 (Statsoft, Tulsa, OK).

## Results

Gas exchange parameters and airway pressures are reported in table 1. Differences in mean arterial pressure between ventilation with and without PEEP or between the postures were not statistically significant (data not shown). Technegas administration was required in an average of 6 min. No data were lost to observation or missed in the analysis.

### PEEP and Regional Blood Flow

Both the change in gradients in table 2 and the plots in figure 2 demonstrate that the addition of PEEP caused a redistribution of blood flow from nondependent to dependent regions in both postures. The differences between gradients with and without PEEP were  $-0.050 \pm 0.029$  and  $-0.054 \pm 0.015$  (relative blood flow per voxel per cm) in the supine and prone postures, respectively, suggesting quantitatively similar redistribution in the two postures (table 2).

### PEEP and Regional Ventilation

The plots in figure 2 show that in the supine posture, PEEP caused a shift of ventilation from nondependent to dependent

regions with no apparent redistribution in the prone posture. Also, the change in gradients,  $-0.062 \pm 0.057$  (relative ventilation per voxel per cm) (table 2), is consistent with a shift in ventilation to dependent regions in the supine posture. The change in gradients in the prone posture,  $-0.017 \pm 0.011$  (relative ventilation per voxel per cm), suggests a much smaller, but statistically significant, redistribution of ventilation from nondependent to dependent (ventral) regions (table 2).

### PEEP and Regional Ventilation-to-Perfusion Ratios

In the supine posture, PEEP caused similar redistributions of both blood flow and ventilation toward dependent regions, resulting in little change in the gradients of ventilation-to-perfusion ratios (fig. 2, table 2). Addition of PEEP in the prone posture caused a redistribution of both blood flow and ventilation toward dependent regions, but the shift was much smaller for ventilation. Consequently, in the prone posture, PEEP increased the ventilation-to-perfusion ratios in nondependent regions and decreased the ratios in dependent regions (fig. 2), resulting in an increase in the dependent-to-nondependent gradient of  $0.045 \pm 0.024$  (relative ventilation-to-perfusion ratio per voxel per cm) (table 2). However, the vertical gradient of ventilation-to-perfusion ratios with no PEEP was smaller in prone subjects than in supine and similar in prone and supine subjects during ventilation with PEEP gradients (data not shown). In summary, PEEP increased ventilation-to-perfusion mismatch in the prone posture, whereas the effect was small in supine.

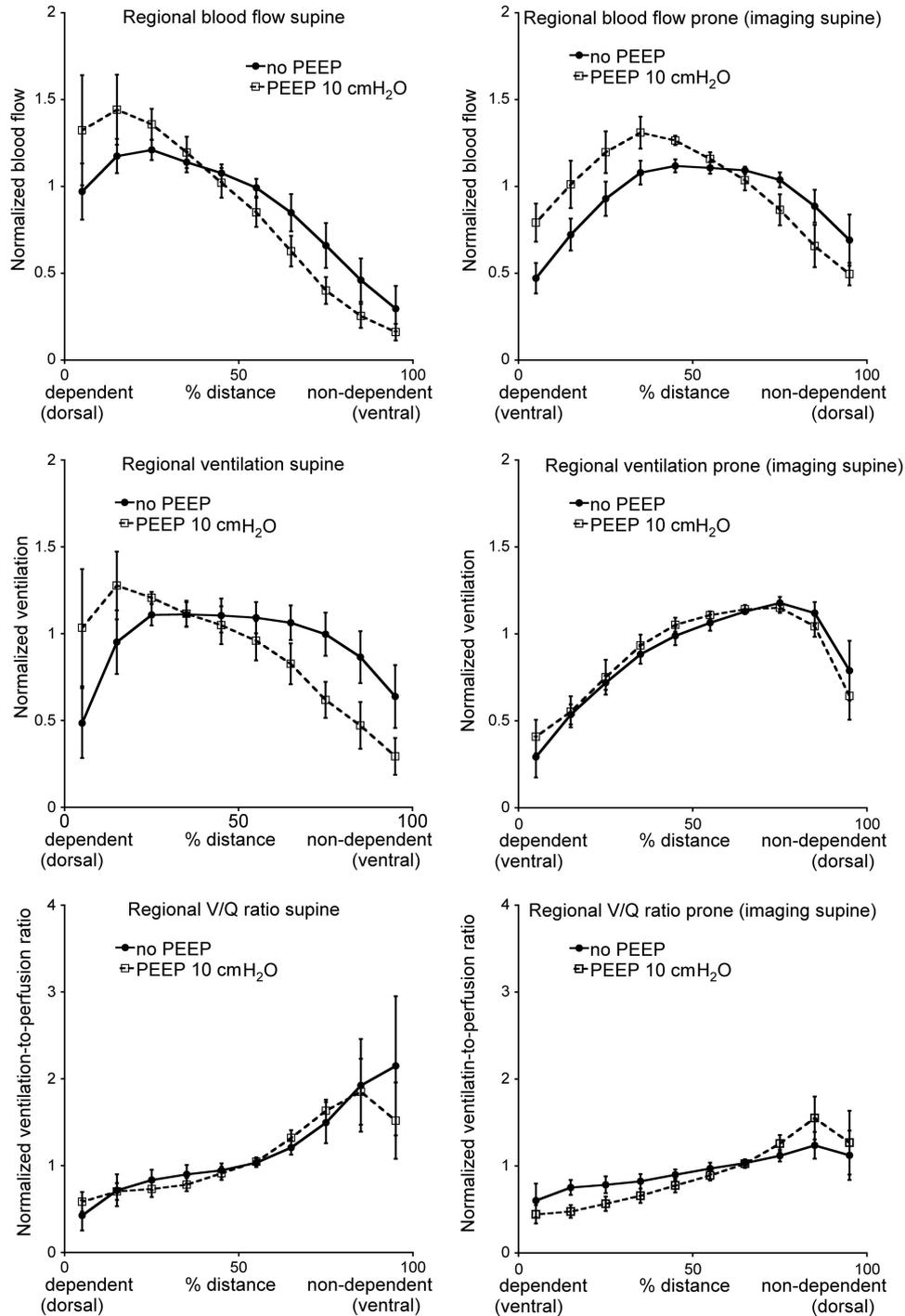
**Table 2.** Effect of PEEP on Gradients from Dependent to Nondependent Lung Regions

	Blood Flow	Ventilation	Ventilation-to-Perfusion Ratio
Supine	$-0.050 \pm 0.029^*$	$-0.062 \pm 0.057^\dagger$	$-0.003 \pm 0.049$
Prone (imaged supine)	$-0.054 \pm 0.015^*$	$-0.017 \pm 0.011^*$	$0.045 \pm 0.024^*$
Prone (imaged prone)	$-0.064 \pm 0.025^*$	$-0.011 \pm 0.021$	$0.065 \pm 0.046^*$

Effect of PEEP on the dependent-to-nondependent distributions of blood flow, ventilation, and ventilation-to-perfusion ratios, estimated as differences in gradients (gradient with PEEP minus gradient without PEEP) from least squares regressions. Values are mean ± SD. Units are normalized blood flow, ventilation, or ventilation-to-perfusion ratio per cm. A difference in gradient  $> 0$  means a PEEP-induced redistribution from dependent to nondependent regions, a difference  $< 0$  means a shift in the opposite direction, and a difference of 0 means that the addition of PEEP did not change the gradient.

†  $P < 0.05$ , \*  $P < 0.01$  for being different from zero (single sample  $t$  test).

PEEP = positive end-expiratory pressure.



**Fig. 2.** For these plots, the lungs were divided into 10 sections of equal height along the dependent-to-nondependent distance. Normalized regional ventilation, blood flow, and ventilation-to-perfusion ratios per voxel were averaged within each section. Plotted values are the mean value across all individuals for each section; error bars illustrate SD for the individual values for each section. Values at the extremes of the dependent-to-nondependent distance are influenced by the edge effect (underestimation of the radiotracer concentration at the lung periphery). PEEP = positive end-expiratory pressure.

### Effect of Posture

Comparison of dependent to nondependent blood flow distribution in prone and supine (fig. 2, table 2) postures demonstrates that a shift from supine to prone causes a redistribution of blood flow from regions dependent in supine (*i.e.*, dorsal regions) to regions dependent in prone (*i.e.*, ventral

regions) and that the effect is augmented during ventilation with PEEP. In other words, there is a clear effect of posture on regional blood flow. Without PEEP, a change from supine to prone posture caused a shift of ventilation from regions nondependent in supine (*i.e.*, ventral regions) to regions nondependent in prone (*i.e.*, dorsal regions). Dur-

ing ventilation with PEEP, a shift from supine to prone caused a small redistribution of ventilation from regions dependent in supine (*i.e.*, dorsal regions) to regions dependent in prone (*i.e.*, ventral regions), opposite the redistribution at change in posture during ventilation without PEEP. In both postures, ventilation-to-perfusion ratios were lower in dependent regions than in nondependent, both during ventilation with and without PEEP. During ventilation without PEEP, a shift from supine to prone posture resulted in a decreased gradient, whereas there was little change during ventilation with PEEP (table 2, fig. 2).

### Imaging Prone

As expected, images obtained in the prone posture after radiotracer administration in prone demonstrated a similar effect of PEEP as images obtained in the supine posture, although the effect on the dependent to nondependent distribution of ventilation was not statistically significant (table 2). During mechanical ventilation without PEEP in the prone posture, regional blood flow was greatest in dependent regions, and addition of PEEP caused a further shift of blood flow to dependent regions and an increase in gradient of  $-0.064 \pm 0.025$  (relative blood flow per voxel per cm) (fig. 3, table 2). In contrast, regional ventilation was preferentially distributed to nondependent regions with little difference between ventilation with and without PEEP (fig. 3, table 2).

### Discussion

To our knowledge, this is the first study that used a high-resolution imaging method to evaluate simultaneously the effect of PEEP and posture on regional lung blood flow and ventilation in humans. A further novelty is the use of a study design that allowed us to exclude the confounding effect of different lung tissue distribution during different conditions. The main results are that, in anesthetized and mechanically ventilated normal subjects, a change from supine to prone causes a redistribution of both regional blood flow and ventilation within the lung parenchyma and that these redistributions are modified by the application of PEEP. In summary, during positive pressure ventilation:

- Regional lung blood flow is greater to dependent regions in both prone and supine postures, and the addition of PEEP increases this gradient in both postures.
- Regional ventilation is preferentially distributed to nondependent (dorsal) regions in prone with little vertical gradient in supine. The addition of PEEP has little effect on regional ventilation in prone but shift ventilation from nondependent to dependent (*i.e.*, from ventral to dorsal) regions in supine.
- During ventilation without PEEP, ventilation-to-perfusion ratios in the dependent to nondependent direction are more uniform in prone than in supine. Addition of PEEP increases the gradient in prone but not in supine, resulting in little difference between the postures.

Our discussion will first focus on some methodological issues and then on the effect of PEEP and posture on regional lung blood flow and ventilation.

### Methodological Issues

The characteristics and limitations of the SPECT method have been discussed at depth in our previous publications.<sup>19,20,22,23</sup> We used radionuclide-labeled particles that are deposited in the lung in proportion to regional blood flow and ventilation, which has been confirmed with other methods.<sup>15,24</sup> Quantitative SPECT measurements are hampered by attenuation and scatter of the radiation emitted from the radiotracer within the body. In this study, we applied new methods of correcting for attenuation and scatter, including low-dose computed tomography to obtain data for the attenuation correction routine. Linear regression coefficients are not perfect descriptors of the profiles presented in figure 1. However, linear regression is easy to comprehend, and it identifies any general trend for blood flow or ventilation to change in a certain direction. In the current study, regional blood flow, ventilation, and ventilation-to-perfusion ratios were compared between images obtained in the same posture during ventilation without PEEP. Differences between images can therefore only be explained by different distributions within the parenchyma at the time of radiotracer administration. This design allowed us to capture the effect of PEEP and posture on the distribution of blood flow and ventilation within the vasculature and airways, respectively.

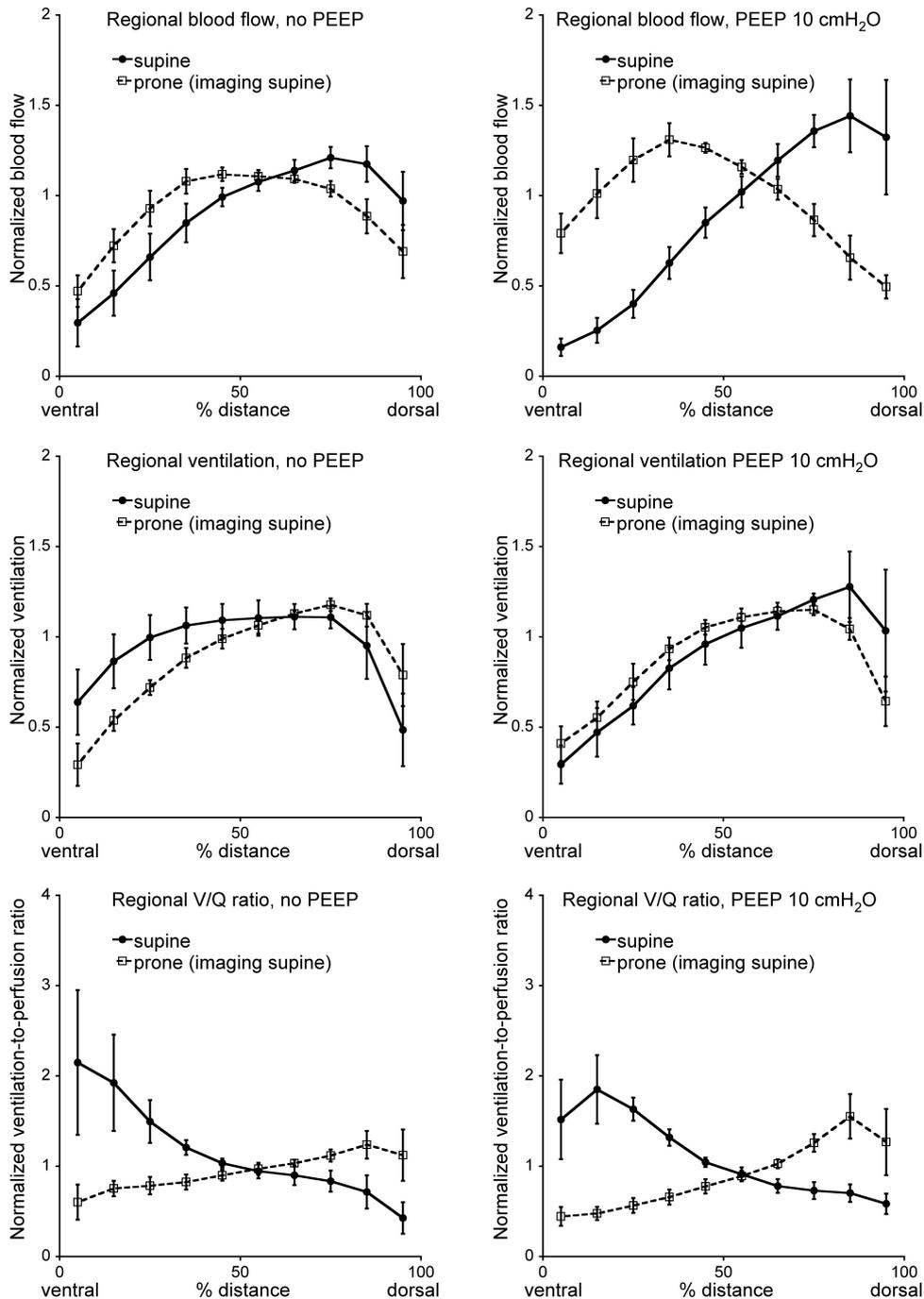
The number of subjects, studying different subjects prone and supine, and measurements at only one PEEP level are obvious limitations of our study. We chose a number of subjects, which has allowed identification of physiologic meaningful differences in previous studies. The maximum dose of radioactivity only allows two conditions to be studied per subject. We studied the same subject during ventilation with and without PEEP but different subjects prone and supine because the focus of the study was the effect of PEEP.

### Effect of PEEP on Regional Blood Flow

Previous work in supine animals have found a similar effect of PEEP (*i.e.*, redistribution of blood flow to dependent regions).<sup>14,16,17,25–27</sup> Studies in prone animals have shown either little redistribution<sup>14,27</sup> or a shift to dependent regions.<sup>16</sup> Speculative suggestions regarding the mechanisms causing redistribution of lung blood flow at addition of PEEP are: reduction of hypoxic vasoconstriction in atelectatic or poorly ventilated dependent regions, hyperinflation of nondependent regions increasing regional vascular resistance, reduced cardiac output and pulmonary arterial pressure, and increased airway pressures. The last three suggestions might increase the vertical blood flow gradient by causing zone 1–2 conditions in a greater part of the lung.<sup>28</sup>

### Effect of PEEP on Regional Ventilation

PEEP is thought to change regional ventilation through changes in regional alveolar expansion at end-expiration and



**Fig. 3.** For these plots, the lungs were divided into 10 sections of equal height along the ventral-to-dorsal distance. The profiles are identical to those in fig. 1, but here they are arranged to clarify the effect of posture on regional blood flow, ventilation, and ventilation-to-perfusion ratios. Note that the x axis is the ventral-to-dorsal distance as opposed to the dependent-to-nondependent distance in fig. 2. Normalized regional ventilation, blood flow, and ventilation-to-perfusion ratios per voxel were averaged within each section. Plotted values are the mean value across all individuals for each section; error bars illustrate SD for the individual values for each section. Values at the extremes of the dependent-to-nondependent distances are influenced by the edge effect (underestimation of the radiotracer concentration at the lung periphery). PEEP = positive end-expiratory pressure.

regional differences in compliance within the interval of inspiratory and expiratory airway pressures. In supine subjects, we demonstrated that PEEP shifted ventilation from nondependent (ventral) to dependent (dorsal) regions, suggesting a decrease in compliance in nondependent regions and/or an

increase in dependent regions. The result is consistent with a gravitational pleural pressure gradient, decreasing alveolar expansion down the lung, and a PEEP-induced hyperinflation in nondependent regions in the supine posture.<sup>29-32</sup> The effect of PEEP was much less in the prone posture,

which is consistent with more uniform pleural pressure and alveolar expansion in prone.<sup>31,33</sup>

### **Effect of PEEP on Regional Ventilation-to-Perfusion Ratios**

In the current study, PEEP increased the vertical gradient in ventilation-to-perfusion ratios in prone but not in supine. The gradient without PEEP was, however, smaller in prone than in supine; the effect of PEEP therefore resulted in similar gradients in the two postures. Similar to the current results, Mure *et al.* showed that continuous positive airway pressure caused increased ventilation-to-perfusion mismatch in prone but not in supine normal subjects breathing spontaneously awake.<sup>34</sup>

### **Effect of Posture and Mechanical Ventilation**

In a previous SPECT study, we demonstrated that a change between the supine and prone postures cause little change in the distribution of regional blood flow and ventilation within the lung tissue in awake normal subjects breathing spontaneously.<sup>22</sup> In contrast, in the current study of mechanically ventilated volunteers, we demonstrated a clear effect of posture with a redistribution of blood flow in the direction of gravity at a change in posture (fig. 2). Moreover, the redistribution was accentuated during ventilation with PEEP. We can only speculate regarding the cause of the greater effect of posture during positive pressure ventilation. During spontaneous breathing in horizontal postures, most of the lung is in zone 3 conditions, whereas positive pressure ventilation through several mechanisms might cause zone 1 and 2 conditions, which would explain a greater gravitational gradient and a greater effect of posture during mechanical ventilation. This hypothesis is supported by the greater effect of posture during greater airway pressures (*i.e.*, ventilation with PEEP).

Our results also suggest that posture has a greater effect on regional ventilation during positive pressure ventilation than during spontaneous breathing.<sup>22</sup> Without PEEP, a change from supine to prone caused a shift of regional ventilation from ventral (in supine nondependent) to dorsal (in prone nondependent) regions. During ventilation with PEEP, a shift from supine to prone caused a redistribution of ventilation in the opposite direction (*i.e.*, from dorsal to ventral [in prone dependent] regions).

When measured in the same posture as during radiotracer administration, regional blood flow per unit lung volume was greater in dependent regions in both postures and more so during ventilation with PEEP (fig. 2). Without PEEP, regional ventilation per unit lung volume decreased down the lung in both postures (fig. 2), which is opposite the gradient during spontaneous breathing awake.<sup>22</sup> In supine, the application of PEEP reversed the gradient, causing regional ventilation to be greater in dependent than nondependent regions (fig. 2, table 2). In other words, PEEP resulted in a vertical distribution of ventilation similar to that during spontaneous breathing.<sup>22</sup> In prone, PEEP caused a small reduction of the gradient, but ventilation per unit lung volume remained greater in nondependent regions (table 2).

### **Clinical Implications**

It is noteworthy that our results primarily apply to mechanical ventilation of normal lungs. Pulmonary edema, alveolar collapse and consolidation, and hypoxic vasoconstriction are all important causes and modulators of arterial hypoxemia in patients with acute respiratory failure but absent, or much less important, in patients without lung disease. The effect of both PEEP and the prone posture might therefore be different in patients with acute lung injury. However, Richard *et al.*<sup>17</sup> studied regional lung blood flow and ventilation in pigs with experimental acute lung injury and demonstrated similar effects of PEEP and the prone posture, such as in the current study. Our results suggest that the effect of PEEP on ventilation-to-perfusion matching is posture-dependent. The redistribution of ventilation at the application of PEEP was much smaller in prone than in supine. We therefore speculate that a beneficial effect of PEEP in supine, causing more uniform ventilation in patients with acute lung injury, might be less in the prone posture. Consequently, optimal PEEP might be different in supine and prone patients.

### **Conclusions**

Addition of PEEP (10 cm H<sub>2</sub>O) causes redistribution of both lung blood flow and ventilation, and the effect is different between the supine and prone postures. Our results suggest that the addition of PEEP in prone might be less beneficial than in supine, and the best use of the prone posture might mean that PEEP should be reduced in relation to optimal PEEP while supine. We also conclude that in normal subjects, the effect of posture (prone *vs.* supine) on regional lung blood flow and ventilation is much greater during general anesthesia and positive pressure ventilation than while awake, breathing spontaneously.

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### **References**

- Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, Brazzi L, Latini R, Prone-Supine Study Group: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568-73
- Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, Palmier B, Le QV, Sirodot M, Rosselli S, Cadieregue V, Sainty JM, Barbe P, Combourieu E, Debatty D, Rouffineau J, Ezingard E, Millet O, Guelon D, Rodriguez L, Martin O, Renault A, Sibille JP, Kaidomar M: Effects of systematic prone positioning in hypoxic acute respiratory failure: A randomized controlled trial. *Jama* 2004; 292:2379-87
- Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, Rodríguez F, Garro P, Ricart P, Vallverdú I, Gich I, Castaño J, Saura P, Domínguez G, Bonet A, Albert RK: A

- multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:1233-9
4. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, Caspani L, Raimondi F, Bordone G, Iapichino G, Mancebo J, Guérin C, Ayzac L, Blanch L, Fumagalli R, Tognoni G, Gattinoni L, Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *Jama* 2009; 302:1977-84
  5. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L, Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646-55
  6. Brower RG, Lanke PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327-36
  7. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE, 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; 299:637-45
  8. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guérin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. *Intensive Care Med* 2010; 36:585-99
  9. Cakar N, der Kloot TV, Youngblood M, Adams A, Nahum A: Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. *Am J Respir Crit Care Med* 2000; 161:1949-56
  10. Gainnier M, Michelet P, Thirion X, Arnal JM, Sainty JM, Papazian L: Prone position and positive end-expiratory pressure in acute respiratory distress syndrome. *Crit Care Med* 2003; 31:2719-26
  11. 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; 25:16-27
  12. 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; 28:295-303
  13. Walther SM, Domino KB, Glenny RW, Hlastala MP: Positive end-expiratory pressure redistributes perfusion to dependent lung regions in supine but not in prone lambs. *Crit Care Med* 1999; 27:37-45
  14. Walther SM, Johansson MJ, Flatebø T, Nicolaysen A, Nicolaysen G: Marked differences between prone and supine sheep in effect of PEEP on perfusion distribution in zone II lung. *J Appl Physiol* 2005; 99:909-14
  15. Johansson MJ, Wiklund A, Flatebø T, Nicolaysen A, Nicolaysen G, Walther SM: Positive end-expiratory pressure affects regional redistribution of ventilation differently in prone and supine sheep. *Crit Care Med* 2004; 32:2039-44
  16. Richard JC, Decalioff F, Janier M, Annat G, Guérin C: Effects of positive end-expiratory pressure and body position on pulmonary blood flow redistribution in mechanically ventilated normal pigs. *Chest* 2002; 122:998-1005
  17. Richard JC, Bregeon F, Costes N, Bars DL, Tourvieille C, Lavenne F, Janier M, Bourdin G, Gimenez G, Guérin C: Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. *Crit Care Med* 2008; 36:2373-80
  18. Burch WM, Sullivan PJ, McLaren CJ: Technegas—a new ventilation agent for lung scanning. *Nucl Med Commun* 1986; 7:865-71
  19. Petersson J, Sánchez-Crespo A, Rohdin M, Montmerle S, Nyrén S, Jacobsson H, Larsson SA, Lindahl SG, Linnarsson D, Glenny RW, Mure M: Physiological evaluation of a new quantitative SPECT method measuring regional ventilation and perfusion. *J Appl Physiol* 2004; 96:1127-36
  20. Sánchez-Crespo A, Petersson J, Nyren S, Mure M, Glenny RW, Thorell JO, Jacobsson H, Lindahl SG, Larsson SA: A novel quantitative dual-isotope method for simultaneous ventilation and perfusion lung SPET. *Eur J Nucl Med Mol Imaging* 2002; 29:863-75
  21. Hopkins SR, Henderson AC, Levin DL, Yamada K, Arai T, Buxton RB, Prisk GK: Vertical gradients in regional lung density and perfusion in the supine human lung: The Slinky effect. *J Appl Physiol* 2007; 103:240-8
  22. Petersson J, Rohdin M, Sánchez-Crespo A, Nyrén S, Jacobsson H, Larsson SA, Lindahl SG, Linnarsson D, Neradilek B, Polissar NL, Glenny RW, Mure M: Posture primarily affects lung tissue distribution with minor effect on blood flow and ventilation. *Respir Physiol Neurobiol* 2007; 156:293-303
  23. Petersson J, Sánchez-Crespo A, Larsson SA, Mure M: Physiological imaging of the lung: Single-photon-emission computed tomography (SPECT). *J Appl Physiol* 2007; 102:468-76
  24. Melsom MN, Flatebø T, Kramer-Johansen J, Aulie A, Sjaastad OV, Iversen PO, Nicolaysen G: Both gravity and non-gravity dependent factors determine regional blood flow within the goat lung. *Acta Physiol Scand* 1995; 153:343-53
  25. Hedenstierna G, White FC, Mazonne R, Wagner PD: Redistribution of pulmonary blood flow in the dog with PEEP ventilation. *J Appl Physiol* 1979; 46:278-87
  26. Kallas HJ, Domino KB, Glenny RW, Anderson EA, Hlastala MP: Pulmonary blood flow redistribution with low levels of positive end-expiratory pressure. *ANESTHESIOLOGY* 1998; 88:1291-9
  27. Walther SM, Domino KB, Glenny RW, Hlastala MP: Positive end-expiratory pressure redistributes perfusion to dependent lung regions in supine but not in prone lambs. *Crit Care Med* 1999; 27:37-45
  28. West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J Appl Physiol* 1964; 19:713-24
  29. Milic-Emili J, Henderson JA, Dolovich MB, Trop D, Kaneko K: Regional distribution of inspired gas in the lung. *J Appl Physiol* 1966; 21:749-59
  30. Glazier JB, Hughes JM, Maloney JE, West JB: Vertical gradient of alveolar size in lungs of dogs frozen intact. *J Appl Physiol* 1967; 23:694-705
  31. Mayo JR, MacKay AL, Whittall KP, Baile EM, Paré PD: Measurement of lung water content and pleural pressure gradient with magnetic resonance imaging. *J Thorac Imaging* 1995; 10:73-81
  32. Rehder K, Sessler AD, Rodarte JR: Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man. *J Appl Physiol* 1977; 42:391-402
  33. 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; 146:300-6
  34. Mure M, Nyrén S, Jacobsson H, Larsson SA, Lindahl SG: High continuous positive airway pressure level induces ventilation/perfusion mismatch in the prone position. *Crit Care Med* 2001; 29:959-64