Effect of Prone Position on Regional Shunt, Aeration, and Perfusion in Experimental Acute Lung Injury

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Rationale: The prone position is used to improve gas exchange in patients with acute respiratory distress syndrome. However, the regional mechanism by which the prone position improves gas exchange in acutely injured lungs is still incompletely defined. **Methods:** We used positron emission tomography imaging of [^{13}N]nitrogen to assess the regional distribution of pulmonary shunt, aeration, perfusion, and ventilation in seven surfactant-depleted sheep in supine and prone positions. **Results:** In the supine position, the dorsal lung regions had a high shunt fraction, high perfusion, and poor aeration. The prone position was associated with an increase in lung gas content and with a more uniform distribution of aeration, as the increase in aeration in dorsal lung regions was not offset by loss of aeration in ventral regions. Consequently, the shunt fraction decreased in dorsal regions in the prone position without a concomitant impairment of gas exchange in ventral regions, thus leading to a significant increase in the fraction of pulmonary perfusion participating in gas exchange. In addition, the vertical distribution of specific alveolar ventilation became more uniform in the prone position. A biphasic relation between regional shunt fraction and gas fraction showed low shunt for values of gas fraction higher than a threshold, and a steep linear increase in shunt for lower values of gas fraction. **Conclusion:** In a surfactant-deficient model of lung injury, the prone position improved gas exchange by restoring aeration and decreasing shunt while preserving perfusion in dorsal lung regions, and by making the distribution of ventilation more uniform.

Keywords: adult respiratory distress syndrome; emission-computed tomography; nitrogen isotopes; prone position; pulmonary gas exchange

Despite increasing use of the prone position as a means to improve gas exchange in patients with acute respiratory distress syndrome (ARDS) (1, 2), few studies have investigated the regional mechanism of this improvement in acutely injured lungs (3, 4). Using single-photon emission computed tomography in an oleic acid model of lung injury, Lamm and coworkers (4) showed that the prone position was associated with a narrower distribution of the ventilation-to-perfusion ratio and with an increase in the relative (i.e., mean-normalized) ventilation-to-perfusion ratio in dorsal lung regions. However, because regional shunt could not

be measured directly by single-photon emission computed tomography, whether the increase in relative ventilation-to-perfusion ratio in dorsal regions corresponded to reversal of shunt and, more importantly, the magnitude of the associated improvement of regional gas exchange could not be determined. Furthermore, single-photon emission computed tomography did not allow assessment of regional aeration. Combining measurement of regional aeration with measurement of regional shunt and perfusion is important for two reasons. First, it allows determination of whether the improvement of gas exchange in the prone position is due to restored aeration to regions of shunt or to redistribution of perfusion away from these regions. In this respect, it has been suggested that the regional mechanism by which the prone position improves gas exchange may bear prognostic significance and that the prone position increases survival of patients with ARDS if the improvement of gas exchange on turning prone is associated with restored aeration to regions of shunt rather than with redistribution of perfusion away from these regions (5). Therefore, further insights into the effect of the prone position on regional shunt, aeration, and perfusion can have important clinical implications. Second, by combining measurements of regional aeration and regional shunt, it is possible to determine the functional consequence of the change in distribution of lung density associated with prone positioning (6).

Positron emission tomography (PET) imaging of infused [^{13}N]nitrogen ($^{13}\text{N}_2$) is a noninvasive technique that allows the *in vivo* assessment of regional gas exchange and the direct quantification and localization of intrapulmonary shunt (7–9). In this study, we used PET imaging of infused and inhaled $^{13}\text{N}_2$ to assess the effect of the prone position on the regional distribution of pulmonary perfusion, shunt, aeration, and ventilation in a saline lavage model of acute lung injury. We investigated whether, in acute lung injury caused by surfactant depletion, the prone position improves gas exchange by restoring aeration and decreasing shunt in dorsal lung regions or by redistributing perfusion away from these regions. A preliminary analysis of some of the results of this study was previously reported in the form of an abstract (10).

METHODS

Experimental Procedures

Seven sheep (22.4 ± 2.9 kg) were anesthetized, paralyzed, and mechanically ventilated (tidal volume, 8 ml/kg; inspiratory-to-expiratory ratio, 1:2; fraction of inspired oxygen, 1.0; and positive end-expiratory pressure, 5 cm H_2O). Respiratory rate was adjusted to normocapnia (19.7 ± 2 breaths/minute; $\text{PaCO}_2 = 39.9 \pm 3.9$ mm Hg) and was not modified during the study. An arterial line and a Swan-Ganz catheter were inserted and a jugular line was placed for infusion of $^{13}\text{N}_2$ in saline solution. The animals were then suspended in a cylindrical tube, which allowed them to remain positioned within the field of view of the PET scanner while body position was changed by rotation of the tube. This suspension system allowed the abdomen to be unsupported in the prone position.

After collection of control physiologic data in both positions, lung lavage was performed by instillation and drainage of warm saline

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Figure 1. Protocol schema. *Until PaO_2 below 100 mm Hg; ** PaO_2 below 200 mm Hg that changed by less than 10% at two consecutive 15-minute intervals. PET = positron emission tomography.

Figure 3. PET images from one animal in supine and prone positions. Four of the 15 original slices of lung are shown (top to bottom, cranial to caudal). For both positions, images in the first column correspond to the peak of infused $^{13}\text{N}_2$ kinetics (5 seconds $< t < 10$ seconds) and reflect the regional distribution of perfusion. Note the preferential distribution of perfusion to dorsal regions in both positions, and the more uniform perfusion when prone. Images in the second column correspond to the plateau of infused $^{13}\text{N}_2$ kinetics (40 seconds $< t < 60$ seconds) and show the regional distribution of perfusion in units that are perfused and aerated. Regions of shunt, which do not retain $^{13}\text{N}_2$ during apnea, can be visualized as regions in which tracer activity is present in the peak apnea images (first column) but absent in the end apnea images (second column). Note the large amount of shunt in dorsal regions, particularly in caudal slices, in the supine position, which is annihilated by turning prone. This is consistent with the regional distribution of gas fraction, measured after equilibration of inhaled $^{13}\text{N}_2$ (third column), which shows restored aeration to dorsal regions and a more uniform aeration in the prone position.

nary arterial pressure, while cardiac output, heart rate, and mean arterial pressure were not significantly affected by the body position change. Pulmonary capillary wedge pressure was slightly lower in the prone position. Inspiratory plateau airway pressure was substantially lower in the prone than in the supine position (Table 1).

Regional Gas Content

The total, voxel-by-voxel mean-normalized variance of gas fraction, $\text{COV}_{\text{tot}}^2$ (see the online supplement), was almost fivefold greater in the supine than in the prone position (0.60 ± 0.24 vs. 0.13 ± 0.09 ; $p < 0.001$). The systematic component of the variance in the vertical direction, COV_v^2 , accounted for 62 ± 21 and $29 \pm 14\%$ of $\text{COV}_{\text{tot}}^2$ in the supine and prone positions, respectively. In contrast, the systematic component of the variance in the craniocaudal direction, COV_{cc}^2 , accounted for a small fraction of the total variance in both body positions ($4 \pm 4\%$ in the supine position and $6 \pm 12\%$ in the prone position).*

* In only two animals, COV_v^2 accounted for less than 60% of $\text{COV}_{\text{tot}}^2$ in the supine position. Excluding them from this analysis raised the contribution of COV_v^2 to $73 \pm 8\%$ in the supine position and to $30 \pm 12\%$ in the prone position, and lowered the contribution of COV_{cc}^2 to $2.4 \pm 1\%$ (supine) and $1.7 \pm 1\%$ (prone).

Both the gas volume and the gas fraction of the imaged lung were higher in the prone than in the supine position (384 ± 102 vs. 286 ± 88 ml, $p < 0.05$; and 0.45 ± 0.09 vs. 0.32 ± 0.10 , $p < 0.001$), whereas the volume of imaged lung was not different between the two positions. There was significant interregional variation in gas fraction (effect of ROI: $p < 0.01$), and the anatomic (i.e., dorsal to ventral) distribution profile of regional gas fraction (Figure 4) was different between the supine and prone positions (interaction between ROI and body position: $p < 0.001$). Accordingly, regional gas fraction showed a steeper vertical gradient favoring nondependent lung regions in the supine position (FGAS_i gradient, $0.035 \pm 0.011/\text{cm}$ in the supine position vs. $0.011 \pm 0.014/\text{cm}$ in the prone position; $p < 0.05$).

Taken together, these results are consistent with a more uniform distribution of aeration in the prone than in the supine position.

Global and Regional Shunt Fraction

Consistent with the reduction of PaO_2 , shunt fraction measured from blood gases (Fs_{O_2}) was significantly higher in the supine than in the prone position (Table 1). The global shunt fraction of the imaged lung, estimated by PET (Fs_{PET}), was also higher in the supine than in the prone position (0.50 ± 0.13 vs. $0.14 \pm$

TABLE 1. PHYSIOLOGIC VARIABLES

	Control		Injury		Significance
	Supine	Prone	Imaging Supine	Imaging Prone	
Pa _{O₂} , mm Hg	598 ± 61	609 ± 72	79 ± 39	518 ± 172	p < 0.001
Pa _{CO₂} , mm Hg	38 ± 3	42 ± 4	49 ± 5	41 ± 4	p < 0.01
pH	7.40 ± 0.04	7.36 ± 0.04	7.26 ± 0.06	7.33 ± 0.06	p < 0.05
Pv̄ _{O₂} , mm Hg	64 ± 10	73 ± 13	37 ± 8	65 ± 13	p < 0.01
Pv̄ _{CO₂} , mm Hg	46 ± 4	47 ± 4	53 ± 6	48 ± 3	NS
F _{SO₂}	0.07 ± 0.05	0.05 ± 0.05	0.48 ± 0.17	0.12 ± 0.13	p < 0.001
Cardiac output, L/min	3.3 ± 1.0	3.6 ± 0.8	3.3 ± 1.2	2.9 ± 0.6	NS
HR, beats/min	118 ± 22	116 ± 17	108 ± 23	109 ± 18	NS
Pa, mm Hg	92 ± 23	96 ± 22	64 ± 23	85 ± 17	NS
Ppa, mm Hg	15 ± 3	17 ± 3	19 ± 4	13 ± 2	p < 0.01
Ppc,we, mm Hg	10 ± 4	8 ± 3	9 ± 2	6 ± 1	p < 0.01
Paw, cm H ₂ O	14 ± 4	15 ± 3	33 ± 9	21 ± 5	p < 0.001
T, °C	37.1 ± 1.5	36.9 ± 1.5	35.0 ± 1.5	35.5 ± 0.8	NS

Definition of abbreviations: F_{SO₂} = shunt fraction; HR = heart rate; NS = not significant; Pa = mean arterial pressure; Pa_{CO₂} = arterial carbon dioxide tension; Pa_{O₂} = arterial oxygen tension; Paw = inspiratory plateau airway pressure; pH = arterial pH; Ppa = mean pulmonary arterial pressure; Ppc,we = pulmonary capillary wedge pressure; Pv̄_{CO₂} = mixed venous carbon dioxide tension; Pv̄_{O₂} = mixed venous oxygen tension; T = body temperature.

Data presented are means ± SD; n = 7 for all conditions. Significance levels are reported only for comparisons between supine and prone positions after injury during imaging (Student *t* test for paired data). Control data are reported for descriptive purposes only.

0.14; $p < 0.001$). In neither position was the difference between F_{S,PET} and F_{SO₂} statistically significant, and F_{S,PET} showed good correlation with F_{SO₂} ($F_{S,PET} = 0.83 \cdot F_{SO_2} + 0.06$; $r = 0.87$, $p < 0.001$).

Analysis of variance showed a significant difference in regional shunt fraction (F_{S,PET}) between body positions ($p < 0.001$) and between ROIs ($p < 0.001$). In both positions the regional shunt fraction tended to decrease from dependent to nondependent ROIs (i.e., F_{S,PET} showed a negative vertical gradient). However, the vertical gradient of regional shunt fraction was significantly steeper in the supine than in the prone position (F_{S,PET} gradient, $-0.054 \pm 0.018/\text{cm}$ in the supine position vs. $-0.013 \pm 0.006/\text{cm}$ in the prone position; $p < 0.01$), indicating that the vertical dependence of shunt fraction was more pronounced in the supine than in the prone position. Consistent with these gradients, analysis of variance showed a significant interaction between the effect of body position and the effect of ROI ($p < 0.001$), which indicates that the anatomic distribution profile of regional shunt was different between the two body positions.

Taken together, these results indicate that the prone position was associated with an overall reduction of regional shunt and with a more uniform distribution of the residual shunt among the ROIs.

Regional Perfusion

The anatomic distributions of regional perfusion ($\dot{Q}_i$) and shunt flow were also affected by body position (Figure 5). There was significant interregional variation of perfusion (effect of ROI: $p < 0.001$), and the anatomic distribution profile of perfusion was different between the supine and prone positions (interaction between ROI and body position: $p < 0.001$). In the supine position, the dorsal (i.e., dependent) half of the ROIs received the greatest fraction of perfusion. In the prone position, the dorsal half of the ROIs still received most of the perfusion. These results were consistent with measurements of the perfusion gradient, which showed reversal of the nondependent-to-dependent gradient in the prone position, as evidenced by the opposite signs of the gradients in the prone position (positive gradient) compared with the supine position (negative gradient; see STATISTICAL

ANALYSIS, in METHODS, in the online supplement for interpretation of the sign of the gradient). However, the absolute value of the vertical gradient of regional perfusion normalized by relative regional tissue volume, which represents a measure of the steepness of the vertical gradient independent of its direction and of the relative amount of lung tissue within each ROI, was significantly lower in the prone position ($0.040 \pm 0.024/\text{cm}$) than in the supine position ($0.098 \pm 0.030/\text{cm}$; $p < 0.01$), indicating some redistribution of perfusion toward ventral regions in the prone position.

As a result of the high shunt fraction and high perfusion in dependent regions in the supine position, fractional pulmonary

Figure 4. Topographic distribution of regional lung volume (V_{Li} , total length of the bars), gas volume (V_{GASi} , dark gray portion of the bars), and tissue volume (V_{TISi} , light gray portion of the bars) in eight horizontal regions of interest of equal height, in the supine and prone positions. The ratio of the length of the dark gray portion of each bar to the total length of the bar represents the regional gas fraction (F_{GASi}), the numeric value of which is reported next to the bar for each region (in this respect it is worth noting that the unit of measure of the *x* axis does not apply to the gas fraction values). Note the restored aeration to dorsal regions in the prone position. Data represent means and SD.

Figure 5. Topographic distribution of regional pulmonary perfusion ($\dot{Q}_i$, total length of the bars) and pulmonary shunt flow ($\dot{Q}_{Si}$, dark gray portion of the bars) in the supine and prone positions. Both flows are expressed as a fraction of total perfusion to the imaged lung. The ratio of the length of the dark gray portion of the bar to the total length of the bar represents regional shunt fraction ($F_{S,PETi}$), the numeric value of which is reported next to the bars for each region (in this respect it is worth noting that the scale of the x axis does not apply to the shunt fraction values). The light gray portion of the bar represents the fraction of pulmonary perfusion flowing to gas-exchanging units within the region. Note the annihilation of shunt and the preservation of perfusion in dorsal regions in the prone position. Data represent means and SD.

shunt flow ($\dot{Q}_{Si}$) was also highest in the dorsal half of the ROIs (i.e., a large fraction of pulmonary perfusion went to shunting units in dorsal, dependent ROIs). In contrast, in the prone position, the dependent (i.e., ventral) half of the ROIs contributed only modestly to shunt flow (Figure 5). Accordingly, fractional shunt flow was significantly lower in the prone position (effect of body position: $p < 0.001$) and its anatomic distribution was different between the supine and prone positions (interaction between ROI and body position: $p < 0.001$), as fractional shunt flow decreased markedly in dorsal regions in the prone position.

Taken together, these results suggest that, despite some degree of perfusion redistribution toward ventral regions in the prone position, a substantial fraction of perfusion was maintained in dorsal regions. Because in the prone position the dorsal half of the ROIs had a major reduction in regional shunt fraction, while still receiving most of the perfusion, this position was associated with a considerable increase in the fraction of perfusion contributing to gas exchange.

Relation between Regional Shunt and Gas Fraction

When regional data from each animal for both body positions were pooled, an inverse relation between average regional values of $F_{S,PETi}$ and F_{GASi} became apparent (Figure 6A). The main effect of the prone position was to shift the data points corresponding to the most dorsal ROIs from the low-gas and high-shunt fraction to the high-gas and low-shunt fraction portion of the relation. When plots of $F_{S,PETi}$ versus F_{GASi} were analyzed for each animal, biphasic behavior was identified in five of them: values of shunt fraction were low for regional gas fraction higher than a threshold ($F_{GASi} \sim 0.3$) and increased linearly for values of gas fraction lower than that threshold (Figure 6B). In these animals, when the equation $F_{S,PET} = 1 - F_{GAS}/F_0$ was fitted to regional data points with $F_{S,PETi} > 0.2$, the intercept on the F_{GAS}

Figure 6. Plots of regional shunt fraction versus gas fraction for the average values (A), and for the individual values obtained from two animals, with and without biphasic behavior (B and C, respectively). In each panel, data points for each of the eight horizontal regions of interest are shown for the supine position (solid symbols) and for the prone position (open symbols). The data points corresponding to the three most dorsal regions are marked with different symbols (diamonds, triangles, and squares in dorsal-to-ventral direction). (A) The main effect of the prone position was to shift the data points corresponding to the most dorsal regions to a more favorable portion of the $F_{S,PET}$ -versus- F_{GAS} relation. (B and C) The dotted line represents the regression line obtained by fitting the equation $F_{S,PET} = 1 - F_{GAS}/F_0$ to data points with shunt fraction greater than 0.2 ([B] $F_{S,PET} = 1 - F_{GAS}/0.36$; [C] $F_{S,PET} = 1 - F_{GAS}/0.57$).

axis was $F_0 = 0.35 \pm 0.10$. In the remaining two animals, biphasic behavior could not be identified (Figure 6C).

Regional Specific Alveolar Ventilation

Specific alveolar ventilation of the imaged lung was similar in the supine and prone positions (0.040 ± 0.012 and 0.039 ± 0.012 second⁻¹, respectively). Regional specific alveolar ventilation (sV_{Ai}) showed significant interregional variation (effect of ROI: $p < 0.001$). Although the linear component of the vertical variation of specific ventilation was not significant in either position, the vertical distribution profile of specific ventilation was more

Figure 7. Topographic distribution of regional specific alveolar ventilation (sV_A , alveolar ventilation per unit of gas volume) in the supine and prone positions. Note the more uniform vertical distribution profile of specific ventilation in the prone position. Data represent means and SD.

uniform in the prone than in the supine position (Figure 7). Accordingly, when the ROIs were ordered by vertical location (i.e., nondependent to dependent), analysis of variance showed a significant interaction between the effect of ROI and body position ($p < 0.01$).

DISCUSSION

The main finding of this study is that the improvement of gas exchange in the prone position was associated with restored aeration and reduced shunt in dorsal lung regions, without a concomitant reduction of aeration or increase in shunt in ventral regions. The improvement of gas exchange was further enhanced by the fact that perfusion to dorsal regions remained substantial in the prone position, thus allowing these regions to take advantage of their restored aeration and leading to an increase in dorsal, and total, gas-exchanging pulmonary blood flow.

Limitations of the Study

The field of view of the PET scanner did not encompass the entire lung. In sheep with similar weight to those of this study, we previously estimated that the imaged lung corresponded to about 70% of the entire lung (14). Although the field of view did not include the most cranial and the most caudal, subdiaphragmatic regions, the internal consistency between values of shunt fraction of the imaged lung, derived by PET, and values of global shunt fraction suggests that the behavior of the imaged lung was representative of the behavior of the entire lung. We also acknowledge that imaging the same cross-section of thorax in both positions did not necessarily ensure that the same cross-section of lung was imaged, as the lung could expand or compress along the craniocaudal axis due to shift of the diaphragm. Although the limitation of PET to resolve fine anatomic markers did not allow spatial coregistration of the supine and prone images, the length of the imaged cross-section of lung (~ 10 cm) was much larger than the possible lung displacement along the craniocaudal axis. This, as well as the small contribution of the craniocaudal direction to the variance of gas fraction, suggest that the effect of this potential artifact was probably small.

We used the saline lavage model, which represents a highly recruitable model of acute lung injury (15). After lung lavage,

the damage to alveolar epithelial, endothelial, and perivascular cells is probably less than that of other lung injury models, such as the oleic acid or the endotoxin infusion models (16, 17), in which the primary insult is delivered from the pulmonary vascular side. Nonetheless, lung lavage creates interstitial and intra-alveolar edema and causes impaired gas exchange by its detrimental effect on surfactant (18–20). Although the pathogenetic mechanism is different, the severity of the impairment of gas exchange that was obtained after lung lavage is comparable to that of other experimental models of acute lung injury and is not the result of a specific pattern of disruption of ventilation-to-perfusion distribution peculiar to this model (21). Therefore, this model reflects the pathophysiology of those cases of ARDS that are characterized predominantly by alveolar instability and collapse, with high potential for alveolar recruitment, rather than by alveolar consolidation or flooding.

We analyzed the regional data in eight horizontal ROIs. We recognize that such an approach neglects intraregional heterogeneity. However, in this model of lung injury, the contribution of the systematic component of the variance in the vertical direction to the total variance of gas fraction was substantially greater than the contribution of the component in the craniocaudal direction. Therefore, analyzing the data by horizontal ROIs allowed us to capture the main systematic trend in regional aeration.

Effect of the Prone Position on Global Gas Exchange and Hemodynamics

After injury, the prone position was associated with improved gas exchange compared with the supine position, in line with the results of previous studies (3, 4, 22, 23). Whereas all these studies consistently reported an improvement of Pa_{O_2} and a decrease in global shunt fraction in the prone position, our results also showed an improvement of Pa_{CO_2} . Because body temperature was not different between the two positions and tidal volume and respiratory rate were kept constant, the improvement of Pa_{CO_2} suggests that ventilation was more efficient in the prone position. This is consistent with our finding that regional specific alveolar ventilation was more uniform in the prone position, indicating a more homogeneous turnover of alveolar gas of perfused units in this position. Furthermore, in the prone position, the vertical distribution profile of absolute alveolar ventilation, estimated from the product of specific ventilation and gas volume, followed closely the vertical profile of relative perfusion (compare Figure 5 with Figure E1 in the online supplement). This finding suggests improved ventilation-to-perfusion matching in the prone position (4) and, because minute ventilation and cardiac output were not different between the supine and prone positions, it would explain the reduction of Pa_{CO_2} . It has been shown that patients with ARDS who responded to a trial of prone positioning with a reduction of Pa_{CO_2} had increased survival at 28 days, and it has been hypothesized that in these patients the improvement of Pa_{O_2} in the prone position was due to alveolar recruitment rather than to redistribution of perfusion away from regions of shunt (5). Our data are compatible with this hypothesis by showing that, when the main effect of the prone position was to restore aeration, while preserving perfusion, to shunting units in dorsal regions, the increase in Pa_{O_2} was accompanied by a significant decrease in Pa_{CO_2} and by evidence of improved ventilation-to-perfusion matching. However, this reduction of Pa_{CO_2} cannot be considered a specific marker of alveolar recruitment, because Pa_{CO_2} should also decrease if the improvement of ventilation-to-perfusion matching were due to redistribution of perfusion away from regions of shunt.

The finding that pulmonary arterial pressure was higher in the supine than in the prone position after injury is consistent with the effect of higher Pa_{CO_2} , lower pH, and lower Pa_{O_2} on

pulmonary vascular tone. Pulmonary capillary wedge pressure was slightly lower in the prone than in the supine position. It is possible, however, that by setting the zero value of the pressure transducer at midchest level, we slightly underestimated left ventricular filling pressure in the prone position, as the prone position displaces the left ventricle inferiorly (23).

Effect of the Prone Position on Regional Perfusion, Shunt, and Aeration

The observation that substantial perfusion was preserved in dorsal lung regions in the prone position is consistent with previous observations in oleic acid–induced lung injury (3, 24, 25) and in healthy animals (26–30), and it could be due to higher vascular conductance in these regions (31, 32). However, the fact that the vertical perfusion gradient was not fully reversed in the prone position suggests some degree of perfusion redistribution toward ventral regions, consistent with results obtained in oleic acid–induced lung injury (25). We previously reported marked interindividual variability in the extent to which perfusion redistributed toward ventral regions in prone normal humans (12). Whether this variability is present also in patients with ARDS and whether patients who maintain substantial dorsal perfusion are those who respond favorably to prone positioning remains to be investigated. In this respect, it is important to emphasize that the extent to which inferences on the importance of structural factors in favoring perfusion to dorsal regions can be extrapolated to humans is unclear. Indeed, whereas it would appear teleologically meaningful for quadrupeds, who are normally prone, to develop mechanisms that, by favoring perfusion to dorsal lung regions, render perfusion more homogeneous, we cannot envision, *a priori*, a physiologic advantage of diverting perfusion toward dorsal regions in bipeds.

Critical to the improvement of gas exchange was the restored aeration to dorsal lung regions. This led to an increase in lung gas volume and to a more uniform distribution of gas fraction, as the gain in aeration in dorsal regions was not offset by loss of aeration in ventral regions. This finding is consistent with the presence of a smaller vertical pleural pressure gradient in the prone position (33). Although improvement of gas exchange in the prone position can occur in the absence of an increase in functional residual capacity (22, 33), the increase in lung gas volume likely contributed to the dramatic improvement of oxygenation that we observed. A potential contributor to the improved aeration of dorsal regions was the lack of abdominal support in the prone position. Unsupporting the abdomen likely decreased intraabdominal pressure (potentially creating negative intraabdominal pressure), reduced the pressure gradient across the diaphragm, and promoted alveolar recruitment preferentially in the dorsal regions of this surfactant-deficient model of lung injury. However, the prone position has also been shown to improve gas exchange when the abdomen was resting on a surface (33–35). Furthermore, the effect of unsupporting the abdomen in the prone position may depend on the pathophysiology of the injury: unsupporting the abdomen may promote alveolar recruitment and more uniform lung aeration in the presence of atelectasis and alveolar collapse, but it may be ineffective in the presence of alveolar consolidation or flooding, as in the oleic acid model (36). Although our method of suspending the animal in the prone position is not applicable to humans, and decreased intraabdominal pressure may be difficult to achieve when patients with ARDS are positioned prone, technical developments have led to critical care beds that can be used to pronate patients and that could potentially incorporate features to leave the abdomen unsupported in the prone position. In this respect, studies in anesthetized humans undergoing surgical procedures in the prone position suggest that respiratory mechanics are optimized

when the abdomen is unsupported (37, 38). Future studies, however, will be needed to clarify the relative contribution of unsupporting the abdomen to the improvement of gas exchange in the prone position.

The beneficial effect that the improvement of regional aeration had on regional gas exchange was apparent from the relation between regional shunt fraction and regional gas fraction. This relation showed that the effect of the prone position was to restore aeration to dorsal regions, thus shifting these regions to a more favorable portion of the shunt-versus-gas fraction relation. Interestingly, in five animals we observed biphasic behavior, with low shunt fraction in regions with gas fraction higher than a critical threshold and a steep linear increase in shunt in regions with gas fraction lower than this threshold. This threshold ($F_0 = 0.35$) was lower than the gas fraction of the normal lung (~ 0.6 [27, 39]). This finding suggests that, in these animals, even poorly aerated regions maintained their ability to exchange gas. Assuming that the shunt fraction is proportional to the fraction of derecruited units, the linear increase in shunt for a gas fraction lower than this threshold is consistent with a “quantal” loss of gas-exchanging units, so that the decrease in aeration of a region is absorbed only by a certain number of its units that become atelectatic and lose the ability to exchange gas, whereas the remaining units preserve their aeration and, accordingly, their gas exchange. Therefore, the biphasic relation between regional shunt fraction and gas fraction would suggest the presence of a gas fraction threshold for the development of subregions that collapse or flood and begin to shunt. The lack of biphasic behavior in the other two animals could have been related to intraregional differences in the degree of surfactant depletion, so that alveolar collapse started to occur at a higher gas fraction in units with more severe impairment of surfactant. Supporting this hypothesis is the fact that these two animals exhibited the highest contribution of the component of variance in the cranio-caudal direction to the total variance of gas fraction, suggesting that the horizontal ROIs used to analyze their data included units with different conditions.

Importantly, the improved aeration and gas exchange in dorsal regions in the prone position were obtained at a lower airway pressure than in the supine position. The prone position might thus be an effective means to promote alveolar recruitment in dorsal regions, while limiting airway pressure and ventilator-associated lung injury (17, 40).

In summary, we demonstrated that, in a surfactant-deficient model of ARDS, the prone position reduced shunt in dorsal lung regions. The reduction of shunt was associated with an increase in pulmonary gas content and with a more homogeneous distribution of aeration, which placed dorsal lung regions on a more favorable portion of the shunt-versus-gas fraction relation without a concomitant, substantial increase in shunt in ventral regions. Preservation of perfusion to dorsal regions contributed to the improvement of global shunt fraction in the prone position. The prone position with unsupported abdomen appears to be a useful means to promote alveolar recruitment and improve global and regional gas exchange, while limiting airway pressure, when the main pathophysiologic alteration is loss of surfactant and the associated alveolar derecruitment.

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