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Pulmonary Blood Flow Distribution in Sheep: Effects of Anesthesia, Mechanical Ventilation, and Change in Posture

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Background: Recent studies providing high-resolution images of pulmonary perfusion have questioned the classical zone model of pulmonary perfusion. Hence the present work was undertaken to provide detailed maps of regional pulmonary perfusion to examine the influence of anesthesia, mechanical ventilation, and posture.

Methods: Pulmonary perfusion was analyzed with intravenous fluorescent microspheres (15 μm) in six sheep studied in four conditions: prone and awake, prone with pentobarbital anesthesia and breathing spontaneously, prone with anesthesia and mechanical ventilation, and supine with anesthesia and mechanical ventilation. Lungs were air dried at total lung capacity and sectioned into approximately 1,100 pieces (about 2 cm^3) per animal. The pieces were weighed and assigned spatial coordinates. Fluorescence was read on a spectrophotometer, and signals were corrected for piece weight and normalized to mean flow. Pulmonary blood flow heterogeneity was assessed using the coefficient of variation of flow data.

Results: Pentobarbital anesthesia and mechanical ventilation did not influence perfusion heterogeneity, but heterogeneity increased when the animals were in the supine posture ($P < 0.01$). Gravitational flow gradients were absent in the prone position but present in the supine ($P < 0.001$ compared with zero). Pulmonary perfusion was distributed with a hilar-to-peripheral gradient in animals breathing spontaneously ($P < 0.05$).

Conclusions: The influence of pentobarbital anesthesia and mechanical ventilation on pulmonary perfusion heterogeneity is small compared with the effect of changes in posture. Analysis of flow gradients indicate that gravity plays a small role in determining pulmonary blood flow distribution. (Key words: Anesthesia: pentobarbital. Body position: prone, supine. Breathing: mechanical ventilation. Lung, blood flow:

perfusion gradient, perfusion heterogeneity. Measurement technique: fluorescent microspheres.)

GRAVITY has traditionally been considered a main determinant of pulmonary perfusion heterogeneity.¹ During anesthesia, pulmonary artery pressure may decrease, impairing perfusion in nondependent lung regions and increasing the gravitational perfusion gradient. Mechanical ventilation may also affect pulmonary perfusion heterogeneity in the same direction, as a result of the interaction among alveolar, vascular, and interstitial pressures. Novel techniques providing high-resolution images of perfusion recently revealed a considerable perfusion heterogeneity within isogravitational planes in humans and animals.²⁻⁴ This suggests that factors other than gravity influence the distribution of pulmonary blood flow. In addition, studies in anesthetized and mechanically ventilated animals have shown no or only small gravitational gradients, implying that gravity is only a minor determinant of pulmonary perfusion heterogeneity.^{5,6}

The influence of anesthesia and mechanical ventilation on the regional distribution of pulmonary perfusion was originally studied using alveolar clearance of radioactive xenon in humans.⁷ This technique, which provides relatively crude two-dimensional maps of perfusion, could not detect any influence of anesthesia and mechanical ventilation, observations that were corroborated by others using similar methods.⁸ These early studies in supine humans showed a gravitational distribution of pulmonary perfusion that corresponded with the classical theory. However, because the spatial resolution of the techniques used in these studies were low, we hypothesized that measurements giving more detailed spatial data on pulmonary perfusion would provide new information and insights into the mechanisms that influence the distribution of pulmonary blood flow. The purpose of the present work thus was to analyze

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the effects of intravenous anesthesia and mechanical ventilation on pulmonary perfusion, using a technique providing a detailed three-dimensional image of pulmonary perfusion. Effects of anesthesia and mechanical ventilation on pulmonary perfusion have not been mapped in similar detail previously. Changes in perfusion heterogeneity with change in posture have been documented earlier,^{4,9} and thus this was also analyzed to provide a reference to the effects induced by anesthesia and artificial ventilation. Because previous observations were made in dogs and the distribution of pulmonary perfusion may be different in species with different pulmonary vasoreactivity, we used young sheep. Young sheep lack collateral ventilation¹⁰ and have vigorous hypoxic vasoconstriction, in contrast to dogs, which have extensive pathways for collateral ventilation and rely less on hypoxic vasoconstriction for ventilation-perfusion matching. Pulmonary blood flow was assessed by repeated intravenous injections of 15- μ m fluorescent microspheres. Perfusion was mapped in three dimensions by making anatomic reconstructions from many (approximately 1,100 per animal) regional flows.

Materials and Methods

Animal Preparation

Six healthy young sheep (four females and two males; mean weight 20.3 ± 1.2 kg [mean \pm SD]) were used. The sheep were fasted overnight but had free access to water. Without premedication, the animals were suspended in a sling in the prone position with their legs protruding through holes, allowing free movement of the neck and head. The sling was shallow to allow for unrestrained motion of the thorax. An intravenous catheter was introduced into a peripheral fore leg vein in this position, and the initial set of pulmonary blood flow measurements were taken. Anesthesia was then induced and maintained with intermittent intravenous doses of pentobarbital as required. Animals were orally intubated, and mechanical ventilation was provided with air (inspired fraction of oxygen [FiO₂], 0.21; tidal volume, 10–12 ml/kg; peak airway pressures, 10–14 cm H₂O) with a piston-ventilator (Harvard, South Natick, MA). A femoral vein and both femoral arteries were cannulated with polyethylene catheters. Arterial blood pressure, airway pressure, and exhaled carbon dioxide (CO₂) profiles (Perkin Elmer Massspectrometer; Perkin Elmer Corp., Norwalk, CT) were collected on a strip

chart recorder. Partial pressures of oxygen (Pa_{O₂}) and carbon dioxide (Pa_{CO₂}) were analyzed in arterial blood with an automated blood gas analyzer (ABL 30; Radiometer, Copenhagen, Denmark).

Pulmonary Blood Flow Determination

We used 15- μ m fluorescent latex microspheres (blue, blue-green, yellow-green, orange, red, crimson, and scarlet FluoSpheres 0.2% solids; Molecular Probes, Eugene, OR) injected intravenously. A different labeled microsphere was used for each separate measurement. The microsphere suspension was sonicated for 5 min and vortexed immediately before slow intravenous injection of 2 ml (3 ml for crimson and scarlet) during 60 s, thus giving an estimate of pulmonary blood flow for many breaths. The catheter was thoroughly flushed with saline after each injection. The first injection was performed in the awake animal in the sling; the second injection was performed 30 min later in the anesthetized animal breathing spontaneously in prone recumbency on an operating table; and the third and fourth injections were done 30 min apart with the anesthetized animal attached to the ventilator in prone and supine posture on the operating table. The sequence of the prone and supine posture was changed for subsequent animals.

At the end of the experiment the animals received a rapid intravenous infusion of saline and a bolus of heparin (20,000 units) and were exsanguinated through the arterial cannulas. After withdrawal of approximately 50% of the blood volume, 60 mg papaverin was given intravenously to dilate the pulmonary vasculature and facilitate flushing of the lungs. A median sternotomy was performed and the pulmonary artery and left atrium were cannulated with wide-bore catheters. A 2% dextran solution was infused by means of gravity (driving pressure, 15–20 cm H₂O) into the pulmonary circulation until the effluent from the left atrium was clear of blood. The lungs were excised, the trachea connected to a pressure source, and the lungs reinflated to total lung capacity (constant airway pressure at approximately 25 cm H₂O) and suspended to dry. The lungs were punctured 15–20 times with a 22-gauge spinal needle to provide air flow through the lungs and to facilitate drying. The anatomic configuration of the lungs was preserved by gluing together the apical and the most ventral rims of the left and right lungs with a small amount of cyanoacrylate glue (Duro Superglue; Loctite Corp., Cleveland, OH).

PULMONARY PERFUSION HETEROGENEITY IN SHEEP

Table 1. Number and Mean Weight of Lung Regions Analyzed per Animal

| Sheep No. | Weight (kg) | Total No. of Regions | No. of Regions Excluded* | No. of Regions Analyzed | Weight per Region (mean \pm SD) (mg) |
|-----------|-------------|----------------------|--------------------------|-------------------------|--|
| 1 | 20 | 1,138 | 87 | 1,051 | 35 \pm 18 |
| 2 | 22.5 | 1,126 | 70 | 1,056 | 37 \pm 18 |
| 3 | 19 | 942 | 71 | 871 | 38 \pm 21 |
| 4 | 19 | 1,225 | 60 | 1,165 | 36 \pm 16 |
| 5 | 21 | 1,282 | 61 | 1,221 | 34 \pm 22 |
| 6 | 22 | 1,454 | 111 | 1,343 | 29 \pm 12 |

* More than 25% airways.

When the lungs were dry they were coated with a 1-cm-thick layer of polyurethane foam (Kwik Foam; DAP Inc., Dayton, OH). The foam-enveloped lungs were suspended in a plastic-lined square box so that their intrathoracic position was reproduced. The box was filled with rapidly setting urethane foam (polyol and isocyanate, International Sales, Seattle, WA). The foam block was sliced into 1.2-cm thick slices with a band saw with a blade designed to eliminate tearing and loss of tissue (six teeth per inch with $\frac{1}{8}$ -inch tooth height). The slices were cut (using a miter box) into squares (1.2×1.2 cm) to yield cubes approximately 1.7 cm^3 in volume. Foam adhering to lung tissue was removed and the pieces were weighed. Samples weighing less than 0.008 g were discarded, and the remaining pieces were identified by lobe and assigned unique x, y, and z coordinates. The amounts of airways present in the pieces were estimated (less than 10% of piece volume, 10–25%, 25–50%, 50–75%, and more than 75%; trachea or part of trachea) and coded.

Fluorescent dye was extracted from lung tissue samples by soaking in 1.5 ml of 2-ethoxyethylacetate (Cellosolve; Aldrich Chemical, Milwaukee, WI) for 48 h. The supernatant was placed into cuvettes using a pipette and read in a fluorescent spectrophotometer (Perkin Elmer LS 50B; Perkin Elmer Corp., Norwalk, CT) at the dye-specific excitation and emission wave lengths.

A kidney was harvested to detect shunting of microspheres through the lungs and a 1–2-g section of the cortex was digested for 24–48 h in 4N KOH, after which it was filtered through a 10- μm pore polycarbonate filter (Poretics, Livermore, CA). The filter containing the microspheres was soaked in Cellosolve for 4 h, and the fluorescence from the supernatant was measured. The detection limit for pulmonary and renal tissues was less than 10 microspheres per sample with some variability due to the fluorescent label and tissue

autofluorescence. Because $2\text{--}3 \cdot 10^6$ beads were injected for each measurement, the detection limit was less than $1 \cdot 10^{-5}$ of cardiac output.

Calculations and Statistical Analysis

Tissue samples with an airway content of 25% or more were not included in the final analysis. Each fluorescent color was corrected for weight and normalized to the mean signal of the given color for all final samples from the same animal and condition. The pulmonary hila were defined with spatial coordinates as the points of entry of the left and right pulmonary artery into the lungs. The hilar-to-peripheral distance in centimeters from the ipsilateral hilum (d_h) for a piece with coordinates x, y, z was calculated as $d_h = 1.2 \cdot [(x - x_h)^2 + (y - y_h)^2 + (z - z_h)^2]^{0.5}$ where the subscript b indicates coordinates for the hilum.

Pulmonary blood flow heterogeneity within each animal was expressed as the coefficient of variation (SD/mean) of regional pulmonary blood flow. The regional pulmonary blood flow as a function of location on the x, y, and z axes or distance from the hila was characterized with least-squares regression analysis. The dimension of the slope was normalized flow units per centimeter, but because the mean normalized flow for the entire animal was 100%, it was possible to express the slope in more familiar terms as a percentage per centimeter. A slope of $-3.5\%/cm$, for example, means that flow decreases 0.035 normalized flow units per centimeter. The slopes of linear relations were compared with zero with a single two-tailed *t* test. The coefficient of linear correlation (*r*) was used to quantify the strength of the relation, and the square of the coefficient of linear correlation (r^2) was used to quantify the proportion of pulmonary blood flow variability that was predicted from the independent variables.

Differences in heterogeneity and flow gradients be-

Table 2. Arterial Pressure, Respiratory Rate, and Arterial Blood Gases per Condition

| | Awake Spontaneous Ventilation Prone | Anesthetized Spontaneous Ventilation Prone | Anesthetized Mechanical Ventilation Prone | Anesthetized Mechanical Ventilation Supine |
|-------------------------------------|--|---|--|---|
| MAP (mmHg) | Not available | 104 ± 13 | 109 ± 6 | 103 ± 8 |
| RR (breaths/min) | 31 ± 7* | 30 ± 8* | 17 ± 3 | 17 ± 3 |
| Pa _{O₂} (mmHg) | Not available | 85 ± 10 | 89 ± 17 | 80 ± 18 |
| Pa _{CO₂} (mmHg) | Not available | 41 ± 3† | 36 ± 3 | 35 ± 2 |

Data are mean ± SD.

MAP = mean systemic arterial pressure; RR = respiratory rate; Pa_{O₂} = arterial O₂ tension; Pa_{CO₂} = arterial CO₂ tension.

* *P* < 0.01 versus mechanical ventilation.

† *P* < 0.05 versus mechanical ventilation.

tween conditions were analyzed with one-way analysis of variance, when significant, multiple comparisons were made calculating the least significant difference. Probability values less than 0.05 were considered significant.

Results

The number of lung regions analyzed per animal was 1,118 ± 163 (mean ± SD) (table 1). Kidney samples did not have any fluorescence in excess of background, indicating that all the microspheres were trapped in the lungs.

Respiratory rate was significantly higher when the sheep were breathing spontaneously (*P* < 0.01), with no change in respiratory rate after induction of anesthesia (table 2). Arterial P_{O₂} was unchanged, but P_{CO₂} was

higher with spontaneous than with mechanical ventilation (*P* < 0.05; table 2).

Pulmonary blood flow heterogeneity was lowest when the animals were awake (table 3). It was unaffected by intravenous pentobarbital (*P* = 0.47 compared with the awake state) and start of mechanical ventilation (*P* = 0.08 compared with pentobarbital and spontaneous breathing), but was significantly larger with the supine posture compared with conditions in the prone position (*P* < 0.01; table 3).

The vertical flow gradients (compare figs. 1A-C) were not significantly different from zero when prone, regardless of whether the animals were awake, anesthetized, or mechanically ventilated (table 3). However, a vertical flow gradient with increasing flow down the lung (compare fig. 1D) was present in animals in the supine posture (*P* < 0.001 compared

Table 3. Pulmonary Blood Flow Heterogeneity and Perfusion Gradients

| | Awake Spontaneous Ventilation Prone | Anesthetized Spontaneous Ventilation Prone | Anesthetized Mechanical Ventilation Prone | Anesthetized Mechanical Ventilation Supine |
|-------------------------------------|--|---|--|---|
| Pulmonary blood flow heterogeneity | 0.259 (0.236 to 0.283) | 0.281 (0.252 to 0.309) | 0.334* (0.266 to 0.402) | 0.414† (0.388 to 0.440) |
| Vertical gradient (%/cm) | -0.4 (-1.3 to 0.5) | 0.3 (-1.8 to 2.4) | 0.0 (-3.9 to 4.0) | 7.8‡§ (6.3 to 9.3) |
| Hilar-to-peripheral gradient (%/cm) | -3.5¶ (-5.2 to -1.7) | -3.3¶ (-5.4 to -1.2) | -0.6 (-5.1 to 3.9) | -1.6 (-4.2 to 1.0) |

Heterogeneity was calculated as SD/mean. Perfusion gradients were converted from normalized flow units per centimeter to percent per centimeter (%/cm). Values are means and 95% confidence intervals.

* *P* < 0.05 versus awake.

† *P* < 0.01 versus prone conditions.

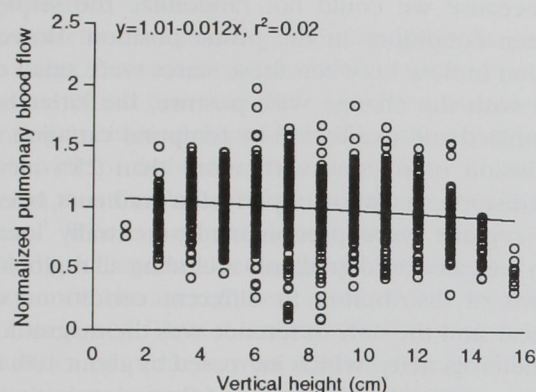
‡ *P* < 0.001 versus prone conditions.

§ *P* < 0.001 versus zero.

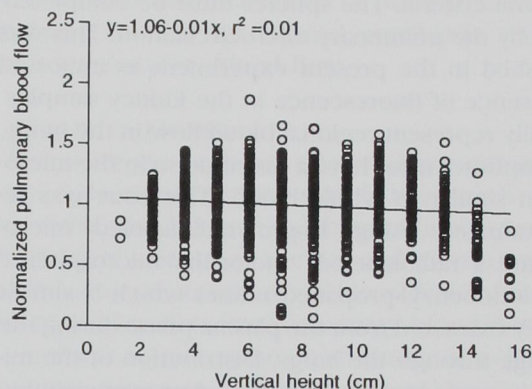
¶ *P* < 0.05 versus zero.

PULMONARY PERFUSION HETEROGENEITY IN SHEEP

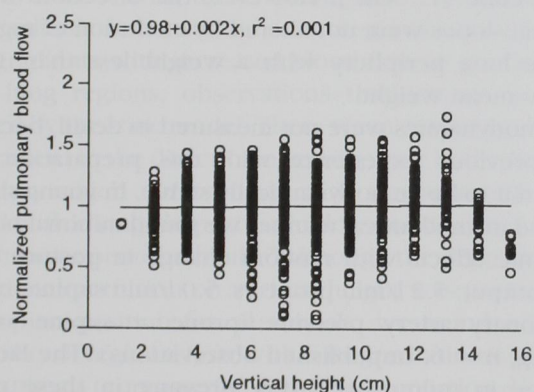
1a. Awake, prone



1b. Pentobarbital, prone, spont. ventilation



1c. Pentobarbital, prone, mechanical ventilation



1d. Pentobarbital, supine, mechanical ventilation

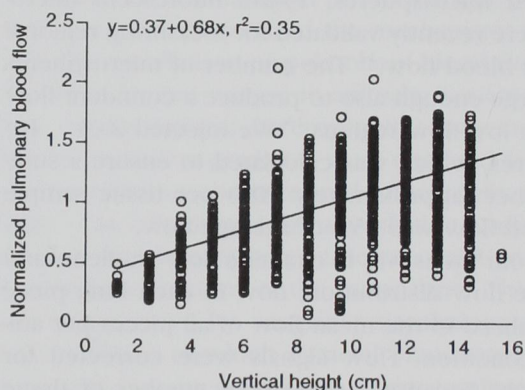


Fig. 1. Regional pulmonary blood flow as a function of vertical height in the lungs in one sheep under four conditions: prone and awake (A), prone and breathing on its own with pentobarbital anesthesia (B), prone with pentobarbital anesthesia and mechanical ventilation (C), and supine with pentobarbital anesthesia and mechanical ventilation (D). The direction of gravity along the x axis is from left to right. Note the large heterogeneity of flow within isogravitational planes and the counter-gravitational slopes with spontaneous breathing.

with zero). This linear description of spatial location explained 25% of flow heterogeneity in the supine posture (r^2 of the linear regression was 0.25; 95% CI, 0.14 to 0.35).

Pulmonary perfusion was distributed with a hilar-to-peripheral gradient with blood flow decreasing with the distance from the hilum in conditions with spontaneous breathing (table 3). The proportion of blood flow heterogeneity explained by the linear distance to the ipsilateral hilum was 16% in awake (r^2 of the linear regression was 0.16; 95% CI, 0.03 to 0.28) and 11% in spontaneously breathing pentobarbital-anesthetized sheep (r^2 of the linear regression was 0.11; 95% CI, 0.04 to 0.18).

Discussion

We made three principal observations in this study. First, pulmonary blood flow heterogeneity was largely unaffected in the prone posture by administering pentobarbital and initiation of mechanical ventilation but increased considerably in the supine posture. Second, there were no significant vertical perfusion gradients in the prone position. Third, there were hilar-to-peripheral perfusion gradients in the prone posture when the sheep were spontaneously breathing.

Before discussing the significance of these findings, we must consider the limitations of the methods used in this study. To estimate regional pulmonary blood

flow reliably, the fluorescent microsphere method must fulfill several criteria. The spheres must be completely extracted by the pulmonary microcirculation. This was accomplished in the present experiment as indicated by the absence of fluorescence in the kidney samples. To faithfully represent regional blood flow in the lungs, the microspheres must have a distribution in the microcirculation similar to whole blood. This issue was recently evaluated using 15- μm radiolabeled microspheres and a radiolabeled "molecular microsphere" (hydroxy-iodobenzyl-propanediamine) which is almost completely extracted from the plasma phase during the first passage through the lungs. Distribution of the microspheres and hydroxy-iodobenzyl-propanediamine were highly correlated in small regions (approximately 1.5 cm^3 in the goat lung).¹¹ Although these authors used radiolabeled microspheres, 15- μm fluorescent microspheres were recently validated for measuring regional pulmonary blood flow.¹² The number of microspheres must be large enough also to produce a confident flow estimate in low-flow regions.¹³ We injected $2-3 \cdot 10^6$ microspheres, which was calculated to ensure a sufficient number (approximately 400) per tissue sample when blood flow was 25% of average flow.

Because our focus was to examine flow gradients and the relative flow distribution, flow in each lung piece was normalized to the mean flow of all pieces per animal and condition. Flow signals were corrected for piece weight because a substantial number of tissue pieces from peripheral parts of the lungs had a volume less than 1.7 cm^3 . Pieces with airway tissue have a higher density than alveolar tissue, thus producing an erroneously low weight-corrected signal. This error was minimized by excluding lung pieces that were composed of more than 25% of airway tissue.

Interpretation of the pulmonary blood flow distribution data depends on preservation of lung size and spatial orientation of the lungs *in vivo*, when coated with foam in the rigid box. We maintained lung size and shape by carefully apposing the left and right sides in anatomic position and drying the lungs at total lung capacity. Some distortion of pulmonary parenchyma was possible when the lungs were kept inflated at total lung capacity with 25 $\text{cm H}_2\text{O}$,¹⁴ but this should have a small influence on the major findings of this study. The lungs were oriented in the rigid box when covered with foam, to ensure sectioning of the lungs in true isogravitational planes.

Variation in blood flow over time as a source of

change between the prone states could not be ruled out, because we could not randomize the sequence between conditions in the prone position. However, variation in flow between these states were small compared with the change with posture, the latter being randomized and unaffected by temporal variation.

Exclusion of regions with more than 25% airways could distort calculation of perfusion gradients, because these regions were predominantly centrally located. When we calculated gradients including all regions, the patterns of distribution in different conditions were identical, and the only difference was the magnitude of flow heterogeneity, which increased by about 10% in all conditions. Weight correction of flow signals similarly could influence the results by having the largest effect in the periphery where regions are likely to be less than a full cube (1.7 cm^3). However, the direction of the vertical slopes were not altered by exclusion of regions in the lung periphery with a weight less than 1 SD below mean weight.

Hemodynamics were not measured in detail, because our previous experience with this preparation has shown it to be hemodynamically stable. In young sheep treated in an identical manner we found minimal hemodynamic effects with random change in posture (cardiac output: 5.2 l/min prone vs. 5.0 l/min supine; mean pulmonary artery pressure: prone = supine = 23 mmHg, $n = 6$, unpublished observations). The lack of change in pulmonary artery pressure in these pilot-study animals suggested that the differences in perfusion patterns induced by positional changes were not due to changes in the relation between vascular and alveolar pressures. It is possible that pulmonary blood flow decreased to some small degree with anesthesia and mechanical ventilation, although this was not reflected in a decrease in systemic arterial pressure.

The Results

Pulmonary blood flow heterogeneity did not change with induction of intravenous anesthesia but increased with the application of mechanical ventilation, and even more so when the animals were in the supine position. Similar estimates of heterogeneity using comparable techniques were reported in awake sheep and dogs^{15,16} and in halothane- or pentobarbital-anesthetized dogs studied in the prone and supine positions.^{4,9} The significant difference in heterogeneity between prone and supine position in the present study, also described previously in anesthetized dogs,^{4,9} was due primarily to

PULMONARY PERFUSION HETEROGENEITY IN SHEEP

the presence of a vertical perfusion gradient in the supine position.

There were no vertical perfusion gradients in the prone states. Because we injected microspheres over 60 s, regional blood flow was averaged for many breaths. According to classical thinking, most lung regions in the animals were probably in zones 2 and 3, and pulmonary perfusion thus should be distributed with a gravitational gradient.¹ When mechanical ventilation was applied, it is likely that mean alveolar pressure increased; as a consequence, the average time spent by lung regions in zone 2 increased. Thus this should lead to an increased dependence of perfusion on vertical height, although the incremental change in blood flow may also be the same within zones 2 and 3. The absence of a gravitational distribution of perfusion in all prone postures was in conflict with these assumptions. Furthermore, some animals demonstrated counter-gravitational perfusion gradients with increased blood flow in nondependent lung regions, observations that cannot be explained by the zone model. There was a consistent vertical gradient in the direction of gravity only in the supine position, which corresponds with similar results obtained with change in posture in dogs anesthetized with halothane or pentobarbital.^{4,9} Although the dependence of regional perfusion on vertical height was present in the supine position for all animals, we found a large variability of regional flow within isogravitational planes in all animals (compare fig. 1D). The proportion of flow variability accounted for by the vertical gradient was only 25%. This indicates that the remaining regional flow variation in the supine position was due to factors other than gravity.

Thus the data suggest that the interplay between alveolar, intravascular, and interstitial pressures does not solely determine the distribution of pulmonary perfusion in normal lungs. Recently, anatomic branching patterns and regional variation in conductance to blood flow have been introduced as other important determinants of the distribution of pulmonary perfusion.^{2,17} The explanation for a hilar-to-peripheral perfusion gradient may reside in the architecture of the pulmonary vasculature, where blood flowing to the periphery encounters more resistance vessels than does blood flowing to the core of the lungs. The cause of the disappearance of the radial gradient with the introduction of mechanical ventilation is unclear. Preliminary data in dogs showed, however, that the magnitude of the hilar-to-peripheral gradient was linearly related to cardiac output with a

larger gradient with higher flows.¹⁸ This observation could explain the diminution of the hilar-to-peripheral gradient, because mechanical ventilation usually decreases pulmonary blood flow.

Clinical Implications

Effects on gas exchange of pathologic processes and clinical interventions have usually been predicted with use of the classical zone model of pulmonary perfusion distribution.¹ Because vascular and alveolar pressures are the major determinants of blood flow in this model, the model predicts that pulmonary blood flow should be uniform within regions with similar alveolar and hydrostatic pressures. However, the striking heterogeneity of blood flow within isogravitational planes, and the lack of a gravitational gradient in prone conditions in this study indicate that other factors must be considered when we try to understand the mechanisms that influence the distribution of pulmonary blood flow. These anomalies are not unique to animals: Similar data with large isogravitational heterogeneity and central-to-peripheral perfusion gradients were obtained from single photon emission computerized tomography of human lungs.³ The hilar-to-peripheral perfusion gradients with less flow in the periphery indicate a relation between flow and the anatomy of the vasculature. This assumption is supported by computer simulations of pulmonary perfusion in which a fractal branching pattern of the vasculature, increased dorsal flow conductance, and gravity were taken into account. Modeling of perfusion with these parameters closely reproduced experimental observations of perfusion gradients and perfusion heterogeneity.¹⁹

These findings are important because they force us to re-evaluate the underlying mechanisms of gas exchange impairment. The small influence on perfusion gradients of pentobarbital, mechanical ventilation, and change in posture suggest a relatively fixed distribution of pulmonary perfusion within the lung. We speculate that increased dorsal blood flow conductance may balance gravitational effects on perfusion in the prone position. This will lead to improved blood flow in nondependent dorsal lung regions that better match ventilation in those regions. In supine posture, however, gravity and vascular anatomy will act in the same direction and redistribute perfusion to dependent dorsal lung regions. Because ventilation is greater in nondependent lung regions in the supine position, this effect will result in mismatching of ventilation and perfusion. This notion

is supported by work that showed better matching of ventilation and perfusion analyzed with the multiple inert gas elimination technique, and better gas exchange in prone than in supine posture in patients with adult respiratory distress syndrome.²⁰ Models that incorporate this new perspective on factors that determine perfusion distribution may guide us better than the classical theory, when novel therapies are tailored to improve pulmonary gas exchange.

Summary

The influence of pentobarbital anesthesia and mechanical ventilation on the distribution of pulmonary perfusion is insignificant, whereas change in posture redistributes pulmonary blood flow to dependent regions in supine and nondependent regions with prone posture. The absence of a vertical gradient in prone positioning, the presence of large isogravitational perfusion heterogeneity, and the presence of hilar-to-peripheral perfusion gradients support the notion that factors other than gravity are important determinants of pulmonary blood flow distribution.

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