Measurement of pulmonary blood flow by fractal analysis of flow heterogeneity in isolated canine lungs

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Regional heterogeneity of lung blood flow can be measured by analyzing the relative dispersion (RD) of mass (weight)-flow data. Numerous studies have shown that pulmonary blood flow is fractal in nature, a phenomenon that can be characterized by the fractal dimension and the RD for the smallest realizable volume element (piece size). Although information exists for the applicability of fractal analysis to pulmonary blood flow in whole animal models, little is known in isolated organs. Therefore, the present study was done to determine the effect of blood flow rate on the distribution of pulmonary blood flow in the isolated blood-perfused canine lung lobe by using fractal analysis. Four different radiolabeled microspheres (¹⁴¹Ce, ⁹⁵Nb, ⁸⁵Sr, and ⁵¹Cr), each 15 µm in diameter, were injected into the pulmonary lobar artery of isolated canine lung lobes (n = 5) perfused at four different flow rates (flow 1 = 0.42 ± 0.02 l/min; flow 2 = 1.12 ± 0.07 l/min; flow 3 = 2.25 ± 0.17 l/min; flow 4 = 2.59 ± 0.17 l/min), and the pulmonary blood flow distribution was measured. The results of the present study indicate that under isogravitational blood flow conditions, all regions of horizontally perfused isolated lung lobes received blood flow that was preferentially distributed to the most distal caudal regions of the lobe. Regional pulmonary blood flow in the isolated perfused canine lobe was heterogeneous and fractal in nature, as measured by the RD. As flow rates increased, fractal dimension values (averaging 1.22 ± 0.08) remained constant, whereas RD decreased, reflecting more homogeneous blood flow distribution. At any given blood flow rate, high-flow areas of the lobe received a proportionally larger amount of regional flow, suggesting that the degree of pulmonary vascular recruitment may also be spatially related.

pulmonary blood flow distribution; microspheres; relative dispersion; vascular recruitment; pulmonary vascular resistance; fractal analysis

Numerous factors are responsible for the distribution of pulmonary blood flow. According to the gravitational pulmonary perfusion model described by West et al. (33) for zone 3 perfused lungs, gravity is the principal determinant of regional blood flow and causes the increase in perfusion from the nondependent to the dependent lung regions. However, more recent studies have provided evidence that is contradictory to the gravitational model, and the gravitational model fails to explain the heterogeneity of blood flow distribution in isogravitational planes (19, 20, 25, 28). Reed and Wood (28) first observed isogravitational perfusion heterogeneity, and Hogg et al. (21) found that regional perfusion variability existed within horizontal planes. Recently, Glenny and Robertson (16) postulated that gravity may be secondary in determining perfusion distribution.

Previous studies have used fractal analysis to characterize the heterogeneity of pulmonary blood flow (10, 16, 17). The concept of fractal analysis or fractal geometry was first conceived by Mandelbrot (24) and is widely used to characterize a variety of morphometric and physiological information (3, 18, 30, 32). Fractal patterns of organ blood flow distribution are spatially correlated such that neighboring regions tend to have similar magnitudes of blood flow (17). To date, fractal analysis has been used to measure the distribution of pulmonary blood flow in both dogs (16, 17, 27) and sheep (10). Glenny and Robertson (16) measured pulmonary blood flow in supine anesthetized dogs and found that the heterogeneity of blood flow distribution was fractal in nature, whereby blood flow to a given lung region was correlated with flow to an adjacent region regardless of size or location. Caruthers and Harris (10) observed that heterogeneity of regional pulmonary blood flow present in the in situ perfused sheep lungs was fractal in nature.

Although information exists on the applicability of fractal analysis to pulmonary blood flow in whole animal models, little is known about the applicability of fractal modeling to blood flow in isolated organs. Therefore, the present study was done to determine the effect of blood flow rate on the distribution of pulmonary blood flow in the isolated blood-perfused canine lung lobe by using fractal analysis. Analysis of blood flow distribution in the isolated lung is important because the isolated lung model is widely used to study a variety of physiological phenomena, including pulmonary vaso-reactivity, microvascular permeability, enzyme activity, and neutrophil sequestration. Blood flow distribution in the isolated lung lobes was measured at different blood flow rates by injecting radiolabeled microspheres into the pulmonary artery. Microspheres distribute proportionately to blood flow in individual lung lobes (12), and Beck (6) provided evidence indicating that in the isolated perfused dog lung the regional distribution of microspheres correlated well with the regional distribution of erythrocytes.

The results of this study indicate that at any given blood flow rate, all regions of the isolated lung lobe were perfused with blood flow increasing toward the caudal regions of the lung, an effect that appeared independent of gravity. In addition, the distribution of pulmonary blood flow in the isolated lung lobe was heterogeneous and fractal in nature.
METHODS

Isolated Lung Lobe Preparation

Mongrel dogs of either sex (weighing 18.5 ± 0.4 kg) were anesthetized with 30 mg/kg pentobarbital sodium and ventilated with 40–60% O2 in room air. A femoral artery and vein were cannulated, and the left chest was entered through the fifth intercostal space. The left upper and cardiac lung lobes were excised, and the bronchus and artery supplying the left lower lung lobe were isolated. Heparin (10,000 U) was given intravenously, and 5,000 U more were added to 500 ml of blood collected to fill the perfusion system. With the heart still beating the left main pulmonary artery was ligated, and the lower left lung lobe was excised and cannulas were placed in the lobar vein and bronchus. With the perfusion system filled with blood and the roller pump (Sarns P/N 206944) in operation, the artery was cannulated with care taken to avoid the introduction of air. The lobes were reperfused within 25 min of excision. The recirculating perfusion system has been previously described (13). Briefly, after leaving the water-jacketed plastic reservoir, the blood passed through a bubble trap (Prime blood filter SP3840, Pall Stat) placed in front of the pump and entered the lobe via the arterial cannula. Blood returned to the reservoir via the venous cannula. A clamp on the venous cannula was adjusted as necessary to produce a pulmonary venous pressure (Ppv) of 5 cmH2O. Cannulas were then clamped to fix their positions for the duration of the experiment. Blood flow temperature was monitored from a thermistor (Yellow Springs Instruments) positioned in the venous catheter, and temperature was maintained at 37°C. Lung ventilation was done with humidified room air to which 95% O2-5% CO2 was added to elevate PO2. Ventilation frequency was 7 breaths/min, and tidal volume was adjusted to provide a peak inspiratory pressure of 12 cmH2O. Expired air was exhausted under a water seal to provide a peak expiratory pressure of 2 cmH2O. The lobe was placed in a plastic bag to prevent desiccation and was positioned horizontally on a trip balance.

Measurements

Pressures and lobe weight changes were continuously recorded on a polygraph (model 7D, Grass). To minimize blood flow velocity effects on recorded pressures, pulmonary arterial pressure (Ppa) and Ppv were monitored from holes drilled 5 mm from the closed tip of hollow 20-gauge stainless steel tubes. The steel tube was inserted into the lumen and advanced to the vascular end of the arterial or venous perfusion cannula. These pressure-tip catheters were attached to transducers (model P23Gb, Statham) zero referenced to the top of the lobe. Airway pressure was monitored from a transducer (model P23ID, Gould) attached to a small catheter inserted into the bronchial cannula.

Blood flow rate was obtained from pump flow settings calibrated by timed collection of the outflow. Blood samples were obtained from the venous cannula for blood gases and pH measurements (model 945, AVL). Sodium bicarbonate was added to the venous reservoir as needed to maintain pH at normal levels. Double vascular occlusion pressure (Pd0) was obtained by simultaneous occlusions of the arterial inflow and venous outflow cannulas at end expiration. During simultaneous 2- to 3-s occlusion of both inflow and outflow catheters, Ppa and Ppv rapidly equilibrate to Pd0 (14), which is an excellent estimate of average microvascular pressure at the filtering midpoint of the lung (29). Lobar vascular resistance was calculated as (Ppa – Ppv)/flow.

Injections of microspheres. The distribution of pulmonary blood flow was measured by using the reference-flow radioactive-microsphere technique (1, 2). Four injections of 15-µm-diameter microspheres tagged with 141Ce, 95Nb, 85Sr, or 51Cr were done in each experiment. Specifically, 50 µCi of 141Ce, 40 µCi of 95Nb, 10 µCi of 85Sr, and 150 µCi of 51Cr were used in each experiment. These levels of radioactivity allowed for a minimum of 1,000 microspheres to be lodged in all of the lung tissue samples, which consequently minimized the distribution variability and noise in the microsphere method (9, 11).

The protocol for microsphere injections was the following: collection of a pulmonary arterial reference blood flow sample was started at time 0 and continued for 2 min after the microsphere injection by using a Harvard withdrawal pump at a flow rate of 7.75 ml/min. Approximately 10 s after the blood withdrawal was started, microspheres suspended in 10% dextran were injected as a bolus into the pulmonary arterial inflow tubing at a site ~30 cm proximal to the cannula in the pulmonary artery. Mixing of the injected microspheres with the blood was facilitated by injecting radially in the direction opposite to the flow of blood (7). It is important to note that all of the microsphere injections were done in a random order. That is, a labeled microsphere was chosen blindly for each particular injection to reduce the chance of injecting microspheres in the same order in each experiment. Blood samples for blood gases and pH were drawn periodically.

Specific protocol. Five animals were used for the study. After the lungs were isolated and perfusion was started, the lobes were allowed to stabilize hemodynamically and become isovolumetric for ~30 min before the microsphere injections were started. Microsphere injections were done under zone 3 conditions at four different blood flow rates chosen in random order and designated as flow 1 (0.42 ± 0.02 l/min), flow 2 (1.12 ± 0.07 l/min), flow 3 (2.25 ± 0.17 l/min), and flow 4 (2.59 ± 0.17 l/min). A differently labeled microsphere was given at each blood flow rate.

After the last microsphere injection, perfusion was stopped and the lung was air dried for at least 48 h and cut into 9–10 vertical regions from hifum to base (Fig. 1). These regions were subsequently sectioned into ~1-cm3 tissue samples, placed into previously weighed test tubes, and again weighed to determine tissue weight. Radioactivity in these tissue samples were counted in a gamma counter that corrected spectrum overlap, radioactive decay, and background counts. Regional tissue blood flows (Qt) were calculated on a per gram weight basis by using the equation

$$Q_t = R_t \cdot Q_{ref} / R_{ref}$$

where \( R_t \) and \( R_{ref} \) are the disintegrations per minute in the tissue and the reference withdrawal blood flow sample, respectively, and \( Q_{ref} \) is the reference withdrawal blood flow rate.

Fractal Analysis

Theory. A simple definition of a fractal is a shape or structure that is comprised of parts that are similar to the whole (16, 24). On measuring a fractal on a scalar basis, an increasingly minute scale, the configuration detail continues to be the same as at the greater scale. As the measurement scale becomes smaller, more description becomes available by the measuring device at each scale reduction. A fractal is self-similar in that it consists of pieces similar to the whole (24). Fractal blood flow models consist of vascular branching of larger to smaller arteries, with each generation branching in the same pattern as the others (10). The degree of blood...
flow heterogeneity depends on the ratio by which the blood flow is divided at each bifurcation. In theory, if flow is equally divided, the model will predict homogeneity of blood flow.

The fractal pattern of regional blood flow distribution in the isolated lung can be described experimentally by microsphere injection into the pulmonary artery. Dividing the SD of the flow by the mean flow will give the measurement that quantifies regional blood flow heterogeneity (relative dispersion (RD)). The method of Caruthers and Harris (10) was used to measure RD for determining the spatial heterogeneity of pulmonary blood flow. RD was calculated from the following equation:

\[
RD = \frac{\sqrt{\sum F_i^2 - (\sum F_i)^2/n}}{\sum F_i/n}
\]

where \(F_i\) is the flow within the \(i\)th region of a total of \(n\) regions. RD was initially calculated from the regional blood flow information in the original pieces for each lobe by using Eq. 2. Subsequently, neighboring pieces from the original number of pieces were recombined and RD was recalculated by using the flow data obtained from the larger element size, with the largest element size being two to three pieces. \(RD_{ef}\) was determined from the value of RD for the smallest realizable volume element (original no. of pieces) for each lung lobe. Fractal plots were constructed for each dog by plotting the logarithm of RD vs. the logarithm of element volume (number of pieces of lung tissue). The observed RD (\(RD_{observed}\)) is a summation of that contributed from the spatial distribution RD (\(RD_{true}\)) and the component of RD attributed to methodological technique and measurements (\(RD_{noise}\)), which can be expressed by the following equation:

\[
RD_{observed}^2 = RD_{true}^2 + RD_{noise}^2
\]

Because at least 1,000 microspheres were lodged in each tissue sample after each microsphere injection minimizing distribution variability and noise (9, 11), \(RD_{noise}\) is negligible and can be ignored. A least squares linear regression was done through the data points at each flow rate to calculate the regression coefficient, and the fractal dimension (D) for each flow rate was calculated as one minus the slope.

**Fig. 1. Effect of different blood flow rates on pulmonary blood flow distribution in isolated canine lung.** Slices 1–10 represent lung regions from base to hilum of lung lobe (see inset). Flow 1 represents lowest blood flow rate; flow 4 represents highest blood flow rate. Flow 1 = 0.42 ± 0.02 l/min, flow 2 = 1.12 ± 0.07 l/min, flow 3 = 2.25 ± 0.17 l/min, and flow 4 = 2.59 ± 0.17 l/min. Inset, illustration of lung regions that are vertically sectioned for determina
tion of pulmonary blood flow distribution. During perfusion, vertical sections of lobe were in plane of gravity. Slice 1 represents most basal (distal) area, and slice 10 represents most hilar (proximal) region of lobe.

**Statistics**

Data are presented as means ± SE. For microsphere blood flow analysis and hemodynamic measurements, significance was determined by using regression analysis and analysis of variance for within-group and between-group comparisons. If a significant F-ratio was found, then specific statistical comparisons were made by using Bonferroni-Dunn post hoc test. Statistical significance was accepted when \(P < 0.05\).

**RESULTS**

Table 1 shows the effect of blood flow rate on pulmonary hemodynamic parameters in the isolated canine lobe. Higher blood flow rates significantly decreased total pulmonary vascular resistance. Figures 1 and 2 show the effect of blood flow rate on regional blood flow distribution. At each blood flow rate used in the present study, all regions of the lobe were perfused. In addition, at each blood flow rate, the caudal regions of the lobe (Fig. 1; slices 1–3) received the highest blood flow while the cephalic regions of the lung near the hilum (Fig. 1; slices 8–10) exhibited the lowest blood flow. Figure 2 shows that the vertical distribution of blood flow in the isolated lobe was variable, indicating that there was no effect of gravity, although perfusion was increased to all areas of the lobes at the higher flow rates as seen in Fig. 1. Figure 3 shows the inverse relationship of the RD coefficient as a function of flow, which suggests that pulmonary blood flow becomes more homogeneously distributed at higher flow rates. Figure 4 is a representation of a fractal plot for a dog lobe with the RD

**Table 1. Effect of blood flow on pulmonary hemodynamics**

<table>
<thead>
<tr>
<th>Flow, l/min</th>
<th>Flow 1</th>
<th>Flow 2</th>
<th>Flow 3</th>
<th>Flow 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow, l/min</td>
<td>0.42 ± 0.02</td>
<td>1.12 ± 0.07*</td>
<td>2.25 ± 0.17*</td>
<td>2.59 ± 0.17*</td>
</tr>
<tr>
<td>Ppa, cmH2O</td>
<td>17.2 ± 1.1</td>
<td>27.2 ± 3.3*</td>
<td>54.5 ± 8.6*</td>
<td>50.5 ± 16.1*</td>
</tr>
<tr>
<td>Ppw, cmH2O</td>
<td>5.0 ± 0.6</td>
<td>4.7 ± 0.3</td>
<td>4.7 ± 0.2</td>
<td>4.5 ± 1.1</td>
</tr>
<tr>
<td>Rt, cmH2O·l-1·min</td>
<td>29.76 ± 4.5</td>
<td>20.8 ± 2.05*</td>
<td>22.23 ± 3.86*</td>
<td>17.36 ± 3.11*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ppa, pulmonary arterial pressure; Ppw, pulmonary venous pressure; Rt, total pulmonary vascular resistance. *Significantly different from flow 1, \(P < 0.05\).
plotted vs. the number of lung pieces of each element size used to calculate RD. In this log-log plot, it can be seen that highest flow rate (flow 4) resulted in lower values for RD for any given volume element (no. of pieces). In addition, as flow rate increased, RD decreased and the linear portion of the slope determined by regression remained constant, indicating that $D$ remained constant because $D = 1 - \text{slope}$. The $r^2$ values were 0.78 for flow 1, 0.84 for flow 2, 0.77 for flow 3, and 0.86 for flow 4. Table 2 shows the value of D for each experiment at the different blood flow rates, and the composite data are shown in Table 3. The data in Table 3 show that D remained relatively constant at all flow rates.

Table 2. Fractal measurements for each experiment at each flow

<table>
<thead>
<tr>
<th>Flow, l/min</th>
<th>No. of Pieces</th>
<th>D</th>
<th>RDref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow 1</td>
<td>0.332</td>
<td>180</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>0.926</td>
<td>220</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>1.916</td>
<td>220</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>2.246</td>
<td>220</td>
<td>1.29</td>
</tr>
<tr>
<td>Flow 2</td>
<td>0.431</td>
<td>145</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td>1.260</td>
<td>145</td>
<td>1.36</td>
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<tr>
<td></td>
<td>2.910</td>
<td>145</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>3.246</td>
<td>145</td>
<td>1.34</td>
</tr>
<tr>
<td>Flow 3</td>
<td>0.450</td>
<td>193</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>1.134</td>
<td>193</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td>2.034</td>
<td>193</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>2.394</td>
<td>193</td>
<td>1.22</td>
</tr>
<tr>
<td>Flow 4</td>
<td>0.446</td>
<td>140</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>1.022</td>
<td>140</td>
<td>1.22</td>
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<tr>
<td></td>
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<td>140</td>
<td>1.25</td>
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<td></td>
<td>2.462</td>
<td>140</td>
<td>1.19</td>
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<td>Flow 5</td>
<td>0.452</td>
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<tr>
<td></td>
<td>1.268</td>
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<td>1.22</td>
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<td></td>
<td>2.288</td>
<td>110</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td>2.628</td>
<td>110</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Values are means ± SE. D, fractal dimension; RDref, relative dispersion coefficient for smallest realizable volume element.
four different blood flow rates and that there was a tendency for RD to decrease with increasing flow rates, in agreement with the data presented in Fig. 3. Figure 5 shows $RD_{\text{ref}}$ normalized with reference to flow 1 and further verifies that RD declined as blood flow was increased to the higher rates.

Figure 6 shows the regional distribution of pulmonary blood flow plotted as a function of regions or quartiles. The entire lobe was sectioned, and the lung pieces were grouped into corresponding quartiles (4 regions) based on their blood flow values relative to the other pieces at the lowest flow (flow 1). Quartile 1 (lowest 25%) consisted of pieces of lung exhibiting the lowest blood flow and quartile 4 (greatest 25%) consisted of the highest blood flow pieces at each blood flow rate (flows 1–4). As shown by the data in Fig. 6, all quartiles received a larger amount of blood flow because total pulmonary blood flow increased, with quartile 4 acquiring the largest amount. This finding is verified when these data are plotted on a percent increase basis (Fig. 7) because the region with the highest initial flow (quartile 4) also received the greatest percent increase in flow as blood flow rate increased.

**DISCUSSION**

The results of the present study indicate that regional blood flow in the isolated perfused canine lung is heterogeneous and fractal in nature. The observed RD is a function of sample size, and the greatest estimate of RD will be obtained from the finest subdivisions of the organ (4). The concept of fractal analysis originated with Mandelbrot (24) and has since been accepted as the standard to characterize a variety of anatomic and physiological phenomena (3, 15, 31). By definition, fractal models are those in which variation of dimension or pattern remain similar through successive magnifications of scale (4). Bassingthwaite and co-

<table>
<thead>
<tr>
<th>Flow, l/min</th>
<th>D</th>
<th>$RD_{\text{ref}}$</th>
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<tbody>
<tr>
<td>0.42 ± 0.02</td>
<td>1.18 ± 0.04</td>
<td>0.74 ± 0.09</td>
</tr>
<tr>
<td>1.12 ± 0.07</td>
<td>1.23 ± 0.05</td>
<td>0.68 ± 0.08</td>
</tr>
<tr>
<td>2.25 ± 0.17</td>
<td>1.21 ± 0.04</td>
<td>0.66 ± 0.04</td>
</tr>
<tr>
<td>2.59 ± 0.17</td>
<td>1.25 ± 0.06</td>
<td>0.57 ± 0.11</td>
</tr>
</tbody>
</table>

Values are means ± SE.
leagues (5) observed that the heterogeneity of blood flow in the heart is fractal and showed that a relationship exists between measured heart mass and $D$ such that the greater the heterogeneity of the system, the larger was the value of $D$. Subsequently, it was mathematically derived that a value of $D = 1.0$ represented total homogenous flow distribution and that a value of $D = 1.5$ would be a pure heterogeneous distribution (17).

In the present study, RD decreased as blood flow increased, indicating that the lobe was becoming more homogeneously perfused at the higher flow rates. In addition, the average value of RD obtained in our study was $1.22 \pm 0.08$, which is similar to that found in other investigations (5, 10, 27). Because $D$, which characterizes RD, remained relatively constant over the entire range of flows, the manner in which the blood flow was dispersed was also constant. Bassingthwaighte et al. (5) measured the mean $D$ in the myocardium of normal baboons ($1.21 \pm 0.04$), sheep ($1.17 \pm 0.06$), and rabbits ($1.25 \pm 0.07$), and Caruthers and Harris (10) calculated a value of $1.14 \pm 0.09$ in situ-perfused sheep lungs. For pulmonary blood flow distribution in the anesthetized dog, Glenny and Robertson (16) found $D$ to be $1.09 \pm 0.02$, and a recent study by Parker and colleagues (27) estimated $D$ in the canine left lung of unanesthetized dogs to be $1.19 \pm 0.01$ at rest, $1.22 \pm 0.07$ at a $45^\circ$ tilt, and $1.21 \pm 0.15$ during moderate treadmill exercise.

Analysis of quartile blood flow in the present experiments indicates that the regions with higher blood flow at the lower flow rates also received the highest blood flow at the highest flow rates (Figs. 6 and 7). This finding suggests that the quartiles with the higher blood flow have the capacity for greater vascular recruitment relative to the low-flow quartiles. Recent studies have shown that perfusion at this high-flow rate fully recruits the pulmonary vascular bed of the isolated dog lung (26), and Caruthers and Harris (10) plotted quartile flows from isolated sheep lungs and observed that as flow increased, the low-flow regions received a proportionally larger amount of blood flow, possibly allowing these regions to become more fully recruited relative to the high-flow regions.

Classically, the gravitational four-zone model of pulmonary blood flow by West et al. (31) has provided the best general description of flow distribution in the lung. However, this model does not adequately explain the heterogeneous blood flow observed within isogravitational planes. Reed and Wood (28) first postulated that factors other than hydrostatic and alveolar pressures may be important in the distribution of pulmonary blood flow, and Nicolaysen and colleagues (25) suggested that pulmonary blood flow heterogeneity is a random process. More recently, Glenny and Robertson (17) reported that gravity is a minor determinant of blood flow distribution.

In the present study, when the isolated lobes were perfused in a horizontal position relative to gravity similar to that seen in dogs lying in a right decubitus position, blood flow was present in all regions, with blood flow increasing from apex ( hilar ) to base ( caudal ). In addition, there appeared to be no effect of gravity because no gradient of blood flow distribution occurred from top to bottom of the lobe, although blood flow increased within each horizontal slice at the higher flow rates. These data agree with studies by Greenleaf et al. (19), who showed that the blood flow fraction increased from apex to base in microsphere-injected dogs placed in the left decubitus position and by Nicolaysen et al. (25), who observed no major gradient of pulmonary blood flow distribution (horizontal or vertical) within any lung slice.

The data from our study showed that the regions ( slices ) of highest blood flow and regions ( slices ) of lowest blood flow in the isolated lobes were predominately adjacent to each other. The fractal model of pulmonary blood flow heterogeneity by Glenny and Robertson (17) may explain the regional perfusion patterns observed in the present study. In this particular model, the observed relationship of flow distribution may be due to the fractal branching of the pulmonary vascular tree, which is independent of gravitational factors. Blood flow distribution is spatially correlated in that high-flow regions are associated with adjacent high-flow areas and low-flow regions tend to occur near other areas of low flow (16). Anatomic factors could also be involved in the distribution of pulmonary blood flow (8). Beck and Rehder (8) suggested that regional vascular conductances were associated with anatomic location and concluded that regional differences in vascular anatomy are great enough to influence pulmonary blood flow, and morphological data have shown that there is a distinct variation in vessel and airway length (22, 34).

The observation that under normal condition pulmonary blood flow distribution is region dependent and heterogeneous may be physiologically significant for ventilation and perfusion matching. The heterogeneous nature of pulmonary blood flow suggests that ventilation-perfusion ratios may also be heterogeneous (17). Under pathological conditions, blood flow redistribution may be necessary to maintain adequate ventilation-perfusion ratios or to preferentially direct blood flow to less-injured areas. It is interesting to note that lung injury may be regionally dependent because studies have shown that pulmonary edema produced in dogs with oleic acid injury occurred mainly in dorsocaudal regions, which suggests that a higher density of fluid-exchange vessels are present in dorsocaudal lung regions (23), an effect independent of posture.

In summary, the results of the present study indicate that under normal blood flow conditions, pulmonary blood flow in the isolated canine lung is heterogeneous and fractal in nature as defined by RD. In addition, as flow rates increased blood flow distribution became more homogeneous because $D$, which characterizes RD, remained constant, whereas RD decreased. At any given blood flow rate, high-flow areas of the lung received a proportionally larger amount of regional flow, which suggests that the degree of pulmonary vascular recruitment may be regionally dependent. Last, the blood-perfused isolated lung appears to be an
excellent model to correlate fractal analysis of pulmonary blood flow distribution in the in situ animal model.

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