Gravity is an important but secondary determinant of regional pulmonary blood flow in upright primates

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Glenny, Robb W., Susan Bernard, H. Thomas Robertson, and Michael P. Hlastala. Gravity is an important but secondary determinant of regional pulmonary blood flow in upright primates. J. Appl. Physiol. 86(2): 623–632, 1999.—Original studies leading to the gravitational model of pulmonary blood flow and contemporary studies showing gravity-independent perfusion differ in the recent use of laboratory animals instead of humans. We explored the distribution of pulmonary blood flow in baboons because their anatomy, serial distribution of vascular resistances, and hemodynamic responses to hypoxia are similar to those of humans. Four baboons were anesthetized with ketamine, intubated, and mechanically ventilated. Different colors of fluorescent microspheres were given intravenously while the animals were in the supine, prone, upright (repeated), and head-down (repeated) postures. The animals were killed, and their lungs were excised, dried, and diced into ~2-cm³ pieces with the spatial coordinates recorded for each piece. Regional blood flow was determined for each posture from the fluorescent signals of each piece. Perfusion heterogeneity was greatest in the upright posture and least when prone. Using multiple-stepwise regression, we estimate that 7, 5, and 25% of perfusion heterogeneity is due to gravity in the supine, prone, and upright postures, respectively. Although important, gravity is not the predominant determinant of pulmonary perfusion heterogeneity in upright primates. Because of anatomic similarities, the same may be true for humans.

regional perfusion; spatial heterogeneity; fluorescent microspheres

The pulmonary circulation is generally thought to be a largely passive circuit in which blood flow distribution is predominantly determined by the hydrostatic gradient due to gravity. This perspective has dominated both the interpretation and direction of studies related to pulmonary perfusion for the past three decades. However, recent studies that used high-resolution methods (12, 20, 28) and experiments performed in microgravity (33) have now shown that pulmonary perfusion is much more heterogeneous than can be explained by gravity alone.

Initial observations on regional pulmonary blood flow documented increasing blood flow down the lung (37), and a gravitational mechanism was postulated (39). The association between gravity and regional blood flow was confirmed by changing the direction or magnitude of gravity relative to the vertical axis of the lung (29, 38). Methods used in these studies had relatively low-spatial resolution that could not measure variability of isogravitational perfusion and, hence, could not quantify the relative contribution of gravity to blood flow heterogeneity.

A second fundamental difference between contemporary studies and original studies that led to the gravitational model of pulmonary blood flow distribution is the use of laboratory animals rather than humans. Although many studies (5, 10, 20, 28, 30, 31, 35) have confirmed gravity-independent perfusion heterogeneity in different species, these observations may not apply to humans. Hughes (22) proposed that, in quadrupeds, gravity may not be as important a determinant of pulmonary blood flow distribution because the posture of quadrupeds produces relatively smaller lung volumes compared with that of humans. Most laboratory animals also have a more muscularized vascular system with a smaller fraction of resistance in the microvascular segments (25).

Laboratory animals have been used in recent studies because high-resolution studies are precluded in humans by the necessary postmortem methods. Although humans are the only true mammalian biped, baboons spend most of their time in the upright posture and have pulmonary structures and physiology remarkably similar to those of humans. The baboon pulmonary vascular tree parallels the human system from its gross anatomy to the degree of muscularization at the arteriolar and venular level (25). Gas exchange and hemodynamic responses to hypoxia in the baboon are also similar to humans (16). In the baboon, changes in gas exchange with postural changes are identical to those in humans (19), and they tolerate the upright posture well.

We, therefore, explored the spatial distribution of pulmonary blood flow in baboons in upright, head-down, supine, and prone postures to answer the question, How important is gravity in determining regional pulmonary blood flow in an animal model similar to humans?

METHODS

Experimental protocol. The study was approved by the University of Washington Animal Care Committee. Four male baboons (Papio anuba), weighing 23.5–33.0 kg, were chemically restrained with intramuscular ketamine injections, intubated, and mechanically ventilated with air. Tidal volumes (8–10 ml/kg) and rates were adjusted to produce initial arterial PCO₂ of 35–40 Torr. Once set, tidal volumes and ventilatory rates were not altered. Anesthesia was maintained with intravenous and intramuscular ketamine. A right
internal jugular cordis and a carotid catheter were placed with the use of local anesthesia. A flow-directed pulmonary arterial catheter was introduced through the right internal jugular cordis. Two forearm peripheral veins were cannu-
lated.

Prone and supine postures were obtained by laying the animals on a horizontal table with their backs parallel to the ground. Animals were placed in the head-down posture by dangling their torso over the edge of a table and using their thighs to support their weight. Their arms and head were allowed to hang freely. A custom-made chair kept the anesthetized animals in a seated upright posture with their backs parallel to the gravitational vector. The animals stabilized in each posture for 20 min before physiological data were acquired and microspheres injected.

Fluorescent 15-µm-diameter microspheres (FluoSpheres, Molecular Probes, Eugene, OR) of seven different colors (blue-green, green, yellow-green, orange, red, crimson, and scarlet) were injected intravenously through a forearm vein over 30 s in 5 ml of saline followed by a 10-ml saline flush. The microspheres were sonicated and vortexed before injection. Microspheres of one color were injected while the animals were in one of four postures: upright, head down, supine, or prone. The upright and head-down postures were repeated for a total of six postures. The order of postures and color used in each posture were varied across animals to negate any effect of order. Repeated postures were not performed consecu-

tively. We injected $2 \times 10^6$ microspheres of the first five colors and $4 \times 10^6$ crimson and scarlet microspheres. The seventh color was injected at the end of the postural study to investigate the effects of prostacyclin on perfusion distributions; data from this injection are not included here. Before each microsphere injection, two sets of stacked breaths were administered; arterial blood gases obtained; cardiac outputs determined by thermal dilution; and systemic, pulmonary, and airway pressures recorded.

After the final microsphere injection, each animal was deeply anesthetized, given heparin, exsanguinated, and killed by intravenous pentobarbital sodium. A sternotomy was performed, large-bore catheters were placed in the pulmonary artery and left atrium, and the thoracic aorta was tied off. The lungs were perfused with 2% dextran (mol wt 74,000) in normal saline until they were clear of blood, removed from the chest, and allowed to dry inflated at an airway pressure of 25 cmH₂O.

When dry, the lungs were coated with Kwik Foam (DAP, Dayton, OH), suspended vertically in a plastic-lined squared box, and embedded in rapidly setting urethan foam (2 lb. polyol and isocyanate, International Sales, Seattle, WA) to create a rigid form to which a three-dimensional coordinate system was applied. The foam block was sliced and cut into uniformly sized 1.9-cm³ cubes. Foam adhering to lung pieces was removed, and each lung piece was weighed and assigned a three-dimensional coordinate and lobe designation.

The fluorescent signals for each color were determined by extracting the fluorescent dyes from each piece with an organic solvent and then measuring the concentration of fluorescence in each sample (9). Spillover from adjacent colors was corrected by using a matrix inversion method. Relative blood flow to each lung piece was calculated by dividing the measured fluorescence of each piece by the mean fluorescence of all pieces for that color. The data set for each baboon consisted of an x, y, and z coordinate (Fig. 1) and weight and relative flow for each lung piece in each posture. The relative flow to each lung piece in each posture was determined by dividing the fluorescent signal by the weight of each lung piece and normalizing it to the mean.

To minimize observed flow heterogeneity caused by artifact or measurement noise, pieces weighing <50 mg were not included, thus eliminating uncertainty in flow and in weight. Also, 16–22 pieces containing >25% airway by visual inspection were excluded before analyses in each of the four animals.

Statistical analysis. Relative weight-normalized flows are used for all analyses and are hereafter referred to as flow or perfusion. Values are means ± SD or 95% confidence intervals (CI). Pearson's correlation coefficient (r) calculated between perfusions to lung pieces within a baboon is used to...
quantify the relationship between regional perfusions in different postures. The coefficient of variation (CV = 100·SD/mean) is used to characterize perfusion heterogeneity within each animal over space. ANOVA is used to determine the differences between hemodynamic and gas exchange variables among postures. Paired t-tests are used to compare perfusion heterogeneity among postures.

Least squares linear regression is used to characterize directional gradients of blood flow. Vertical gradients are characterized by the slope of regional flow as a function of distance up the lung from the most dependent surface. Because the lung is not uniformly distributed in space (basal lung regions are also dorsal), the spatial distributions of lung parenchyma along the three orthogonal axes are not independent of one another. Ventral-to-dorsal gradients of perfusion in the upright posture are, therefore, explored only within isogravitational planes by simple linear regression of blood flow as a function of distance along the ventral-dorsal direction. Similarly, cephalad-to-caudad gradients of perfusion in the supine and prone postures are explored within isogravitational planes by simple linear regression of blood flow as a function of height up the lung from the most dependent surface. Because flow appears to decrease in the most dependent lung regions, a linear relationship will not account for this curvature. A quadratic function of flow as a function of height is, therefore, also used to quantify the variability in flow

\[ \dot{Q}_{\text{posture}} = \alpha \cdot \overline{Q}_i + \beta \cdot \text{height}_i + \delta \cdot \text{height}_i^2 + \epsilon_i \]  

RESULTS

Physiological data. Basic physiological data for each animal are shown in Fig. 2. Gas exchange and hemodynamics remained relatively stable in baboons across all postures. Peak airway pressure increased slightly during head-down posture, although not statistically significantly by ANOVA. Alveolar-arterial O₂ differences are calculated by using respiratory quotients of 1.0 because of the high-metabolic rates induced by ketamine (6). Spatial heterogeneity. The number of lung pieces from each animal and the mean spatial CV in the different postures are presented in Table 1. Pulmonary perfusion heterogeneity was greatest in the upright posture, averaging 65.3%. Compared with the upright posture, blood flow variability was significantly less in
head-down, supine, and prone postures (Table 1). Perfusion heterogeneity was also significantly less ($P < 0.03$) in the prone compared with supine posture.

**Vertical gradients.** Figure 3 presents reconstructed planar images of blood flow distribution in one animal during upright posture. A transverse section demonstrates the heterogeneity of perfusion within an isogravitational plane, whereas the sagittal section shows the gradients of perfusion from cephalad to caudad and ventral to dorsal. Figure 4 shows the vertical distribution of blood flow in upright and head-down postures. Vertical gradients in the upright posture average $20.088$ relative flow units/cm up the lung (Table 2); i.e., if regional blood flow at one vertical level in the lung is equal to the mean flow (relative flow $= 1.0$), regional blood flow will be $1.88$ times the mean flow at a level $10$ cm lower in the lung. Slopes are negative because flow decreases toward greater lung heights. In the upright posture, flow decreases in the basal-to-apical direction, whereas, in the head-down posture, flow decreases along the apical-to-basal axis. The 95% CI on the slope is $-0.101$ to $-0.075$ relative flow units/cm. In the upright posture, a strong relationship exists between height up the lung and relative blood flow ($\text{mean } r^2 = 0.474$; 95% CI, 0.368–0.579). When the animal is turned head down, vertical gradients are less (Table 2), averaging $-0.048$ relative flow units/cm (95% CI, $-0.067$ to $-0.028$). The relationship between vertical height and blood flow is also weaker in the head-down posture (mean $r^2 = 0.242$; 95% CI, 0.121–0.364).

The difference in the vertical gradients between upright and head-down postures suggests that a mechanism in addition to gravity is responsible for a vertical gradient of perfusion in the upright posture. This additional influence can be explored by averaging the blood flow to each piece between opposing postures, thus nullifying the gravitational influence by canceling its effect. Figure 5 shows that a vertical gradient remains in the upright lung after the gravitational influence is removed. On average, the vertical gradient in the upright posture after the effect of gravity is nullified is $-0.020$ relative flow units/cm (95% CI, $-0.050$–$-0.010$). Hence, there appears to be an anatomic bias for blood flow to be greater in the caudad lung regions independent of gravity. This anatomic bias is confirmed by cephalad-caudad gradients of perfusion when animals are supine. Figure 5 shows the increase in blood flow from cephalad to caudad in a supine posture.

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**Table 1. Perfusion heterogeneity**

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Lung Pieces</th>
<th>Upright 1</th>
<th>Upright 2</th>
<th>Head down 1</th>
<th>Head down 2</th>
<th>Supine</th>
<th>Prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,302</td>
<td>62.2</td>
<td>64.1</td>
<td>48.4</td>
<td>41.3</td>
<td>52.3</td>
<td>45.4</td>
</tr>
<tr>
<td>2</td>
<td>1,208</td>
<td>53.1</td>
<td>43.1</td>
<td>42.5</td>
<td>48.4</td>
<td>39.0</td>
<td>34.2</td>
</tr>
<tr>
<td>3</td>
<td>1,265</td>
<td>77.0</td>
<td>76.2</td>
<td>60.4</td>
<td>65.0</td>
<td>58.1</td>
<td>51.7</td>
</tr>
<tr>
<td>4</td>
<td>1,629</td>
<td>72.0</td>
<td>74.4</td>
<td>60.4</td>
<td>58.8</td>
<td>58.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>66.1 ± 10.6</td>
<td>64.5 ± 15.2</td>
<td>52.9 ± 9.0*</td>
<td>53.4 ± 10.6*</td>
<td>52.0 ± 9.2*</td>
<td>43.8 ± 7.2*†</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>49.1–83.0</td>
<td>40.3–88.6</td>
<td>38.6–67.1</td>
<td>36.6–70.2</td>
<td>37.5–66.6</td>
<td>32.3–55.3</td>
</tr>
</tbody>
</table>

$CV_{spatial}$, spatial coefficient of variance; CI, confidence interval. *Statistically different from upright posture, $P < 0.05$; †statistically different from supine posture, $P < 0.05$. 

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**Fig. 3.** Reconstructed images of a transverse and sagittal plane from 1 animal during upright posture. Each square represents location and relative blood flow to a lung piece in the given plane. Note heterogeneity of perfusion in isogravitational plane. Note also that flow is not randomly distributed, but rather neighboring pieces tend to have similar magnitudes of flow. Cephalad-caudad (vertical) gradient is apparent in sagittal section.
Animal. The gradients are small with an average of 
$-0.016$ relative flow units/cm (95% CI, $-0.036–0.000$).

Figure 6 presents the vertical distribution of blood flow for one animal in supine and prone postures. On average, the vertical gradient during the supine posture was $-0.055$ relative flow units/cm (95% CI, $-0.073$ to $-0.037$), and, while the animal was prone, this gradient did not differ from zero (95% CI, $-0.014–0.01$).

Vertical gradients in the different postures are summarized in Fig. 7. Vertical gradients of perfusion vary among different postures, suggesting that factors other than hydrostatic pressure are important determinants of blood flow distribution in the vertical direction.

Partitioning flow heterogeneity. When multiple-stepwise regression is used to quantify the determinants of perfusion heterogeneity in three postures, a structural component accounts for 59, 79, and 80% of the total variability in the upright, supine, and prone postures, respectively (Table 3). Stated another way, when the animals are upright, about two-thirds of the variability in regional pulmonary perfusion are due to some factor that remains consistent across all of the postures. After we account for this source of perfusion heterogeneity in the upright posture, height up the lung accounts for 25% of the total variability. Similarly, height up the lung accounts for only 7 and 5% of perfusion heterogeneity when the animals are supine and prone, respectively.

When flow is modeled as a quadratic function of height up the lung, the relative contributions of structure and height do not change significantly. This suggests that other factors, besides height up the lung, affect perfusion distribution.

Table 2. Vertical gradients of blood flow in different postures

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Upright Slope</th>
<th>Upright $r^2$</th>
<th>Head down Slope</th>
<th>Head down $r^2$</th>
<th>Supine Slope</th>
<th>Supine $r^2$</th>
<th>Prone Slope</th>
<th>Prone $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$-0.090$</td>
<td>0.528</td>
<td>$-0.018$</td>
<td>0.034</td>
<td>$-0.035$</td>
<td>0.057</td>
<td>$-0.002$</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>$-0.104$</td>
<td>0.670</td>
<td>0.004</td>
<td>0.002</td>
<td>$-0.062$</td>
<td>0.308</td>
<td>0.005</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>$-0.054$</td>
<td>0.354</td>
<td>$-0.074$</td>
<td>0.536</td>
<td>$-0.077$</td>
<td>0.226</td>
<td>$-0.016$</td>
<td>0.012</td>
</tr>
<tr>
<td>4</td>
<td>$-0.081$</td>
<td>0.286</td>
<td>$-0.062$</td>
<td>0.232</td>
<td>$-0.048$</td>
<td>0.113</td>
<td>0.028</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Mean ± SD: $-0.088 ± 0.018$, $0.474 ± 0.152$, $-0.048 ± 0.027$, $0.0242 ± 0.175$, $-0.055 ± 0.023$, $0.176 ± 0.113$, $0.004 ± 0.018$, $0.021 ± 0.032$

95% CI: $-0.101–0.075$, $0.368–0.579$, $-0.067–0.028$, $0.121–0.364$, $-0.073–0.037$, $0.066–0.286$, $-0.014–0.021$, $-0.010–0.053$

Slopes are derived from least squares linear fits of relative blood flow per lung piece as a function of height up the lung (cm). Goodness of fit is represented by $r^2$ for each posture. Repeat measures of perfusion distribution are shown for each animal in upright and head-down postures.
suggests that the proposed zone 4 of decreasing flow in the dependent lung regions is not significant in these four animals.

Ventral-to-dorsal gradients. In the upright posture, regional perfusion increased significantly toward dorsal regions in only one animal. The ventral-to-dorsal gradient did not differ from zero in the other three animals.

Cephalad-to-caudad gradients. Whereas some animals have significant gradients, a general pattern cannot be discerned. In the supine posture, regional perfusion increased significantly toward caudad re-

![Fig. 5. Distributions of blood flow in 1 animal in upright (A) and supine postures (B). A: vertical perfusion distribution after nullifying effect of gravity by averaging blood flow to each piece between opposing postures. Note small gradient of perfusion toward caudad regions. Independent and dependent axes have been reversed so that graphs are similar to those familiarized by West (36). B: horizontal distribution of blood flow along the lung in supine posture. Note small gradient of perfusion toward caudad regions. Linear regressions are performed with height up the lung as the independent variable. n, No. of lung pieces.](image)

**Fig. 5.** Vertical distributions of blood flow in 1 animal in supine (A) and prone (B) postures. Independent and dependent axes have been reversed so that graphs are similar to those familiarized by West (36). Linear regressions are performed with height up the lung as the independent variable. n, No. of lung pieces.
regions in two animals and toward the cephalad regions in one animal. In the prone posture, regional perfusion increased significantly toward caudad regions in only one animal and was not different from zero in the other three.

Radial gradients. Figure 8 shows blood flow per piece as a function of radial distance from the ipsilateral lung to each piece. Although all four animals had small decreases (−0.15 to −0.01 relative flow units/cm) in perfusion from hila to periphery, the magnitude and variability in the gradients preclude statistical significance (95% CI, −0.16–0.03). On average, radial distance from the hilum explains ~7% of the variability in regional blood flow.

DISCUSSION

The data obtained from this study are unique in that they describe regional pulmonary blood flow in a primate model with lung structure and vascular anatomy similar to humans. The methods used allow regional blood flow measurements to be compared among different gravitational vectors (changing postures). The data are of high-fidelity and spatial resolution without reconstruction artifacts of imaging methods. The important findings of this study are as follows: 1) pulmonary blood flow is heterogeneously distributed in the upright primate model, 2) the relative contribution of gravity to pulmonary perfusion heterogeneity is similar in supine and prone primates compared with other laboratory animals, 3) gravity plays a greater role in perfusion distribution when animals are upright, and 4) although important, gravity remains a secondary determinant of regional pulmonary blood flow distribution in the upright primate. These observations confirm recent studies of pulmonary perfusion heterogeneity in microgravity and provide a new perspective from which to explore determinants of pulmonary blood flow distribution.

We estimate that 25% of the observed perfusion heterogeneity in the upright primate can be attributable to the gravity-induced hydrostatic gradient down the lung. The residual perfusion heterogeneity observed in isogravitational planes cannot be explained by hydrostatic gradients. This is an overestimate because our experimental design attributes changes in perfusion observed with postural changes to an effect of hydrostatic pressure differences. Mediastinal structures, abdominal contents, and the diaphragm likely shift position in the head-down compared with the upright posture. Any alterations in regional perfusion induced by these structural changes are attributed to a gravitational effect. Any change in regional ventilation that alters local alveolar O₂ pressures may invoke local changes in perfusion through hypoxic pulmonary vasoconstriction. Hence, we may be overestimating the

Table 3. Relative contribution of structure and height up the lung to perfusion heterogeneity in the upright, supine, and prone posture

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>r² Structure</th>
<th>r² Structure + Height</th>
<th>r² Added by Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upright</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.64</td>
<td>0.82</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
<td>0.52</td>
<td>0.81</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>0.65</td>
<td>0.88</td>
<td>0.23</td>
</tr>
<tr>
<td>4</td>
<td>0.55</td>
<td>0.85</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean</td>
<td>0.59</td>
<td>0.84</td>
<td>0.25</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.77</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>0.71</td>
<td>0.86</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>0.95</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>0.78</td>
<td>0.86</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean</td>
<td>0.79</td>
<td>0.86</td>
<td>0.07</td>
</tr>
<tr>
<td>Prone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.77</td>
<td>0.78</td>
<td>0.01</td>
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<tr>
<td>2</td>
<td>0.72</td>
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<td>0.05</td>
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<td>3</td>
<td>0.93</td>
<td>0.96</td>
<td>0.03</td>
</tr>
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<tr>
<td>Mean</td>
<td>0.80</td>
<td>0.85</td>
<td>0.05</td>
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</tbody>
</table>

Repeated measures in upright posture were run separately and then averaged to obtain a single value in each animal.
effect of gravity on perfusion heterogeneity in a single posture.

Our estimate that gravity is responsible for 25% of perfusion heterogeneity in the upright posture is considerably greater than what we predicted from a similar study in supine and prone dogs (11). One explanation for the lesser gravitational effect in these dogs is a smaller vertical gradient in supine and prone dogs (14 cm) compared with upright and head-down baboons (25 cm). This hypothesis is supported by our observation that primates and dogs have similar gravitational contributions in the supine and prone postures. A second explanation for this lesser gravitational effect in dogs may be inherent differences between quadrupeds and primates, as proposed by Hughes (22). Hughes et al. (23) believe that relative lung volumes may be smaller in quadrupeds because of their horizontal posture and that gravity plays a less important role at smaller lung volumes. Most laboratory animals also have a more muscularized pulmonary vascular system with a smaller fraction of resistance in the microvascular segments (25). If a smaller fraction of vascular resistance resides in microvascular segments of primates and these segments have relatively little tone, hydrostatic pressures may have a greater influence on blood flow distribution (22).

Vertical gradients of perfusion may result from hydrostatic pressure differences between the top and bottom of the lung and regional structural differences in the pulmonary vasculature. If the hydrostatic pressure differences were the sole determinant of regional perfusion, vertical gradients of perfusion should be similar in postures with equivalent vertical heights. The vertical gradient of perfusion is much greater in the upright than in the head-down posture, and it is also greater in the supine compared with the prone posture, suggesting that anatomic factors may be important in determining the vertical distributions of blood flow. These slopes are similar to those seen in other laboratory animals (10, 20, 31, 35).

Radial blood flow gradients and dorsal perfusion biases are small in upright primate lungs. Prior studies have documented a large hilar-to-peripheral gradient in dogs (17) and humans (18) by using single-photon-emission computed tomography. Radial gradients have been variably documented (35) or dismissed (30) by others using nonimaging methods. A dorsal blood flow bias has been suggested to explain the more homogeneous flow distribution in the prone vs. supine posture (4). Although blood flow is more uniform in prone than in supine baboons, a dorsal predisposition for perfusion is not apparent.

Supporting evidence. In 1970, Reed and Wood (34) first suggested that pulmonary blood flow may not be as homogeneous as predicted by the gravitational model. Using methods with improved spatial resolution, they found that perfusion is not uniform within isogravitational planes and concluded that "the interrelationships of determinants of regional pulmonary blood flow in the intact animal are sufficiently complex so that achievement of an adequate description by a relatively simple model is not possible at this time." Greenleaf and associates (15) confirmed the observation of heterogeneous blood flow within isogravitational planes using methods with even greater spatial resolution. A number of recent studies have confirmed the large heterogeneity of isogravitational pulmonary blood flow in a variety of laboratory animals (10, 20, 28, 31, 35). In those studies exploring isogravitational perfusion heterogeneity, the CV within horizontal planes was almost as large as the perfusion heterogeneity across all planes (12, 20). In standing, awake horses with hydrostatic differences of 50 cmH2O between the top and bottom of the lung, blood flow increased up the lung rather than down the lung as predicted by the gravitational model (20). Exhaled gas-concentration profiles from humans in microgravity on the space shuttle quantify the role played by gravity in determining perfusion, ventilation, and ventilation-perfusion heterogeneity (32, 33). In these studies, oscillations in exhaled CO2 were analyzed, and gravity was estimated to be responsible for 38% (95% CI, 22–54%) of perfusion heterogeneity in standing humans (33).

Methodological considerations. Embolization of microspheres has been used extensively to measure regional organ blood flow (13, 20). Because of the particulate nature of the microspheres, there has been concern that microspheres may not faithfully represent blood flow distribution at the capillary level (26). Using lung pieces similar in size to those in the present study, Melsom and co-workers (28) demonstrated that 15-µm-diameter microsphere estimates of regional blood flow correlated well (r = 0.99) with estimates from a nonparticulate (molecular) marker. Studies by Beck and Rehder (4) have confirmed that regional pulmonary blood flow determined by 15-µm microspheres correlated well (r = 0.91) with regional perfusion measured by indicator dilution techniques that used 99mTc-labeled red blood cells. Deposition of microspheres is a generally accepted and well-validated method for measuring blood flow to regions with volumes similar to those in this study (~2 cm³).

Drying lungs at total lung capacity (TLC) alters their conformation from the in vivo state. Because microspheres were administered over a number of breaths, their distribution represents blood flow over the entire range of tidal breathing. Studies by Liu et al. (27) suggest that displacement for any given piece from its in vivo position to its TLC position is probably quite small and insignificant compared with the magnitude of the gradients and heterogeneity observed. When the flow per piece is normalized by weight, the observations in this study are comparable with earlier regional perfusion studies that used xenon, in which flow was measured per alveolar volume. Because all alveoli are nearly uniform in size at TLC, the weight of an individual lung piece should be roughly proportional to the number of alveoli per piece. Because airway composition may artifactually add to the observed perfusion heterogeneity, Melsom and associates (28) compared perfusion heterogeneity between central lung regions containing airways and peripheral pieces void of con-
ducting airways. They found that perfusion heterogeneity was similar between the two regions and concluded that the observed isogravitational perfusion heterogeneity is real and not artifactually increased by lung parenchymal heterogeneity.

Lung volume and shape are difficult to assess in the head-down posture; they are probably smaller because abdominal contents push the diaphragm in a cephalad direction. The effect may be local along the diaphragmatic surface or impact the entire lung. The only evidence we have that this effect is small is that airway pressures increased minimally in head-down posture.

Reconciling discrepancies. Spatial distribution of pulmonary blood flow was first studied directly in elegant physiological experiments during the early 1960s. Radioactive gases were used to measure regional distribution of blood flow by one of two methods (1, 2, 7, 24): either an insoluble gas was given intravenously and radioactive counts recorded over the chest wall, or a soluble gas was inhaled and gas clearance from the alveolar space measured in a similar fashion. In all of these studies, blood flow appeared to increase with distance down the lung.

Because the scintillation counters in these initial studies were unable to measure perfusion variability within isogravitational planes, only the vertical heterogeneity of perfusion was observed. Spatial resolution of recent animal experiments can be reduced to the level of earlier experiments using chest wall scintillation counters by averaging data within isogravitational planes. When high-resolution data sets are averaged to yield a few isogravitational planes, vertical height up the lung becomes the key determinant of blood flow distribution. Thus recent findings do not conflict with older data; higher resolution methods simply reveal other mechanisms that could not be observed previously. Even higher resolution observations representative of blood flow at the alveolar capillary level will show a greater degree of heterogeneity and a lesser contribution of gravity to perfusion variability.

Isogravitational heterogeneity and zone model. Banister and Torrance (3) and Howell et al. (21) were the first to publish on the notion of alveolar pressures influencing pulmonary blood flow. Hughes, West, and others (23, 24, 37) synthesized the observations existing at the time into a model of pulmonary blood flow distribution (39) describing horizontal "zones" of flow. Within these vertically stacked zones, regional blood flow is determined by the relationship between the three pressures (arterial, venous, and alveolar).

In a branching vascular tree, structural heterogeneities produce variabilities in local driving pressures and resistances. Traditionally, the gravitational model is presented with single arterial and venous hydrostatic pressures at a given vertical height (39). Whereas the hydrostatic pressure is determined by a stagnant column of blood, pressure drops and driving pressures at the microvascular level are determined by vascular branching angles and serial resistances to flowing blood. Driving pressures within isogravitational planes should, therefore, be heterogeneous (26). When regional conditions are considered, the driving pressures of interest are not arterial and venous pressures but rather the local microvascular and alveolar pressures.

Because of this heterogeneity in driving pressures, multiple zonal conditions must exist within a horizontal plane (14). In a departure from the classic gravitational model, each isogravitational plane can, therefore, have a distribution of pressure relationships. Gravity exerts its effects on blood flow distribution by increasing the hydrostatic pressure toward dependent lung regions, altering the statistical distribution of these regions. The frequency distribution likely shifts toward zone 2 and 3 conditions down the lung, eventually resulting in only zone 3 conditions in the most dependent regions.

Conclusions and implications for gas exchange. The gravitational hypothesis that attributes distribution of both blood flow and ventilation in the lung has been a cornerstone of pulmonary physiology. We wish to advance the concept that gravity alone cannot adequately account for recent experimental observations of pulmonary perfusion; additional factors must be considered. These proposals are based on new concepts of fractal vascular trees and perfusion heterogeneity (12, 13); they offer a new perspective from which to explore determinants of regional blood flow.

The reorientation induced by this new perspective provides important insights into the primary function of gas exchange in the lung. Despite heterogeneous distribution of perfusion at the alveolar-capillary level, gases are exchanged efficiently. The traditional model of gas exchange proposes a small unit of ventilation and its companion capillaries. The common effect of gravity is invoked to explain matching of ventilation and perfusion (22). However, given the degree of isogravitational perfusion heterogeneity, matching of ventilation and perfusion cannot be governed by gravity alone. This prediction was verified recently in studies by Prisk and colleagues (32) in Spacelab Life Sciences (SLS)-1 and SLS-2; under conditions of microgravity, ventilation-perfusion inequalities persist. The authors of this study conclude that the principle determinants of ventilation-perfusion inequalities are not gravitational in origin.

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