MDCT-based quantification of porcine pulmonary arterial morphometry and self-similarity of arterial branching geometry


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The branching geometry of the pulmonary vasculature plays a significant role in determining the distribution of pulmonary perfusion (3, 11) and hence the response of the lung to disease. Porcine models are often used in experimental studies that are aimed at improving understanding of human disorders. This is because pigs have a greater physiological and anatomical similarity to humans than smaller animals, which permits a variety of clinical scenarios to be simulated (e.g., Refs. 5, 25). A quantitative description of the porcine pulmonary vasculature is essential to understanding structure-function relationships in this species and how this translates to the human lung.

However, knowledge on morphometry of the pig pulmonary vasculature remains rudimentary.

Most studies of the porcine vasculature have focused on the bronchial and coronary arteries (10, 24, 28). Previous works describing the morphometry of the porcine pulmonary circulation are few in number and lack detailed geometric information (29, 30, 33). The most extensive morphological study was conducted by Maina and Gils (29), who measured the size of arteries over 22 generations of the right lungs of 2 pigs. Data were presented as mean vessel length and diameter per generation, which may be insufficient for representing vessel size in an arterial tree with significant branching asymmetry. Rendas et al. (33) conducted a morphometric analysis on the postnatal development of the pig lung; however, the geometric details were not fully described.

Although the data from previous studies are limited, they have suggested that the porcine pulmonary arterial tree geometry differs from human. For example, the porcine pulmonary arteries tend to branch monopodially, where a parent artery gives rise to a major daughter branch with a relatively large diameter and at a small branching angle to the parent, and a minor daughter branch with a far smaller diameter at a larger branching angle. Human pulmonary arterial branching is relatively more symmetric than in the pig (when discounting the supernumerary vessels; Ref. 8), which may be due to species differences in lung shape. Because the asymmetry of the vascular tree is important in determining the characteristic perfusion distribution for a species (3), morphometric data are crucial to further advancing our understanding of structure-function relationships in the porcine lung and its translation to human physiology.

Previous studies have used microfocal X-ray computed tomography (micro-CT) to examine morphometry and self-similarity in the rat pulmonary arteries (22). MR imaging to analyze the morphometry of the rat pulmonary airways (7), and multidetector row computed tomography (MDCT) to quantify the geometry of the human and ovine bronchial airways (39). Here we use a similar approach to quantify the porcine pulmonary arteries using MDCT imaging of the intact porcine lung. We demonstrate that the porcine pulmonary arteries exhibit intersubject and self-similarity, such that quantifying the rate of reduction in diameter along any vascular pathway is sufficient to describe the rate of reduction along any other pathway. We also provide new measurements of key geometric parameters, which show clear structural differences between the human and porcine pulmonary arterial trees. This has an implication for physiological studies of the pulmonary circulation that justify...
using the pig as an experimental animal on the basis of its similarity to the human lung. Finally, we propose a simplifying model for the arterial tree.

MATERIALS AND METHODS

Animal preparation and imaging. In vivo imaging of the porcine lung was conducted at the University of Iowa, Iowa Comprehensive Lung Imaging Center following approval by the University of Iowa Institutional Review Board and Animal Ethics Committee. A total of five healthy pigs of both genders were used in the studies (weight 20–40 kg) as summarized in Table 1. Animals were premedicated with 20 mg/kg ketamine and 2 mg/kg xylazine intramuscularly and anesthetized with 1–3% isoflurane via nose cone inhalation. Anesthesia was maintained with continuous intravenous administration of pentobarbital (0–30 mg/kg loading, 3–5 mg⋅kg⁻¹⋅h⁻¹ maintenance). Pancuronium was administered at 2.5 mg initially, 0.5–1.0 mg as needed. A tracheostomy was performed, and the animals were mechanically ventilated with 100% oxygen for the duration of the study. The animals were in the prone position for volume scans, which were acquired during breath hold at an airway inflation pressure of 25 cmH₂O. A pulmonary catheter was inserted via the right external jugular vein and positioned by means of pressure monitoring in a jugular vein and estimated cardiac output (CO) for cardiac output measurements. Another catheter was inserted in the abdominal aorta via the right carotid artery for pulmonary artery pressure and pulmonary capillary wedge pressure measurements of pulmonary artery pressure and pulmonary capillary wedge pressure. Another catheter was inserted in the abdominal aorta via the right carotid artery for cardiac output measurements. Animal 1 experienced an arrhythmia before the acquisition of physiological measurements. This animal was included in the structural analysis but not in calculations of pulmonary vascular resistance (PVR).

Volume scans were obtained using a dual X-ray source spiral CT scanner (Siemens Medical Systems, Erlangen, Germany), whereby two X-ray guns serve to double the temporal resolution of the scanner system. The animals were imaged during a breath hold using a retrospective cardiac gating method with an image resolution of 0.51 mm/pixel and slice thickness of 0.5 mm. Each of the planar images consisted of a 512 × 512 array of pixels in X-ray intensity scale in the range 0–255.

Measurements. The process of geometric measurement is illustrated in Fig. 1. The pulmonary vasculature was segmented from the imaging data using the custom-written software Pulmonary Analysis Software Suite (PASS; University of Iowa; Refs. 14, 19). A three-dimensional (3D) rendering of these blood vessels in a single animal is shown in Fig. 2A. The PASS vessel segmentation algorithm integrates a line-filtering approach based on eigenvalues and eigen vectors of a Hessian matrix, followed by an optional vessel tracking approach to compensate for missing small vessel segments in the first step (36) for extracting pulmonary vascular trees (arteries and veins) from CT images. Arteries and veins were then manually distinguished from each other by defining the region of interest (ROI) label locally, using the PASS segmented airway tree as a guide (arteries branch with the airway tree and veins between the airways). Mask images with an ROI index defined (with arteries and veins separated) were then created for further quantification of the vessel tree.

Segmented vessel masks were imported into MATLAB (Version 7.10, The MathWorks, 2010) in sequential order. Each individual mask slice was then represented as a 512 × 512 matrix in binary format. The blood vessels in each slice were represented by a pixel value of 1, and other material (lung parenchyma, bone, and air) was represented by a pixel value of zero. Each blood vessel region (a cluster of pixels with value 1) was labeled as a ROI. The ROI, its centroid, and its minor axis length were calculated using the MATLAB function “regionprops.” Caro and Saffman (4) suggested that blood vessels of different sizes would progressively transition from an eccentric to a circular cross section as the intravascular pressure increases. In our studies, we assume that the vessels are most circular at total lung capacity (TLC), which corresponds approximately to the 25 cmH₂O inflation pressure at which the animals were scanned. We have then taken a geometric approach to estimate the diameter of the vessels. The minor axis length of an ROI is equivalent to the diameter of the vessel, assuming that the vessel is approximately circular in cross-section.
section (see Fig. 2, B and C). Even in the case when the vessel is orthogonal to the segmented mask slice, the minor axis length of a circular ROI is also equivalent to the diameter of the vessel. Each ROI was then characterized by these measures with \(x\) and \(y\) coordinates identified by pixel coordinates and the \(z\) coordinate identified by slice number. The data describing the vascular tree structure [containing centroid location and minor axis length (i.e., diameter)] were imported into CMGUI (GUI front-end for the Continuum Mechanics, Image Analysis, Signal Processing and System Identification Program, www.cmiss.org) and used for 3D visualization and quantitative structural assessment. That is, the ROIs corresponding to each blood vessel were manually identified and each blood vessel segment (the portion of artery between 2 successive branching locations) was associated with a diameter.

The left and right pulmonary arteries that branch out from the main pulmonary artery were identified manually (see Fig. 5B). The main pulmonary artery that connects the pulmonary vasculature to the heart could not be easily distinguished by the automated software (PASS) as this software has been designed to only segment blood vessels that are within the lung parenchyma. The main pulmonary artery was visually identified by using the heart and left and right main bronchi as reference, as the artery begins at the base of right ventricle and accompanies the airways. The diameters of the left and right main arteries were then manually measured from the imaging data using the length measurement tool of OsiriX (www.osirix-viewer.com), hence completing the definition of the arterial tree. OsiriX was used instead of PASS for this task because of the convenience of its manual measurement tools, although any software that allows manual measurement of lengths would have been usable.

Quantifying tree geometry. The geometric center of each ROI was used to define a skeleton for the vascular tree based on CT imaging. With the use of the skeleton as a guide, line elements were created to span the length of each vessel segment. Line elements of adjacent segments were joined by “nodes” with known spatial coordinates, located at the branch points, which were identified using the skeleton and CT imaging as a guide. In this manner, a line element, or one-dimensional (1D), tree was created for the segmented arteries of each animal, where each line element was associated with a diameter that was estimated using the approach described previously.

The following metrics were calculated for all branch divisions and separately for the major and minor branches: rotation angle (angle between the plane of branching of the branch division and the plane of branching of the parent branch division); branch angle (angle between the proximal-to-distal directions of the parent and child branch); ratio of branch length to diameter \(L/D\); ratio of diameter to parent diameter \((D/D_p)\); and ratio of length to parent length \((L/L_p)\).
The branches in the arterial trees were classified by Strahler order (38). The smallest arteries (most distal vessels as identified on the segmented data) were defined as order 1. The order of the parent branch was increased by 1 when two child branches of the same order converged. The order of the parent branch is the same as the highest order of the daughter branches if two branches of different order meet. Each branch segment was further classified as “major” or “minor.” A major branch is the child with the smallest branch angle with respect to the parent; a minor branch is the child with the largest branch angle.

Simplifying self-similar model. Based on the above-mentioned metrics that were calculated for all branch divisions, and morphometric parameters from pulmonary artery measurements, we propose a model for the porcine pulmonary arterial tree that consists of self-repeating units. Figure 3 shows a schematic for the arterial tree model from orders 10 to 1 that comprises self-repeating units. The number of arteries in an order \( n \) \((N_n)\) is given as

\[
N_n = \begin{cases} 
2N_{n+1}, & 9 \geq n > 7 \\
2N_{n+1} + 2N_{n+2} + N_{n+3}, & 7 \geq n > 5 \\
2N_{n+1} + 2N_{n+2} + N_{n+3} + N_{n+4} + N_{n+5}, & n \leq 5 
\end{cases}
\]

where the subscripts refer to the order number and the superscripts to major or minor branches. For the order \( n \leq 5 \) equation, the first term corresponds to arteries labeled \( a \) and \( b \) in Fig. 3, and the second to fifth terms correspond to labels \( c-f \), respectively. The order 9 branches are identical and do not give rise to lateral branches. The order 10 branch (the main pulmonary artery) and the order 9 branches are dimensioned to the average of the four animals. Orders 1–8 have diameters and lengths dependent on \( D_{\text{major}}/D_{\text{p}}, D_{\text{minor}}/D_{\text{p}}, L/D_{\text{major}}, \) and \( L/D_{\text{minor}} \). As shown in RESULTS (see Table 4), the dimension of a major artery in order \( n \) is similar to the dimension of a minor artery in the same order.

This is a consequence of the major arteries in the model giving rise to three lateral minor arteries, and the arterial diameter decreasing by a factor of 0.87 at each branch division. The diameter of a major artery is then \( D_n = D_{n+1}/0.87^n \).

The branch labeling in Fig. 3 indicates arteries below which the tree structures are identical. This feature of the model allows estimation of pulmonary arterial resistance by recursive summation of all resistances in series and parallel. Blood flow resistance \((R)\) was described by Poiseuille’s equation:

\[
R = \frac{\Delta P}{Q} = \frac{128\mu L}{\pi D^4}
\]

where \( \Delta P \) is the pressure drop along the vessel, \( \mu \) is the viscosity of blood in the vessel \((\mu = 3.36 \times 10^{-3} \text{ Pa-s})\), \( Q \) is the volumetric blood flow rate, \( L \) is vessel length, and \( D \) is the vessel diameter. By assuming that all minor (or major) arteries in a given order are of equal size, then the total resistance below any minor (or major) artery of a given order is identical. The schematic in Fig. 3 provides sufficient information on the tree connectivity to facilitate summation of the resistances: the total resistance below a branch of order \( n \) is the sum of the resistances of each segment of the order \( n \) branch with the parallel summation of the total resistances below the subtended major and minor branches.

Statistical methods. Relationships between measured quantities were assessed via a linear-regression analysis, with Student’s \( t \)-test used to assess whether regression slopes were significantly different to zero and to compare slopes to the mean. Curvilinear relationships were also assessed and compared with the simpler linear relationships using \( F \)-ratio tests.

RESULTS

Data from each of the five animals are first analyzed individually and then pooled. It is uncertain whether the volumetric MDCT image segmentation detected all of the arteries that arise along the length of the main arterial pathways. Therefore, the analysis is presented using distance from the arterial tree inlet rather than by branch “generation,” which would be imprecise in an incomplete tree.

Figure 4A shows the diameter of the main pulmonary artery for each of the five animals. There is a positive correlation between animal weight and main pulmonary artery diameter \((P = 0.039; R^2 = 0.71)\). Figure 4B shows the diameter of the left and right main pulmonary arteries of each of the five animals. There is a weaker relationship between vessel size and animal weight, with inlet diameter increasing proportionally with animal weight \((P = 0.032; R^2 = 0.38)\).

Rate of reduction of main arterial pathways. Figure 5A illustrates the two main pathways in the left and right lung that were selected for initial analysis. Figure 5B plots arterial diameter and distance from the inlet vessel for ROIs along these pathways in the five animals, as well as a linear relationship between diameter and distance that was fit to data from each lung of each animal. The diameter of the pathway decreases progressively from the inlet to its end in Fig. 5A. The linear relationships provide good fits for each of the 10 data sets \((R^2 > 0.93; P < 0.07 \text{ in each case})\). Exponential decay and curvilinear relationships were also considered (22, 23). However, an \( F \)-ratio test showed that the linear relationship was a more appropriate fit to the data in each case at the 95% confidence level. The mean slope of the fitted linear relationships for the rate of change of diameter with distance from the main pulmonary artery was \(-0.039 \pm 0.008 \text{ mm/mm}. \) No data
set had a rate of diameter reduction that was significantly different from the mean (\(P = 0.47\) in each case). If \(y\) represents the diameter of the artery in mm, and \(x\) represents distance along the artery pathway in millimeters, then the regression equation describing the results is \(y = -0.04x + 8.15\) (derived from the mean values of regression equations of left and right arteries in 5 animals).

**Intersubject and self-similarity in the rate of diameter reduction.** To determine whether there is intersubject similarity in the relationship between diameter and distance from the inlet artery, the data were normalized and shifted to a common start point. That is, diameter was normalized by the inlet diameter, and in a similar approach to Liu and Ritman (27) and Karau et al. (23), the distance was normalized by the total pathlength. The normalized data approximately superimpose upon one another and they show similar gradients (mean \(-0.82 \pm 0.04\) and range \(-0.76\) to \(-0.88\)), indicating that the rate of decrease in diameter along the main pathways is similar in each animal.

To further evaluate whether the arterial tree exhibits self-similarity, minor arteries (branches emerging from the left and right main pathways as shown in Fig. 6A) were included in the analysis. The data of ten individual pathways were fitted linearly (\(R^2 > 0.77\); \(P < 0.04\)). All 10 individual pathways follow a similar rate of reduction in diameter from their inlet to the distal portion of the artery (\(-0.027 \pm 0.008\) mm/mm). The slope of each curve was not significantly different from the mean (\(P > 0.48\) in each case). Only a subset of a main pathway and five minor pathways are shown in Fig. 6 for clarity. As shown in Fig. 6C, all individual pathways follow a similar rate of reduction in diameter from their inlet to the distal portion of the artery. The slope of each curve was not significantly different from the mean. In Fig. 6D, the data for the minor branches are shifted to align the minor path entrance diameter with the equivalent diameter on the main arterial pathway. That is, data for each minor path were shifted along the \(x\)-axis by the distance from the major pathway entrance to the point where the main pathway diameter was equal to the minor pathway entrance diameter. When data for the minor branches are shifted to superimpose on the main pathway, as shown in Fig. 6D, despite the visual difference, there is no significant statistical difference in slope.

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**Fig. 4.** A: relationship between main pulmonary artery diameters and animal weight, with linear fit through the data. B: relationship between left and right pulmonary artery diameters and animal weight, with linear fit through the data, and with M denoting male and F denoting female.

**Fig. 5.** A: rendering of the pig pulmonary arterial tree, with left and right arteries identified by bold lines. B: vascular diameter (mm) vs. distance (mm) relationships for the left and right main arteries of 5 subjects identified, with linear fit through the data.
Fig. 6. A: rendering of pulmonary arterial tree structure with 6 arteries (right pulmonary artery and 5 minor arteries) identified by color lines. B: 5 color lines (minor arteries) have been bent and placed along the right pulmonary artery to demonstrate diagrammatically where the minor arteries would superimpose on the main artery. C: diameter vs. distance relationships for 6 individual arteries identified, with linear fit through the data. D: superposition of the 5 minor arteries on the main artery by shifting the distance axis. E: cumulative number of branches, \( N \) vs. distance along the 6 arteries identified at top, with linear fit through the data. F: superposition of the 5 minor arteries on the main artery.
Table 2. Arterial tree geometry statistics generated from the entire MDCT-based data set

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pig Arteries</th>
<th>Human Airways</th>
<th>Animal Airways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of branches analyzed</td>
<td>2,222</td>
<td></td>
<td>89.04 ± 44.64‡ (39)</td>
</tr>
<tr>
<td>γ</td>
<td>83.05 ± 46.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>θ</td>
<td>35.93 ± 20.99</td>
<td>36.11 ± 20.85‡ (39); 37.28§ (16)</td>
<td>35.88 ± 22.32‡ (39)</td>
</tr>
<tr>
<td>θminor</td>
<td>45.51 ± 19.45</td>
<td>36.60 ± 19.54‡ (39)</td>
<td>45.99 ± 21.94‡ (39)</td>
</tr>
<tr>
<td>θmajor</td>
<td>25.38 ± 17.75</td>
<td>35.53 ± 22.32‡ (39)</td>
<td>25.17 ± 16.85‡ (39)</td>
</tr>
<tr>
<td>L/D</td>
<td>5.65 ± 3.74</td>
<td>3.04 ± 2.20† (39)</td>
<td>2.69 ± 1.76‡ (39)</td>
</tr>
<tr>
<td>L/Dminor</td>
<td>7.07 ± 4.09</td>
<td>3.63 ± 2.57† (39)</td>
<td>2.92 ± 2.15§ (39)</td>
</tr>
<tr>
<td>L/Dmajor</td>
<td>4.28 ± 2.73</td>
<td>2.48 ± 1.79† (39)</td>
<td>2.33 ± 1.49‡ (39)</td>
</tr>
<tr>
<td>D/Dp</td>
<td>0.72 ± 0.29</td>
<td>0.71 ± 0.14† (39)</td>
<td>0.71 ± 0.18‡ (39); 0.75 ± 0.19* (26)</td>
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<tr>
<td>%D/Dp &lt; 1</td>
<td>89.74 ± 5.77</td>
<td>96.97‡ (39)</td>
<td>90.35‡ (39)</td>
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<tr>
<td>Dminor/Dp</td>
<td>0.58 ± 0.23</td>
<td>0.66 ± 0.12† (39)</td>
<td>0.61 ± 0.12‡ (39)</td>
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<tr>
<td>Dmajor/Dp</td>
<td>0.87 ± 0.27</td>
<td>0.79 ± 0.12† (39)</td>
<td>0.86 ± 0.12‡ (39); 0.90 ± 0.12* (31)</td>
</tr>
<tr>
<td>L/Dp</td>
<td>1.24 ± 1.17</td>
<td>1.18 ± 1.20† (39)</td>
<td>1.03 ± 0.74§ (39)</td>
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</table>

Values are means ± SD. Subscripts “minor” and “major” refer to the minor and major child branches. γ, Rotation angle in degrees; θ, angle between parent and child branch in degrees; L/D, ratio of branch length to diameter; D/Dp, ratio of child to parent diameter; L/Dp, ratio of child to parent length; Values from published studies are followed by their reference in parentheses. *Dog cast airways; †human multidetector row computed tomography (MDCT) airways; §sheep MDCT airways; ‡human cast airways.

Self-similarity in the number of child arteries. In a self-consistent tree, the number of branches arising from any artery should be similar (23). The cumulative number of upstream branches (N) arising from a main pathway and from nine minor arterial pathways, for a single animal, are plotted against distance from inlet in Fig. 6E, along with linear fits to these data (R² > 0.81; P < 0.05 in each case). The cumulative number of branches that arise from an artery, regardless of whether main or minor arteries, follows a similar rate of increase with distance (0.104 ± 0.025 branches/mm). The slopes of the linear regression lines were not significantly different from the mean (P > 0.36 in each case). Only a subset of a main pathway and five minor pathways are shown for clarity. Figure 6E shows, for a single animal, the cumulative number of upstream branches (N) arising from a main pathway and from the five minor arterial pathways in Fig. 6A, against distance from the inlet, and linear fits to these data. Figure 6F shows the data for each minor path shifted by the cumulative number of upstream branches on the main pathway from the point at which the minor path arises. This superimposes the minor pathway data on that of the main pathway, with increasing variation with minor path length.

Arterial tree geometry. Morphometric parameters based on measurements of the pooled left and right pulmonary arterial trees for the five animals are summarized in the first column of Table 2, along with geometry metrics from cast and MDCT-based studies of human, ovine, and canine airways. Mean values for branch angle (θ) and ratio of child to parent diameter (D/Dp) are very similar between species. In contrast, the minor (θminor) and major (θmajor) branch angles are similar in human but differ by ~20° in the quadrupeds (pig and sheep). This equates to a ratio of θminor to θmajor of 0.56 in pig compared with 0.97 in human. The ratios of minor and major child to parent diameter (Dminor/Dp and Dmajor/Dp, respectively) differ from each other by only 0.13 in human (Dminor/Dmajor = 0.84) in contrast to >0.25 in quadrupeds (Dminor/Dmajor = 0.67).

The relationship between Strahler order and geometric parameters is shown in Fig. 7 and listed in Table 3. Branching ratio R0S is similar to values for sheep, dog, rat, and hamster, each of which is larger than R0S for the relatively more symmetric human airway tree. Interspecies differences in diameter ratio R0S and length ratio R0S are less distinct, although R0S is largest in the quadrupeds.
DISCUSSION

The geometry of the porcine pulmonary arteries has been quantified in five animals at a single airflow inflation pressure using MDCT. The analysis provides new data to define the geometry of the porcine arteries, which reveals self-similarity in the rate of reduction in diameter along vascular pathways, and intersubject similarity in pulmonary artery size and branching geometry. The new data also highlight significant geometric differences between pig and human. The close agreement between our data for the in vivo lung and data from previous cast-based studies of quadruped animals suggests that MDCT-based morphometry is a robust approach for quantifying the gross structure of the pulmonary vasculature.

Measurements of branching tree geometry. There is a striking similarity between all but one of the geometry metrics listed in Table 2 with those from previous studies of airway trees in other quadruped lungs. We compared our data primarily against airflow measurements from sheep and dog because from approximately generation 3–4 the accompanying (conventional) arteries closely follow the airway tree; hence, the basic geometry of the two trees is similar (17). The pulmonary arterial tree, however, has numerous additional side branches (supernumerary arteries) that do not accompany the airway tree. For the relatively large parent arteries that are considered in the current analysis, the supernumerary arteries are likely to have diameters in the range of 50–1,000 μm (35) and, therefore, are unlikely to be visualized on MDCT (9). They would, however, be present in cast-based measurements due to recruitment by relatively large filling pressures. The lack of supernumerary arteries (or other small lateral branches) could explain the larger D/Dp (0.72 ± 0.29) in our data compared with estimates of 0.62 (21) and 0.64 (20) from casts of rat and human pulmonary arteries, respectively (these ratios were estimated as the mean diameter of an order divided by the mean diameter of the parent order). That is, with inclusion of these smaller vessels would decrease the D/Dp ratio.

An obvious difference between the current and previous studies is the approximately double length to diameter ratio (L/D in Table 2) for pig arteries compared with human or quadruped airs. This much larger value appears consistent with the left pulmonary arterial tree of a rat lung (21) and the human pulmonary arteries (20) (4.66 and 6.13, respectively).

Table 3. Morphometric parameters from measurements of pulmonary trees, where trees were ordered using Strahler ordering

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<tr>
<th>Order</th>
<th>Rs</th>
<th>Rw</th>
<th>Rp</th>
<th>L</th>
<th>D</th>
<th>L*</th>
<th>Rs</th>
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Columns 1 lists the Strahler order; column 2 lists the number of child arteries in order n (Nn) that arise from the distal end of order n + 1 arteries. Columns 3–6 give the number of child arteries that arise laterally (as minor branches) from the major or minor arteries in orders n + 1 and n + 2, as indicated by the sub- and superscripts. Columns 7–9 give the total number of branches in order n, and the total number of major and minor branches in the order. Columns 10–15 list the diameters and lengths of the major and minor arteries, and the mean values (D and L) based on the proportion of major and minor arteries for the order.
These previous studies included lateral vessels (which could have been supernumerary) but defined an “element” as a contiguous set of “segments” (i.e., between successive lateral branches) of the same order.

In contrast to dichotomous branching of human pulmonary arterial trees, the porcine trees exhibit characteristics of monopodial branching (37). That is, greater branching asymmetry with respect to the size and order of a pair of child branches than in human. The animals studied here had $R_0S = 3.49 \pm 0.24$, which was similar to all other monopodial species listed in Table 3 but significantly larger than the 2.69 ± 0.16 listed for human airways. The greater asymmetry in pig is most evident when branches are classified as major or minor. It is for human airways. The greater asymmetry in pig is most evident when branches are classified as major or minor. It is intriguing that despite the marked difference in the major-minor branch geometries, the mean geometry values for the bifurcations were very similar between quadruped and human: the mean values for $D/D_p$, $\theta$, and total branch angle (minor plus major angle, $\sim 70^\circ$) were not statistically different between human and pig ($P > 0.5$ for all comparisons).

**Intra- and intersubject similarity.** The assumption of self-similarity has previously been used to simplify data analysis (22, 23) and to make predictions of pulmonary blood flow via computational models (12). A self-similar tree has a simple underlying order such that the tree can be fully characterized by measuring the dimensions of only the vessels along the main trunk and its immediate branches. In a self-similar tree, a principal pathway should contain vessel segments extending through the entire range of diameters present in the tree, the rate of reduction in diameter with distance should be constant, and the number of branches arising from any artery should be similar (23). The principal pathways selected for analysis in this study were distinct, with major branch segments that had small deviation in direction from the parent segment. While studies have revealed self-similarity in lung vasculature of other animals, this has not previously been confirmed in pigs. Our data support that the porcine lung shows both intersubject and intrasubject (self-) similarity in the size and rate of reduction in diameters and the number of arteries that arise from any main or minor arterial pathway. When normalized for main artery size, the rate of reduction in diameter with normalized path distance from the main artery was not significantly different between animals, which is evidence that the tree displays intersubject similarity.

Our evidence for self-similarity is consistent with Karau et al. (22, 23), who used similar imaging methods to demonstrate self-similarity in the rat pulmonary arteries. Our results differ, however, in finding that a linear relationship gave a better fit to our data for rate of reduction in diameter with distance than the curvilinear relationship

$$D(x) = D(0)(1 - (x + s_i)/L_{tot})^y,$$

where $D(x)$ is the artery diameter distal to the main pulmonary artery, $x$ is the distance along the main trunk, $D(0)$ is the diameter at the inlet at $x = 0$, $s_i$ is the distance that an individual artery has to be shifted to match the equivalent portion of the main artery, $L_{tot}$ is the total length of the artery, and $c$ is a measure of concavity ($c < 1$ represents a convex taper, $c > 1$ represents a concave taper, and $c = 1$ represents a linear taper). They found that $c = 0.695$ in rat (23), whereas fitting equation (1) to the porcine data obtained here gives $c = 1.992$ ($R^2 = 0.26$). Although our data in Fig. 6, $C$ and $D$, appear to show curvilinearity in the smaller vessels, similar to the data of Karau et al. (23), an $F$-ratio test (at the 95% confidence interval) showed the linear taper ($c = 1$) to be a better fit to the data compared with a concave taper in each case. This difference could be because the current study uses MDCT imaging-based in vivo measurements, whereas the Karau et al. study used micro-CT on excised lungs with a low viscosity contrast agent, i.e., in the in vivo case the blood pressure is not constant along the arterial pathways (blood pressure decreases with distance from the main pulmonary artery due to energy dissipation and can increase or decrease due to the hydrostatic pressure, depending on the artery’s location); whereas in the excised lung studies, the entire arterial tree is subjected to a relatively high arterial pressure of 30 mmHg (40.8 cmH2O) at all locations. The in vivo approach is likely to introduce additional variability into the diameter sizes, whereas filling the excised lung could alter the pattern of distension of the vessels compared with in vivo and hence give the convex taper in the rat studies. The different techniques employed to estimate the diameter of the vessels are also likely to have a greater impact in smaller vessels. The difference in resolution between the two studies will also contribute to this difference, as the convex taper could be a property of the smallest blood vessels that are beyond the resolution of MDCT. We note that the smallest diameter that can be estimated for our study is 1.02 mm (for pixel dimension of 0.51 × 0.51 mm). For the smallest arteries, this implies a potential error in overestimation of diameter of 27% and underestimation of 36%. The rat cast is also likely to include supernumerary vessels, which may have different rate of reduction in diameter to the conventional vessels.

**Asymmetry, blood flow, and resistance.** The description of the porcine vasculature as a monopodial branching, self-similar tree has implications for calculations of PVR, flow distribution, and shear stress, compared with a symmetrically branching model as is typically employed to estimate perfusion in different species. In any asymmetrically branching system theflow, $Q$, from a parent vessel, $p$, is not evenly distributed between its child branches, $d_1$ and $d_2$. Bennett et al. (1) discuss in detail the theoretical implications of this flow asymmetry on amplification of shear stress through the tree and optimization of design. For example, an expansion coefficient, here denoted $\delta$, can be used to postulate optimization criteria, with $0.7 < \delta < 2.1$ optimizing lumen surface area, $2.1 < \delta < 2.8$ optimizing volume, and $2.8 < \delta < 3.5$, for minimum power optimization. Briefly, if $Q$ is proportional to diameter, $D$, then $Q = kD^{\delta}$, where $k$ is constant and $\delta$ is calculated from $D_p^\delta = D_{d_1}^\delta + D_{d_2}^\delta$. $\delta$ Can be estimated from Table 2: for the porcine vasculature $\delta = 2.35$ and for the human airway tree $\delta = 2.18$, which are both suggestive of volume minimization. The division of flow at a bifurcation can be estimated by $Q_d/Q_p = (D_{d_1}/D_p)^{\delta - 3}$, where $i = 1, 2$, and shear stress follows $\tau_{Dp}/\rho = (D_{d_1}/D_p)^{\delta - 3}$. This means that the flow division (ratio of major to minor flow) at an average bifurcation in the porcine vasculature is 0.72:0.28, compared with 0.60:0.40 in human airways and 0.5:0.5 in a symmetric tree. Shear stress amplifications of 1.1 and 1.43 for the major and minor child branches, respectively, are hence estimated in the pig from the current study results. The shear amplifications in human would be 1.21 and 1.40 (major and minor), and a symmetric bifurcation with the same mean value for $D_{d_1}/D_p$ as pig (0.72) would amplify shear stress by a factor...
of 1.34 from parent to child. This clearly indicates that a symmetric (single path) model is not representative of the porcine arteries.

We propose that in addition to lack of asymmetry in flow and shear stress division, a single path model would overestimate porcine arterial resistance. To assess this, we have used the property of self-similarity to propose a simplifying model for the entire pulmonary arterial tree (Fig. 3 and Table 4). The resistance of the arterial model is 1.12 mmHg/(l/s). This compares with 3.51 mmHg/(l/s) for total PVR from the experimental studies. PVR is the total resistance of the arterial, capillary, and venous vasculatures. The model arterial resistance should, therefore, only be a fraction of this. The model resistance is 32% of the experimental PVR, which is within the range of the 20–50% previous estimated in dog (2, 6, 13). In comparison, a symmetric pathway model that has 16 generations (to provide a similar number of terminal arteries as the asymmetric model) and rates of decrease in vessel diameter and length to give the same mean terminal artery size as the model gives an arterial resistance of 3.37 mmHg/(l/s), i.e., three times higher than the self-repeating asymmetric model presented here. This is further evidence that the asymmetry of the porcine vasculature is a key feature to account for when comparing porcine to human data in studies of vascular function.

Study limitations. Our method to calculate arterial diameter assumes that the arteries have a circular cross section. If the artery were elliptical in cross section, then our diameter values would be equivalent to the minimum axis length. Other imaging-based approaches calculate the cross-sectional area in slices that are reconstructed perpendicular to the centerline of the artery, and values are typically reported for a circular diameter. In theory both approaches should give consistent results, but both will have error associated with the assumption of strict circularity. We opted to use our method as it is simple, rapid, and requires few computations.

The pulmonary arteries are distensible, as they are required to accommodate the right ventricular output. Variation in intravascular pressure may affect both vessel lengths and diameters. The data presented here were acquired during an airway inflation pressure of 25 cmH₂O. This pressure inflates the lung close to TLC and hence maximizes the length of the pulmonary arteries. Inflation to TLC could dilate the arteries (via parenchymal tethering) or alternatively the increase in axial dimension could negate diameter increase due to wall stiffening and conservation of arterial wall volume. Liu and Ritman (27) found that inflation to TLC in the dog lung maximized the cross-sectional area of the pulmonary arteries and minimized the systolic-to-diastolic differences in dimension. If pig and dog have similar elastic vessel behavior, then this suggests that our data represent maximally dilated arteries.

Conclusions. Our data support the existence of self-similarity in the branching geometry of the porcine lung and that the rate of reduction in diameter is not significantly different between animals when the arterial tree size is accounted for. The asymmetry of major and minor child branch diameters and angles is very similar to measurements from the ovine airway tree and indexes of total tree branching and dimensional asymmetry are consistent with values derived from sheep, dog, rat, and hamster. The similarity between the current data and measurements of quadraped airways, as well as the larger ratio of child to parent diameter, suggests that supernumerary arteries were absent from our data. This supports previous suggestions that these small vessels are not recruited under baseline conditions.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


