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A fractal analysis of the radial distribution of bronchial capillaries around large airways

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Anderson, Joseph C., Albert L. Babb, and Michael P. Hlastala. A fractal analysis of the radial distribution of bronchial capillaries around large airways. *J Appl Physiol* 98: 850–855, 2005. First published November 12, 2004; doi:10.1152/jappphysiol.00801.2004.—We analyzed published measurements of the bronchial circulation and airway wall (Anderson JC, Bernard SL, Luchtel DL, Babb AL, and Hlastala MP. *Respir Physiol Neurobiol* 132: 329–339, 2002) and determined that the radial distribution of bronchial capillary cross-sectional area was fractal. We limited our analysis to bronchial capillaries, diameter $\leq 10 \mu\text{m}$, that resided between the epithelial basement membrane and adventitia-alveolar boundary, the airway wall tissue. Thirteen different radial distributions of capillary-to-tissue area were constructed simply by changing the number of annuli (i.e., the annular size) used to form each distribution. For the 13 distributions created, these annuli ranged in size from $\frac{1}{2}$ to $\frac{1}{128}$ of the size of the airway wall area. Radial distributions were excluded from the fractal analysis if the sectioning procedure resulted in an annulus with a radial thickness less than the diameter of a capillary. To determine the fractal dimension for a given airway, the coefficient of variation (CV) for each distribution was calculated, and $\ln(\text{CV})$ was plotted against the logarithm of the relative piece area. For airways with diameter $>2.4 \text{ mm}$, this relationship was linear, which indicated the radial distribution of bronchial capillary cross-sectional area was fractal with an average fractal dimension of 1.27. The radial distribution of bronchial capillary cross-sectional area was not fractal around airways with diameter $<1.5 \text{ mm}$. We speculated on how the fractal nature of this circulation impacts the distribution of bronchial blood flow and the efficiency of mass transport during health and disease. A fractal analysis can be used as a tool to quantify and summarize investigations of the bronchial circulation.

anatomy; morphometry; vasculature; microcirculation; linear

ALTHOUGH TINY AND UNSUNG, the bronchial circulation plays an important role in many lung processes. In health, it acts as “the nutritive vessels of the lung” (10). The pulmonary nerves, connective tissue, and muscle surrounding the airways are all supported by this circulation. It rehydrates mucus desiccated from normal breathing and plays an active role in thermoregulation (3). The bronchial circulation can eliminate highly soluble gases (i.e., ethanol) and participate in airway clearance of soluble aerosols (23). In disease or injury, the bronchial circulation has been described as the “Red Cross” of the lung (11). With inflammation or asthma, the circulation hypertrophies and recruits vessels to begin the healing process (7). Additionally, it can perform limited respiratory gas exchange if the pulmonary circulation fails (8).

Fundamental to understanding the physiological role of the bronchial microcirculation is understanding its anatomy. Investi-

gators have studied many facets of the bronchial circulation. Pump (22) and Magno and Fishman (19) have described the circulation’s gross anatomy in humans and sheep, respectively. Others have searched for bronchopulmonary anastomoses (9, 24). Still other investigators have given a three-dimensional description (15, 18). In all, the studies have been mainly qualitative in nature. Quantitative measurements of how the bronchial vessels are distributed about the airways are scarce but, if available, could provide insight into the underlying structure-function relationship of this circulation.

Recently, we measured the radial location and size of 9,997 bronchial vessels residing in the airway wall of the sheep to determine the geometric factors governing the diffusing capacity of the airways (2). Later, we thought that this large data set could provide more details about the radial distribution of the bronchial vessels. We hypothesized that the radial distribution of the bronchial circulation cross-sectional area was fractal in a similar manner to the fractal nature of the myocardial and pulmonary circulations (14).

A fractal structure has self-similarity as its essential characteristic. A structure is considered self-similar when the “finer details [of the structure] are revealed at higher magnifications [and] the form of the details is similar to the whole” (5). Thus fractal structures look essentially the same on whatever scale they are examined and do not have any natural scale for measurement.

In this study, we use this concept of fractals to examine the bronchial circulation. If the bronchial circulation is fractal, new experimental hypotheses can be formed concerning the distribution of bronchial blood flow, the relationship between energy expenditure and transport of material to the airway wall, and the efficiency of airway function in disease. Additionally, if the bronchial circulation is fractal, the fractal analysis can be used as a new tool to quantify and summarize investigations of the bronchial circulation during altered physiological states. In this study, we focus on one aspect of the bronchial circulation, the radial distribution of the bronchial capillaries, because their role as exchange vessels is important to the rehydration of the mucus, delivery of nutrients to the tissue, and participation of gases in airway exchange. We analyze data from a previous experiment (2) to determine whether the radial distribution of the bronchial capillary cross-sectional area is fractal around all airways $>0.75 \text{ mm}$ in diameter.

METHODS

Experimental. A detailed methodology has been reported previously (2). The lungs of four adult sheep (30–36 kg) were excised and

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fixed overnight with neutral-buffered formalin. Airway samples, ranging in diameter from 0.75 to 18 mm, were embedded in methyl methacrylate, microtomed to a thickness of 5 μm , stained with Lee's stain, and mounted on slides for measurement.

The cross sections of airway tissue were examined using a light microscope. The image from the light microscope was captured with a video camera and sent to a computer. Using the digital image, measurements on the airway tissue and bronchial vasculature were made on 48 tissue sections. The airway tissue measurements were used to calculate the following dimensions for each tissue section: 1) the airway diameter was defined by the epithelial basement membrane, and 2) the airway wall area was defined as the tissue area between the epithelial basement membrane and the alveolar-adventitia boundary. The bronchial vascular measurements were used to distinguish capillary vessels (i.e., diameter $\leq 10 \mu\text{m}$) from all noncapillary vessels, to calculate the cross-sectional area of each capillary, and to determine the radial location relative to the epithelial basement membrane of each capillary within the airway wall.

Bronchial vessels were identified and distinguished from lymphatic vessels using the following criteria (2). The wall of the bronchial vessels was thicker, more prominent, and contained endothelial cells with more plump and numerous nuclei than the lymphatic vessels. Viewed from the inside out, the bronchial vessels had only concave surface geometry, whereas the lymphatic vessels had both concave and convex geometries. Almost all of the bronchial vessels contained blood cells, and very few ($\sim 3\%$) were entirely void of media.

Fractal analysis. A fractal structure or process has self-similarity as its core feature; that is, the characteristic form of the structure or process is retained with successive levels of magnification. For example, the coastline of Britain is fractal because it retains a characteristic pattern if viewed from far (e.g., the moon) or near (e.g., a cliff overlooking the coast) (20). Similarly, the length of this coastline depends on the size of the ruler. From the moon, a 1,000-km-long ruler can only measure the gross features, but, from a nearby cliff, the irregular and winding features of the coastline can be measured using a relatively small 1-m ruler. Because of this increase in resolution, the length of this coastline or any fractal structure depends on the size of the measuring stick. As the ruler length approaches zero, the length of the structure becomes infinitely large. To mathematically determine whether a natural object is fractal, a power-law relationship must be present between the size of the measuring stick and the size of the structure as determined by the corresponding measuring stick.

In this study, we ask the following question: "Is the radial distribution of bronchial capillary cross-sectional area fractal around an airway?" We use the coefficient of variation (CV) as a summary statistic describing this distribution. We know that the CV is a function of the bin size (i.e., measuring stick) used to make the distribution. If a similar power-law relationship exists between the CV and bin size as exists between the coastline of Britain and the ruler size, the radial distribution of bronchial capillary cross-sectional area is fractal.

To determine whether the radial distribution of bronchial capillary cross-sectional area was fractal around a single airway, two procedures were done. First, many radial distributions of the capillary cross-sectional area were constructed. Each distribution was unique because the bin size (i.e., the length of the measuring stick) differed among distributions. Second, a statistic to quantify the heterogeneity of each distribution, the CV, was compared with the same statistic from the other distributions to determine whether the underlying radial structure of bronchial capillary cross-sectional area was fractal. If fractal, the radial structure of the capillary cross-sectional area would be independent of the scale of measurement.

To construct a radial distribution of capillary cross-sectional area, the airway wall area was sectioned into a number of annuli of equal area (Fig. 1). The annuli are analogous to the bins described above; more annuli produce smaller bin sizes. The quantity of capillary cross-sectional area within each annulus was summed and divided by

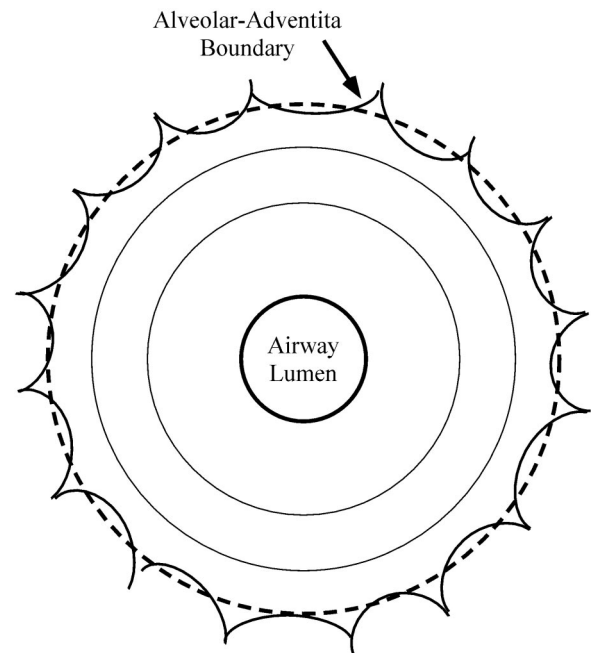


Fig. 1. Schematic of airway cross section. For the calculations, the alveolar-adventitia boundary is approximated as a circular boundary (dashed line). The airway wall is divided into 3 annuli of equal area.

the area of the annulus. This value was normalized by the ratio of total capillary cross-sectional area to total wall area, and the result was called the relative capillary-to-tissue area. A distribution of relative capillary-to-tissue area vs. radial location was created. For a single airway, as many as 13 different distributions were constructed simply by changing the number of annuli (i.e., the annular size) used to form each distribution. To recover 13 different distributions, the airway wall was divided into 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 64, 96, or 128 annuli of equal area. A distribution was excluded from the fractal analysis (described below) if the sectioning produced an annulus with a radial thickness of $< 10 \mu\text{m}$, the diameter of a capillary.

The extent to which wall divisions had a relative capillary-to-tissue area significantly different from 1.0 (the average value) provided a measure of the degree to which the capillary cross-sectional area was heterogeneously distributed radially throughout the airway wall. If the capillary area were distributed homogeneously, all annular pieces would have the same capillary cross-sectional area per unit tissue area. For this fractal analysis, the measure of the heterogeneity of each distribution was given by the CV. The CV was equal to the standard deviation of a relative capillary-to-tissue area distribution divided by the average relative capillary-to-tissue area (equal to 1 as defined above). The radial distribution of bronchial capillary cross-sectional area was fractal around an airway if the logarithm of the CV of the relative capillary distribution was linearly related to the logarithm of the scale of measurement used to construct the distribution. The scale of measurement was equivalent to the size of the annuli of equal area and, for this study, was expressed as a relative piece size (ala_0). The area a was the area of each individual annuli for a given distribution. The area a_0 was the area of each individual annuli of the sectioning procedure that produced the distribution with the following characteristics: 1) the area of each annular piece was smaller than any of the other distributions and 2) the radial thickness of each annulus was $> 10 \mu\text{m}$, the diameter of a capillary. In other words, the area, a_0 , was the smallest annular area of all the annular areas from all the distributions used in the fractal analysis for the given airway.

The logarithm of the coefficient of variation, $\ln(\text{CV})$, of the distribution of the relative capillary-to-tissue area was plotted against the logarithm of the relative piece size, $\ln(ala_0)$ for a single airway (Fig.

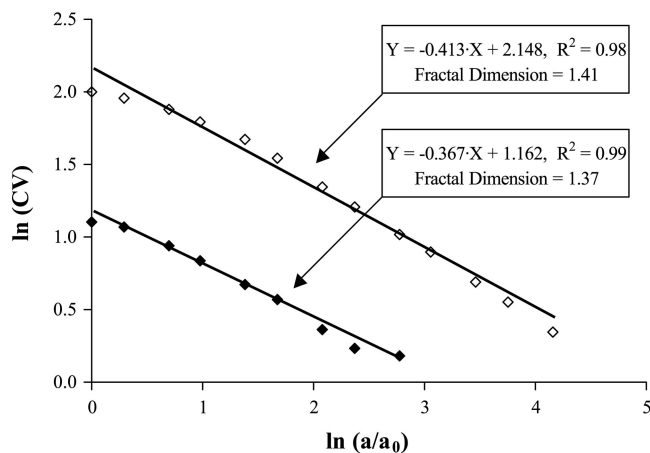


Fig. 2. Plot of the logarithm of the coefficient of variation [$\ln(\text{CV})$] vs. logarithm of relative piece area [$\ln(a/a_0)$], where a is the area of each individual annuli for a given distribution, and a_0 is the smallest annular area of all the annular areas from all the distributions used in the fractal analysis for the given airway] for 2 different-sized airways, a large airway (diameter = 14.3 mm; \diamond) and a smaller airway (diameter = 4.2 mm; \blacklozenge). More sectioning procedures were applied to the larger airway than the smaller airway. As a result, the larger airway was divided into more radial annuli than the smaller airway before reaching the limiting radial size of 10 μm , the diameter of a capillary.

2). Using the slope, we calculated the fractal dimension, which was the slope of this linear relationship subtracted from 1 (13). This fractal dimension served as a measure of complexity of the bronchial capillary cross-sectional area and was independent of the scale of measurement. For this study, a fractal dimension equal to 1.0 corresponded to a homogeneously distributed capillary cross-sectional area, and a fractal dimension equal to 1.5 corresponded to a capillary cross-sectional area distribution that was distributed randomly in the radial direction across the airway wall. This procedure was done for each airway, 48 in total, and resulted in a fractal dimension and an

associated correlation coefficient (R^2) for the distribution of bronchial capillary cross-sectional area around each airway.

In order for the distribution of capillary cross-sectional area to be considered fractal, it was necessary for the relationship between $\ln(\text{CV})$ and $\ln(a/a_0)$ to be linear. Linearity of this relationship was determined by the value of R^2 . If $R^2 > 0.7$, then the relationship was deemed linear and the distribution of capillary cross-sectional area was said to be fractal. If $R^2 < 0.7$, then the linearity of the relationship could not be determined, and the distribution of capillary cross-sectional area was said to be nonfractal.

RESULTS

Figure 2 shows $\ln(\text{CV})$ plotted against $\ln(a/a_0)$ for two representative airways. For each set of data, a best fit line, an equation describing this line, and a correlation coefficient (R^2) are presented in Fig. 2. Because the relationship between $\ln(\text{CV})$ and $\ln(a/a_0)$ was linear and $R^2 > 0.7$, the radial distribution of capillary cross-sectional area for these two airways was fractal. The fractal dimensions of the radial capillary distribution for the 4.2-mm-diameter airway and 14.3-mm-diameter airway were 1.37 and 1.41, respectively.

The fractal dimension and standard error of the bronchial capillary cross-sectional area are plotted against airway diameter for *sheeps 1–4* in Fig. 3, A–D, respectively. Fractal dimensions from distributions of capillary cross-sectional area that were found to be fractal (i.e., $R^2 > 0.7$) or nonfractal (i.e., $R^2 < 0.7$) are indicated with different symbols.

For distributions of capillary cross-sectional area that were fractal, the fractal dimension increased with increasing airway diameter for *sheeps 1* and *2* but remained constant with increasing diameter for *sheeps 3* and *4*. This relationship was determined using an F -test ($P < 0.05$) on the slope of a best fit line between the fractal dimension and the airway diameter for each sheep. For these same airways, the average fractal dimension across these airways for each *sheep 1–4* was 1.32, 1.27,

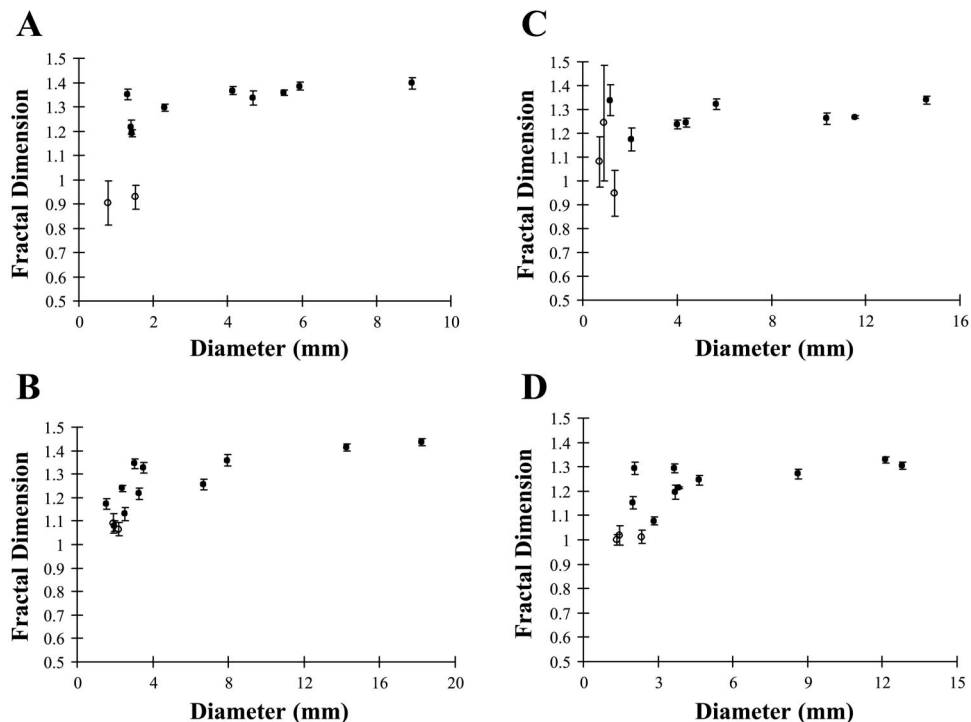


Fig. 3. Fractal dimension of the radial distribution of bronchial capillary cross-sectional area as a function of airway diameter. Fractal dimension with standard error was plotted against airway diameter for *sheep 1* (A), *sheep 2* (B), *sheep 3* (C), and *sheep 4* (D). \bullet , Airways with radial distributions of bronchial capillary cross-sectional area that were fractal (i.e., $R^2 > 0.7$); \circ , airways with nonfractal distributions.

1.27, and 1.25, respectively. The average R^2 of the best fit lines used to calculate the fractal dimension for these same airways for *sheeps 1-4* was 0.97, 0.93, 0.91, and 0.94, respectively.

Of the 48 airways analyzed, 10 of these airways had radial distributions of capillary cross-sectional area that were found to be nonfractal (i.e., $R^2 < 0.7$). These airways had diameters < 2.4 mm, and the average fractal dimension across these airways for each *sheep 1-4* was 0.92, 1.08, 1.09, and 1.01, respectively.

DISCUSSION

We analyzed published measurements of the bronchial circulation within the airway wall (2) to determine whether the radial distribution of bronchial capillary cross-sectional area was fractal. Our analysis was limited to bronchial capillaries, diameter ≤ 10 μm , that resided within the airway wall tissue, the tissue between the epithelial basement membrane and adventitia-alveolar boundary. Thirteen different radial distributions of capillary-to-tissue area were constructed simply by changing the number of annuli (i.e., the annular size) used to form each distribution. For the 13 distributions created, these annuli ranged in size from $\frac{1}{2}$ to $\frac{1}{128}$ of the size of the airway wall area. Radial distributions were excluded from the fractal analysis if the procedure resulted in an annulus with a radial thickness less than the diameter of a capillary. To determine the fractal dimension for a given airway, the CV for each distribution was calculated, and $\ln(\text{CV})$ was plotted against $\ln(a/a_0)$. We found the radial distribution of bronchial capillary cross-sectional area to be fractal around all airways > 2.4 mm in diameter. The average fractal dimension across these airways was 1.27.

The fact that the radial distribution of the bronchial circulation is fractal allows us to speculate on some of the characteristics and behavior of the bronchial circulation. First, we hypothesize that the radial distribution of bronchial blood flow is fractal because the radial distribution of the conduits that carry the blood is fractal. This conjecture assumes that the pressure difference and capillary resistance are equivalent for each capillary within that distribution. Currently, measurements on the radial distribution of bronchial blood flow are unavailable. However, analyses using structure-function relationships have been established for other pulmonary structures, the airway tree and pulmonary vascular tree. Both of these structures were proven to be fractal, and subsequently, the distributions of ventilation and pulmonary blood flow were shown to be fractal as well (1, 14). Second, fractal patterning minimizes energy expenditure and optimizes the relationship between energy expenditure and transport of materials (12). We speculate that the fractal structure of the bronchial microcirculation enables it to efficiently perform its many simultaneous functions: thermoregulation of respired air, rehydration of the airway mucus, transportation of nutrients to the airway tissue, and elimination of waste from the tissue. Third, a major function of the bronchial circulation is to humidify the inspired air by hydration of the airway mucus. This critical process is dependent on the radial distance between the capillary and mucus layer. Disease can cause airway wall remodeling (i.e., a change in the radial distribution of bronchial capillaries), which will change capillary-to-mucus distance. However, West (26) has demonstrated that fractal structures with self-similar scaling can tolerate error or "internal changes" better than classical structures with a natural scaling (e.g., the size

of a cell). We hypothesize that the fractal structure of the bronchial capillary distribution allows it to adequately humidify inspired air even if pathology has changed the bronchial capillary distribution.

As we have shown, the radial distribution of bronchial capillary cross-sectional area is fractal. Thus the fractal analysis can be used as a tool to quantify and understand the physiology of the bronchial circulation in large airways. For example, studies in sheep and on human tissue have shown that pulmonary hypertension (16, 21), increased bronchial blood flow (25), chronic obstructive pulmonary disease (17), and asthma (6, 17) can alter the size (i.e., cross-sectional area) and number of bronchial vessels in the airway wall. However, changes in the radial distributions of these bronchial vessels and bronchial capillaries have not been investigated. A fractal analysis can provide a nondimensional summary statistic that would reveal changes in the radial distributions of the bronchial vessels. Such an analysis may provide new insights to the underlying mechanisms leading to vessel hyperplasia, vessel hypertrophy, or airway wall remodeling that result from these pathological conditions. Additionally, the fractal dimension is independent of units or scale of measurement. As a result, the fractal dimension is an excellent means for presenting observations because measurements made in different laboratories, species, and experiments can easily be compared.

All airways with a nonfractal bronchial capillary distribution had airway diameters < 2.4 mm. All airways with diameters < 2.4 mm (20 airways in total) were reexamined, and 10 of these airways had a nonfractal (i.e., $R^2 < 0.7$) bronchial capillary distribution. The average fractal dimension across these 10 airways was 1.03. The remaining 10 airways had radial distributions of capillary cross-sectional area that were found to be fractal. The average fractal dimension across these 10 airways was 1.23. To understand why some airways < 2.4 mm in diameter had a fractal bronchial capillary distribution and others a nonfractal distribution, we compared the two sets of airways and found one distinguishing feature. Airways with a fractal bronchial capillary distribution had, on average, a tissue wall area that was 88% larger than the tissue wall area of the airways with a nonfractal bronchial capillary distribution. When the tissue wall area was normalized by airway diameter, the airways with a fractal bronchial capillary distribution had, on average, a normalized tissue wall area that was 72% larger than the normalized tissue wall area of the airways with a nonfractal bronchial capillary distribution. Thus a greater number of unique distributions (i.e., different annuli of equal area) could be constructed from the airways with a fractal bronchial capillary distribution than the airways with a nonfractal capillary distribution. The greater number of distributions provided more data points for use in determining whether the relationship between $\ln(\text{CV})$ and $\ln(a/a_0)$ was linear and whether the distribution of capillary cross-sectional area was fractal.

Because of the relationship between airway wall size and the fractal and nonfractal structure of the distribution of the capillary cross-sectional area, we examined how the number of distributions and, ultimately, the size of the smallest annulus affected the significance of the fractal dimension. To do this analysis, we relaxed the constraint that the smallest annulus must have a radial thickness larger than the diameter of a capillary (10 μm) and used all 13 different distributions created for each airway to determine whether the distribution of cap-

illary cross-sectional area was fractal or nonfractal around each airway, 48 airways in total. Under these assumptions, only two airways had a nonfractal bronchial capillary distribution as measured by an $R^2 < 0.7$ for the best fit line between $\ln(\text{CV})$ and $\ln(a/a_0)$. These two airways were < 1.5 mm in diameter.

Bassingthwaighte showed that many structures are fractal only over a limited range (4). For the radial distribution of bronchial capillary cross-sectional area, the lower limit of this fractal structure is the size of the capillary, and the upper limit is the size of the airway wall. The size of the airway wall increases, in general, with airway diameter and may determine a critical airway size. Airways larger than this critical airway size have a radial distribution of bronchial capillary cross-sectional area that is fractal. Our analysis shows that the radial distribution of capillary cross-sectional area is fractal for airways with an airway diameter > 2.4 mm but nonfractal for airways with an airway diameter < 1.5 mm. Thus this critical airway size appears to reside between the airway diameters of 1.5 and 2.4 mm in sheep and depends on the size of the airway wall, which may depend on the location of the airway within the lung and pathology of the lung.

We distinguished between airways with a fractal distribution of bronchial capillary cross-sectional area from airways with nonfractal radial distributions. For the radial distribution to be fractal, the relationship between $\ln(\text{CV})$ and $\ln(a/a_0)$ must be linear. This relationship was judged to be linear if R^2 was > 0.7 . In addition to this requirement, we tested whether the slope of the relationship between $\ln(\text{CV})$ and $\ln(a/a_0)$ was nonzero by using an F -test. A zero slope indicated that the fractal dimension is one, and the distribution could be described by using a Euclidian dimension instead of a fractal dimension. We found all airways with fractal distributions to have slopes that were statistically different than zero and all airways with nonfractal distribution to have slopes that were statistically equal to zero. The nonfractal radial distributions were found exclusively in the smallest airways studied, most likely because the difference between the smallest length scale (the capillary diameter) and the largest length scale (the radial thickness of the airway wall) used in the fractal analysis was relatively small. Thus fewer statistical distributions could be constructed for these airways to evaluate the fractal nature of the bronchial capillary cross-sectional area. For this study, it appeared that a value of $R^2 = 0.7$ was a reasonable cutoff for determining whether the radial distribution of bronchial capillary cross-sectional area was fractal or nonfractal.

Conclusions. We analyzed published measurements of the bronchial circulation and airway wall and determined that the radial distribution of bronchial capillary cross-sectional area was fractal. We limited our analysis to bronchial capillaries, diameter ≤ 10 μm , that resided between the epithelial basement membrane and adventitia-alveolar boundary, the airway wall tissue. Thirteen different radial distributions of capillary-to-tissue area were constructed simply by changing the number of annuli (i.e., the annular size) used to form each distribution. For the thirteen distributions created, these annuli ranged in size from $1/2$ to $1/128$ of the size of the airway wall area. Radial distributions were excluded from the fractal analysis if the sectioning procedure resulted in an annulus with a radial thickness less than the diameter of a capillary. We found the radial distribution of bronchial capillary cross-sectional area to be fractal

around all airways > 2.4 mm in diameter. The average fractal dimension across these airways was 1.27. The radial distribution of bronchial capillary cross-sectional area was not fractal around airways with diameter < 1.5 mm. A critical airway diameter may have existed between 1.5 and 2.4 mm, above which the radial distribution of bronchial capillary was fractal and below which it was not fractal. Airway wall size appeared to be an important factor in determining this critical airway diameter.

This fractal structure of the radial distribution of bronchial capillary cross-sectional area provided a new perspective on this circulation. We speculated that the radial distribution of capillary blood flow in the airway wall was fractal. Additionally, we hypothesized that the fractal structure of the bronchial circulation could ensure efficiency and robustness to functions of the bronchial circulation such as thermoregulation of the respired air and transport and elimination of nutrients and waste from the airway tissue. As importantly, a fractal analysis can be used as a tool to quantify and summarize investigations of the bronchial circulation, and the resulting fractal dimension can be used to easily compare measurements on the radial distribution of bronchial capillary cross section made in different laboratories, species, and experiments because the fractal dimension is independent of units or scale of measurement.

GRANTS

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