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Species-Specific Pulmonary Arterial Asymmetry Determines Species Differences in Regional Pulmonary Perfusion

K. S. Burrowes^{1,3}, E. A. Hoffman², and M. H. Tawhai³

¹Oxford University Computing Laboratory, Wolfson Building, Parks Road, Oxford OX1 3QD, UK

²Departments of Radiology and Biomedical Engineering, University of Iowa, Iowa City, IA 52242, USA

³Auckland Bioengineering Institute, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand

Abstract

The functional significance of differences in pulmonary vascular branching and diameter asymmetry between the human and quadruped lung has not previously been addressed. To evaluate the contribution of branching asymmetry to observable species differences in blood flow gradients, computed distributions of blood flow were compared in structure-based models of the human and ovine pulmonary arteries. The models were derived using a combination of computed tomography and a volume-filling algorithm. Pressure, flow, and deformed vessel diameter were calculated in both species models using equations representing conservation of mass and momentum, and a pressure–diameter relationship. The major difference between the human and ovine results was the presence of a large region of “zone 4” flow and higher mean flows in the central region of the ovine lung compared to that in the human. Heterogeneity in tissue perfusion and the contribution of gravity were similar in both species models; however, the gravitationally directed gradients of perfusion in the human and ovine models were different and each consistent with human and quadruped measurements, respectively. The results suggest that measured species differences in pulmonary perfusion gradients are largely determined by differences in branching asymmetry.

Keywords

Modeling; Pulmonary blood flow; Ovine

INTRODUCTION

Pulmonary perfusion gradients have been reported in animals and humans, measured in various postures and at different lung volumes.^{1,6,7,14,15,22,28,33,37} These measurements show differences between quadruped and human pulmonary perfusion gradients.²⁹

Understanding whether species differences in regional pulmonary perfusion exist, and the source of those differences, is important for translating outcomes from animal experiments to human physiology and pathophysiology. Vascular branching asymmetry has been proposed to be an important determinant of regional pulmonary perfusion^{4,11,19}; however, other factors could also differ between species to influence the perfusion gradient, for

example the capillary flow dynamics, tissue deformation, and vascular reactivity including hypoxic vasoconstriction.^{27,29} These mechanisms are not yet well understood, and their variation between species is not known. In contrast, species-specific branching and diameter asymmetry in the conducting airway and vascular trees have been well documented.^{24,26}

The conducting branching structures of the lung (airways, arteries, and veins) have characteristic species differences in asymmetry.^{24,26} The quadruped airway and pulmonary vascular trees tend to branch monopodially, where a parent airway or blood vessel gives rise to a major branch at a small branching angle to the parent, and a minor branch at a large branching angle. The minor branch typically has a far smaller diameter than the major branch. The human conducting trees are relatively more symmetric than in the quadruped lung. These differences in branching structure may be a consequence of the differences in lung shape between the different species. The functional consequence of this difference in structure is not clear, nor is its implication for relating low resolution perfusion gradient measurements in human²⁸ to high resolution destructive measurements in animals.¹⁵

The central question in this study is whether species differences in vascular asymmetry are sufficient to produce characteristic differences in pulmonary perfusion gradients, without the additional influence of other factors that could serve to modify the perfusion gradient. To this end, regional perfusion was calculated in structure-based computational models of the human and ovine pulmonary arterial trees. Perfusion was calculated with and without gravity acting on the blood and pleural pressure (P_{pl}) gradient, in the prone and supine postures at total lung capacity (TLC). It is important to emphasize that the models used in this study are not a complete representation of the pulmonary circulation; only the pulmonary arteries—independent of capillaries and veins—were used for the species comparisons. Here we focus solely on the contribution of species differences in arterial branching to species differences in regional perfusion of the lung. The pulmonary capillaries and veins are therefore not neglected because they are considered unimportant, but because their inclusion adds complication to the model without benefit to the central question of our study.

METHODS

Imaging Protocol

Ovine imaging studies referred to in this work were approved by the University of Iowa Animal Care and Use Committee. Imaging of the ovine lung was carried out with the animal in the prone posture with lungs held at TLC. Lung volume was controlled by a custom-built pneumotachometer-based lung volume control device. This device closed a balloon valve at the mouth under computer control at 25 cm H₂O airway pressure, assumed to represent TLC. Spiral scanning was performed using an MDCT (multi detector row X-ray computed tomography) Scanner (Marconi MX8000) with a pitch of 1.5 and collimation of 1.2, 100 mAs, 120 kV, slice thickness of 1.3 mm, slice increment of 0.65 mm, a reconstruction matrix size of 512 × 512, and a field of view of 28 cm.

Image-Based Pulmonary Arterial Model Geometries

Tawhai *et al.*³⁹ gives a detailed description of the segmentation and skeletonization algorithms used to extract airway and arterial structures, and the methodologies for construction of a 1D centerline model of the conducting airway tree from the volumetric imaging.

Segmented lung surface data and large blood vessel locations were used to derive a subject-specific model of the pulmonary arterial tree for the experimental animal. The lung surfaces and airways were segmented using Pulmonary Analysis Software Suite (PASS, the

University of Iowa). PASS²⁰ has been customized for segmentation of the human lung, including the lobes and airways; segmentation of ovine imaging is restricted to the two lungs and the airways because recognition of ovine-specific lobe geometry has not been integrated into the software. The blood vessels were segmented manually from the images, using the segmented airway tree as a guide for locating the blood vessels and distinguishing between arteries and veins. Locations of arterial branches spanning as far as the 23rd branching generation (including the main vascular conductance pathway and some side branches) were identified using this approach (a total of 1030 arteries, vessels shown in yellow in Figs. 1b and 1c).

Finite element volume meshes of the left and right lung (Fig. 1a) were geometry fitted to the lung surface data,¹⁰ and 1D finite element models of the segmented arteries were calculated to coincide with the vessel centerlines. A volume-filling method was initiated from the most terminal points of the segmented arterial tree, and used to fill the left and right lung volumes with morphometrically consistent tree structures.^{2,39} The arterial tree was generated down to the level of its accompanying terminal bronchiole. The density of acinar data points used to generate the ovine arterial model was chosen to produce a similar acinus volume to that in the human lung.¹⁸ The full ovine arterial tree is shown in Figs. 1b and 1c with front and side on views, respectively. Assuming that the terminal arterial nodes are approximately uniformly distributed within the lung volume, then the spatial resolution of calculations for terminal artery perfusion is of the order of 0.2 cm^3 , equivalent to voxels with side dimensions of approximately 5 mm.

The human arterial model used for comparisons in this study was derived by Burrowes *et al.*² This subject-specific model was created using the same method as described for the ovine lung, but generated into five lobes instead of two lungs. Burrowes *et al.*² also included supernumerary arteries, but in the current work the supernumerary arteries are assumed not to be perfused⁹ and therefore their structure is not included in either species model.

Arteries in the models were classified by generation (numbering from the top of the tree), and Horsfield and Strahler orders (numbering from the tree periphery). When two daughter branches meet the Horsfield order number is incremented by one, even if the order numbers are not the same. In the case of Strahler ordering, the order number is only increased if both convergent branches are of the same order. If two branches of different order converge the parent branch will retain the same Strahler order number as the daughter branch with the highest order number. The Strahler branching ratio (R_{BS}) can be calculated from an ordered tree as an index of tree branching asymmetry, where R_{BS} is the antilog of the absolute value of slope of the plot of log (number of branches) against order. $R_{BS} = 2$ for a symmetric tree. R_{BS} for the ovine arterial model is 3.0 ($R^2 = 1.00$), compared with 2.8 ($R^2 = 0.99$) previously reported for the human model excluding the supernumerary arteries.² The larger value for the ovine lung indicates a larger degree of branching asymmetry than in human, which is consistent with measurements of quadruped and human lungs (studied in most detail in the airway tree geometry^{24,26}). Note that for both species the branching ratio should be smaller than values calculated from cast-based measurements, because the supernumerary vessels are included in cast analyses but not in the current analysis.

Allocating Unstrained Artery Diameter

Arterial diameters in the human model are allocated using a Strahler order based diameter ratio calculated from morphometric measurements. This relationship is based on values of arterial diameters measured in excised human lungs,^{23,26} and has been used to define mean values per Strahler order in the human artery model.² The measured diameters are close to maximally expanded, so were considered as TLC dimensions. Unstrained diameters were estimated from Eq. (1):

$$\frac{D}{D_0} = \left[\left(\frac{P - P_{pl}}{G_0} \right) + 1 \right]^{\frac{1}{\beta}} \quad (1)$$

where D is artery diameter, D_0 is unstrained diameter, P is blood pressure, P_{pl} is pleural pressure, and G_0 (6.7 kPa) and β (1.0) are distensibility parameters.³⁰ To calculate unstrained diameter P_{pl} and P were set to -2.45 and 2.0 kPa, respectively. The unstrained diameter provides a reference state from which the arteries expand due to local transmural pressure.

Less detailed morphometric data are available for the ovine lung than for human. Experimental studies have shown that the quadruped airways and blood vessels have an approximately cube root relationship between the rate of increase of branching and rate of decrease of branch radius: $R_D S = \sqrt[3]{R_B S}$, where $R_D S$ is the diameter ratio (1.44 for the ovine model). $R_D S$ defines the rate of increase of vessel diameter with Strahler order. It can be calculated from morphometric data in the same way as $R_B S$ is calculated using diameter values in place of number of branches (as explained previously, see also Eq. 2 for definition). Unstrained diameters in the ovine lung were therefore defined using this relationship according to Eq. (2):

$$\log D_0(x) = (x - N) \log R_D S + \log D_N \quad (2)$$

where D_0 is the unstrained diameter for all branches of Strahler order x , and N is the highest Strahler order ($N = 10$ for the ovine model) with a branch diameter of D_N . A value of $D_N = 10.7$ mm was measured from MDCT at TLC. This was scaled to an unstrained diameter of 6.4 mm using Eq. (1).

Simulating Blood Flow

In this study, we have considered only steady-state flow distributions. We have used Poiseuille flow, which describes axisymmetric steady-state, fully developed laminar fluid flow. An additional term has been included in the governing equation to account for the effect of gravity acting on the blood (Eq. 3).

$$\Delta P = \frac{128\mu L}{\pi D^4} Q + \rho g \cos \Theta L \quad (3)$$

where Θ is the vertical angle between the gravitational vector and the vector of the vessel centerline, and g is the acceleration due to gravity [$g = 9.81 \text{ m s}^{-2}$ (1G) or 0 m s^{-2} (0G)]. Blood density (ρ) and the dynamic viscosity of blood (μ) were set to $1.05 \times 10^{-6} \text{ kg mm}^{-3}$ and $3.36 \times 10^{-3} \text{ Pa s}$,³⁶ respectively, for all simulations in this study. L is the length of a blood vessel (mm) and D is the average diameter for a blood vessel (mm).

Equation (3) is used for each arterial segment, and conservation of mass is applied at each bifurcation. Together with the definition of pressure boundary conditions at the model inlet and outlets, these equations form a linear system which is solved to predict blood flow (Q) and pressure (P) distribution. Diameters are calculated from Eq. (1), using the local P_{pl} and the solution for P . Calculation of Q and P followed by an update of D is repeated until the solution converges. The convergence criterion is that the sum of squared differences for all values of Q , P , and D is less than 10^{-8} . Flow distributions were predicted in both the ovine

and human arterial models without gravity (0G) and with gravity (1G) in the prone and supine postures.

Pressure boundary conditions in the 0G simulations were 2 and 1.65 kPa at the inlet and outlet vessels, respectively, for both models. For the 1G simulations, a gravitational gradient was applied to the terminal pressure boundary conditions where the inlet arterial location was imposed as the gravitational reference height. Therefore, the terminal pressure at the same gravitational height as the inlet artery has a value of 1.65 kPa and all others varied according to the hydrostatic pressure relationship ($\rho g \Delta \text{height}$). Inversion of the gravitational vector from supine to prone resulted in an inversion of the terminal pressure gradient with respect to height along the dorsoventral axis. Without gravity, all terminal artery pressures were equal at the boundary condition value of 1.65 kPa.

Perfusion in the models was calculated for the lung at TLC. P_{pl} at the level of the inlet pulmonary trunk was set to -2.45 kPa (-25 cm H_2O). The gravitational effect on P_{pl} was included by assuming that the lung tissue density is equal to one-quarter of the blood density, which results in an estimated P_{pl} gradient of 0.25 cm H_2O per cm of height.⁴³ It is important to note that the location of the vessels did not change during the simulations. That is, postural change was only accounted for via the direction of the P_{pl} gradient, and via the hydrostatic term in Eq. (3) which was also applied to the terminal pressure boundary conditions.

Flow Solution Analysis

The solutions at all terminal arteries were extracted from the ovine and human models. Flow was averaged within iso-gravitational (coronal) slices (average values = total flow in each slice divided by the total number of terminal vessels within the slice) 15 mm thick to mimic typical lower resolution data and to remove heterogeneity thereby more clearly demonstrating the effect of gravity.

Microsphere measurements of perfusion have often excluded regions of reduced flow in “zone 4”²⁸ from the calculation of perfusion gradients, to provide a more realistic relationship between the effect of gravity and flow.^{14,15} Linear regression was therefore applied for three different cases: (i) using all slice values, (ii) exclusion of the two most dependent slices, and (iii) with exclusion of all reduced flow values in the dependent region. These gradients are shown in Fig. 3 and listed in Table 1 along with r^2 regression values.

Fractal Analysis

The heterogeneity of pulmonary perfusion becomes increasingly apparent (that is, an increase in relative dispersion (RD) will be observed) as tissue sample volumes become progressively smaller. Fractal analysis was used to assess the relationship between RD and sample size (v) and to provide a measure of spatial heterogeneity (the fractal dimension, D_s). A fractal dimension of 1.0 indicates homogeneous flow and a value of 1.5 implies random flow.¹⁶ Experimental measurements have demonstrated that pulmonary perfusion remains fractal throughout the lung right down to the level of gas exchange.¹³ A fractal relationship can be represented by the following equation and was used to calculate D_s ¹⁶:

$$RD(v) = RD(v_{ref}) \left[\frac{v}{v_{ref}} \right]^{(1-D_s)} \quad (4)$$

where v_{ref} is a given reference volume (here we use a cubic volume of 1 cm^3), v is the sample volume made up of multiple reference volumes by combining adjacent tissue cube samples, and D_s is the spatial fractal dimension.

RESULTS

Regional Perfusion

Figure 2 illustrates the effect of gravity on the pressure distributions within the ovine arterial geometry. Pressures in the arterial model in the supine posture (Fig. 2b) were generally higher than those in the prone position. This is due to the greater hydrostatic pressure head imposed in the supine posture as a result of the relative position of the inlet pulmonary trunk: the pulmonary trunk is located closest to the ventral surface at approximately 80% of the distance from the dorso to the ventral surface. The arterial inlet point is taken as the gravitational reference height; that is the hydrostatic pressure head is zero at this location. Terminal pressures in the prone posture ranged from approximately 0.1 to 2.0 kPa compared with 1.3 to 3.2 kPa in the supine model.

The pressure gradient resulted in a similar gravitationally dependent gradient of vessel radius (not shown). When moving from nondependent to dependent tissue, the magnitude of the pleural pressure decreased but this was outweighed by the increase in blood pressure due to gravity. The terminal arteries had a relatively small variation in radius, ranging from approximately 0.35 to 0.40 mm in the prone posture and from 0.38 to 0.43 mm in the supine posture, due to the posture-related differences in pressure.

Blood flow at terminal arterial locations in the ovine and human models under the various gravitational conditions—(a) prone, (b) supine, (c) 0G—are plotted with respect to vertical height (dorsoventral axis) in Figs. 3 and 4, respectively. The posture-dependent differences in terminal artery flow result from the effect of gravity acting on both the blood and the vessel radii. For each slice, mean and median flow values plus error bars representing the sample minimum to lower quartile and upper quartile to sample maximum are included in the plots showing the large amount of heterogeneity within slices resulting from nongravitational factors. Data points with values greater than 1.5 times the interquartile range were considered to be outliers and were excluded from these simplified box and whisker style plots. Linear regression was used to define the relationship between flow (averaged 15 mm slice values) and (gravitational) height along the dorsoventral axis; gradient values are listed in Table 1.

Linear regression to the entire ovine model data set [criteria (i)] produced perfusion gradients of $-1.63\%/ \text{cm}$, $-1.12\%/ \text{cm}$, and $-0.30\%/ \text{cm}$ for supine, prone, and 0G, respectively. After removal of the two most dependent slices [criteria (ii)], gradients decreased to $-5.95\%/ \text{cm}$ and $-4.98\%/ \text{cm}$ for supine and prone results. This was not repeated for the 0G simulation because the concept of “gravitationally dependent” tissue is not applicable without gravity. Fitting to only the region of increasing flow [from approximately 50–100% height, criteria (iii)] decreased the gradients further to $-11.98\%/ \text{cm}$, for $-13.67\%/ \text{cm}$, and $-10.89\%/ \text{cm}$ supine, prone, and 0G, respectively. These gradients provided an improved straight line fit with respect to gravitationally dependent height as reflected by the increased r^2 correlation coefficients.

Gradients were also calculated for the human results using the criteria (i) and (ii) above (Fig. 4). Flow gradients calculated using all points for the human model were $-1.75\%/ \text{cm}$, $-2.55\%/ \text{cm}$, and $0.28\%/ \text{cm}$ in supine, prone, and 0G conditions, respectively. These values are consistent with (although slightly smaller than) imaging-based measurements.^{1,7,22,33} Removing the two most gravitationally dependent slice values (for prone and supine only)

gives gradients of $-3.77\%/cm$ and $-4.63\%/cm$ (see Table 1 for gradient and r^2 values). The larger gradient in the quadruped lung model (after removal of zone 4 flow data) compared with the human arterial model is consistent with previous experimental measurements.
7,15,40-42

Comparison with Quadruped Experimental Measurements

Flows from the ovine model in the supine posture were isolated at the terminal arteries and averaged within 5 mm slices for comparison with flow distributions measured in supine pig¹⁵ and dog²¹ lungs. Flow (relative to the mean) is plotted with respect to vertical gravitationally dependent height (dorsoventral axis, %) in Fig. 5. The model shows the same characteristic pattern of perfusion as the experimental measurements, with substantially reduced flow in the dorsal and ventral regions. Flows are as low as 0.1 times the mean in the ventral (upper) and dorsal (lower, gravitationally dependent) regions of the animal lungs, with a large peak flow (of almost 1.6 times the average flow rate) observed in the mid-region of the lung.

Predictions of Ovine vs. Human Perfusion

Terminal artery flows in the supine ovine and human models are compared in Fig. 6a. Solutions are averaged within 5 and 30 mm slices, and plotted with respect to normalized gravitationally dependent, vertical height (dorsoventral axis, %). Flow in the ovine arterial model increases in the dorsal direction for the upper half of the lung, and decreases markedly in the dorsal region. In comparison, flow in the supine human arterial model increases dorsally over most of the gravitational height, with a small reduction in flow (zone 4) in the most dorsal tissue. Peak terminal artery flow in the ovine lung model reaches almost 1.6 times the mean, whereas the human peak flow is ~ 1.2 times the mean and at a relatively lower height.

Path lengths in the two species models (Fig. 6b) are not proportional to the terminal flow distributions in Fig. 6a. The human model has path lengths that are relatively more symmetric about the height of the pulmonary trunk than is seen for the sheep. Path lengths in the ovine model are on average longer in the dorsal half of the lung compared to the ventral half. Path lengths at the dorsal surface are similar for both human and sheep, whereas the human path length is far longer than the ovine path length at the ventral surface.

Heterogeneity and Fractal Analysis

Terminal flows were partitioned into 1 cm^3 voxel cubes for fractal analysis. Heterogeneity calculated as the relative dispersion ($RD = \text{standard deviation}/\text{mean}$) for flow across all voxels was 0.98, 1.00, and 0.99 for the ovine model (supine, prone, and 0G, respectively) and 1.09, 1.11, and 1.09 for the human model (supine, prone, and 0G, respectively).

Fractal dimensions were calculated in the ovine and human models by plotting $\log(RD/RD_{\text{ref}})$ vs. $\log(V/V_{\text{ref}})$ and applying linear regression to find the gradient of the best fit line (Fig. 7a). D_s (the fractal dimension) is equal to 1 minus the gradient. Fractal dimensions of 1.16 and 1.30 were determined for the supine ovine and human models, respectively. These values compare well with experimentally measured fractal dimensions of 1.14 (range, 1.07–1.17) and 1.18 (range, ~ 1.1 –1.3) in the ovine⁵ and human lungs,³² respectively. Fractal dimensions in both models in the various postures and without gravity (not shown) did not vary significantly. Figure 7b shows a probability density plot of results in the ovine and human models (voxel volume = 1 cm^3). Both species demonstrate a right skewed probability density function of blood flow which is typical of measurements in animals.¹⁶

DISCUSSION

The extent to which animal and human lungs differ in terms of their vascular response to hypoxia or the elastic properties of the parenchyma is not clear. However, what is certain is that the asymmetry of pulmonary arterial branching (including the artery radii) is different between human and most other species.^{24,26} This is the single factor that is examined in this study. We have previously used an anatomically based computational model of the pulmonary arterial network to support the hypothesis that the branching structure of the human pulmonary arteries plays a role in determining regional blood distribution in the lung.^{3,4,38} Other studies have also suggested a close coupling of structure and function in pulmonary perfusion using both computational^{8,31,34} and experimental methods.^{12,15,17,40} What has not previously been studied is whether there is any systematic difference in perfusion of human and quadruped lungs due to their unique structures.

In this study, we predicted and validated regional blood flow in models of the human and ovine pulmonary arteries without considering the influence of the pulmonary capillaries and veins. We then compared predictions of blood flow within these models. We constructed a subject-specific model of the ovine pulmonary arterial tree down to the level of the accompanying terminal bronchioles, with geometric information for the 3D locations of the largest vessels and the lung shape defined from MDCT imaging. The Poiseuille and conservation of mass equations were solved in elastic vessels to predict flow distribution within the ovine arterial network without gravity (0G), and with normal gravity (1G) in the prone and supine postures. The same simulations were applied within a geometric model of the human pulmonary arterial tree. The advantage of this approach is that we can isolate the influence of a single mechanism (arterial geometry), and exclude the interdependence that would be present in a physical experiment. The predictions for human and sheep each compare well with experimental data, therefore the physical laws, physical parameters, and arterial geometry used here go some way toward explaining the regional distribution of pulmonary perfusion.

The governing equations, method for numerical solution, and all of the parameters controlling simulations in the two species models were the same, except for the branching pattern and branch diameters. This implies that any difference in flow distribution in our results between human and sheep (e.g., in Figs. 3, 4, and 6a) is due to species-specific pulmonary arterial geometry.

Model Limitations

Simplification of fluid flow equations to steady-state and 1D enables efficient predictions of perfusion within the large arterial network domain, which would not be possible using 3D time-dependent equations. However, reduction to 1D reduces the detail in the solution, for example excluding the effect of branch angles on flow partition at bifurcations. This may eventually prove to be significant, particularly for monopodial branching in the ovine lung. However, no systematic difference between human and quadruped perfusion heterogeneity has been reported experimentally. If the influence of branch angle were significant, then the quadruped lung would be expected to have consistently greater perfusion heterogeneity.

Use of the Poiseuille flow equation assumes fully developed laminar flow. Although studies have predicted that the Reynolds number may exceed 2,000 (the approximate limit for laminar flow) in the largest pulmonary arterial vessels, turbulent flow probably does not occur, and certainly does not occur in smaller vessels where the Reynolds number is much lower.²⁵ Calculation of the Reynolds numbers within the models showed the possibility of turbulent flow in only a very small percentage of the arterial system (~0.4% and ~0.07% of branches in the ovine and human models, respectively). Potential turbulence in the central

vessels may, in reality, cause larger pressure drops across these vessels; however, this will not affect the distribution of flow rates in the terminal branches of the model. The length/diameter ratio in both models is around 3.0; therefore, fully developed laminar flow may not be present throughout the trees. However, both human and ovine models will incur similar amounts of flow profile misrepresentation from this factor. We, therefore, believe that the comparison of terminal flow rates between the two models is valid. The Poiseuille flow equation describes flow of a Newtonian fluid. Shear thinning, non-Newtonian characteristics are found in blood vessels less than ~0.3 mm in diameter, whereby red blood cells alter the blood viscosity as a result of the Fahraeus and Fahraeus–Lindqvist effects.³⁶ The current model terminates with vessels of ~0.4 mm in diameter therefore these effects are neglected.

Distensibility parameters used in Eq. (1) were based on a compilation of experimental measurements across different species.³⁰ Krenz and Dawson³⁰ illustrated that even though the pulmonary arterial wall structure varies considerably from the main pulmonary artery to the precapillary terminal arteries, the distensibility is essentially constant and independent of vessel diameter and wall composition. Their study also showed relatively consistent values across six different species (including humans) therefore in this work consistent values of distensibility parameters were used throughout the arterial trees in both the human and ovine models. The allocation of consistent parameters between the human and ovine models also helps to isolate the effect of the arterial branching structure on flow distribution.

Comparison with Previous Experimental Measurements

The regional distribution of perfusion calculated in the ovine model (Fig. 5) displays a flow distribution consistent with microsphere measurements in supine pig¹⁵ and dog²¹ lungs. The microsphere measurements showed the same characteristic distribution as the model, with flow lowest near the ventral and dorsal surfaces, and maximum at about 40% height (dorsoventral). In the experimental studies, microspheres were infused during tidal breathing, then the lung was excised, inflated (at ~20–25 cm H₂O), and air dried before collating data on regional perfusion.¹⁵ The microsphere studies therefore have the most similar conditions to our model, because the modeling study also presents regional perfusion in a uniformly expanded volume (excluding tissue deformation, or the “slinky” effect²²).

Glenny *et al.*¹⁵ and Walther *et al.*⁴² observed regions of decreasing flow in the dependent tissue of animals in 1G. They therefore calculated perfusion gradients for only the portion of tissue where flow increased in the direction of gravity. The calculated gradients were –12.4%/cm, –13.8%/cm, and 12.0%/cm supine, prone, and 0G within the for pig lung¹⁵ and –14%/cm for supine sheep.⁴² Glenny *et al.*¹⁴ measured perfusion gradients in supine and prone dogs. They calculated gradients using (i) all experimental data and (ii) excluding data in the two most dependent slices. For case (i), they calculated gradients of –3.4%/cm ($r^2 = 0.37$) and –1.4%/cm ($r^2 = 0.17$) for supine and prone, respectively. For case (ii), the gradients were –5.0%/cm ($r^2 = 0.69$) supine and 2.0%/cm ($r^2 = 0.50$) prone. Removing the flow in the dependent tissue increased the r^2 correlation substantially. These values compare well with calculated gradients from the model using the same analysis as in (i) and (ii). The gradient values listed in Table 1 show the large range of potential gradients that could be calculated depending on the analysis methodology used. Other studies—particularly image-based measures which include tissue deformation—did not report such a significant decrease in flow in the dependent tissue and therefore presented perfusion gradients in animals for linear regression to the full range of measurements.^{7,40,41} Supine gradients have been calculated in dogs near functional residual capacity (FRC) using positron emission tomography (PET; –9.55%/cm⁴¹), in dogs at FRC using CT (–13.6%/cm⁷), and in sheep using microspheres at FRC then expanded to TLC for analysis (–7.8%/cm⁴¹). It should be noted that different lung volumes may also affect perfusion gradients; however, this effect has not been well quantified.

Inspection of Fig. 3 shows that zone 4—which occurs in the dependent tissue—may not be readily evident when there is marked variability in experimental measurements. The trends in regional perfusion in Fig. 3 are revealed by effectively downsampling the higher resolution data (flow per terminal artery). Figure 3 illustrates the effect of using a straight line fit—and including different subsets of data in this fit—instead of presenting the results as slice averages as in Fig. 5. The gradient for straight line fitted through all terminal artery blood flow data suggests that the perfusion gradient in the human model (Fig. 4) is larger than in the ovine model (Fig. 3), however comparison with the 15 mm slice averaged values shows that this conclusion is inaccurate. When zone 4 flows are excluded from the fit a much better correlation (demonstrated by the r^2 values) is obtained. The approach adopted by Glenny *et al.*¹⁵ and Walther *et al.*⁴² is therefore the most effective at representing the real perfusion gradient with respect to gravitational dependence.

Our perfusion gradients fitted to all data points are smaller than those measured via imaging. This is most likely a result of the exclusion of tissue deformation in the model. The exclusion of tissue deformation is also the reason for the large model zone 4. The vessel models were generated into a TLC volume where the tissue was assumed approximately uniformly expanded. The only change in geometry of the model with gravity and posture was adaptation of the radius dependent on transmural pressure. The *in vivo* lung has a gradient of increasing tissue density from the non-dependent to the dependent tissue. The imaging-based gradients should therefore be expected to be larger than the gradients in the static model. This is particularly true for gradients measured at FRC where tissue compression in the dependent region will be relatively large.

Glenny *et al.*¹⁵ reported a small (but not statistically significant) decrease in the perfusion gradient between 1G supine and 0G, with the gradient decreasing from $-10.9\%/cm$ to $-8.6\%/cm$ in one subject. This is similar to our results where removing gravity (compared with supine) moderately decreases the perfusion gradient in the ventral half of the tissue (Figs. 3b and 3c). Again we note that the model and microsphere measurements give mutually consistent predictions that would be modified if tissue deformation was included.

In both the model (after exclusion of zone 4) and the measurements, animal perfusion gradients are larger than in human (with the exception of Brudin *et al.*¹). Gradients have been measured in the supine human lung using MRI near FRC ($-3\%/cm^2$), CT imaging at full inspiration ($-2.6\%/cm^7$), and PET near FRC ($-4.4\%/cm$,³³ and $-11\%/cm^1$). The gradient calculated for the supine human model ($-1.75\%/cm$) is again smaller than the measurements, and this is likely to be for the same reason as in the ovine model. That is, including realistic tissue volume changes and incorporating tissue deformation is likely to increase the gradient.

Heterogeneity

There has been a large range of RD values reported in the literature for quadruped animals (0.68 average for prone, supine, 0G in pigs,¹⁵ 0.50 and 0.44 supine and prone in dogs,¹⁴ other values around 0.40^{1,6,40,41}) and humans (0.69 ± 0.18 —average over prone and supine postures,³⁷ 0.78 ± 0.23 in the supine posture²²). No consistent difference in RD has been reported between species. The model values are similar to but slightly higher than reported values. The source of heterogeneity in the models is the variability in resistance and connectivity of the branching paths and the presence of a range of different length pathways. Addition of capillary resistance may act to reduce heterogeneity in the model by regulating flow within microcirculatory units thereby reducing the overall RD of flow. An alternate measure of heterogeneity is to examine the fractal nature of the results. For example, Caruthers *et al.*⁵ studied the effect of increasing blood flow on the fractal dimension and RD of perfusion in ovine lungs. They concluded that the fractal nature of pulmonary blood flow

distribution was not altered by changes in overall flow, but that flow heterogeneity decreased with increasing blood flow rate. They calculated an average fractal dimension of 1.14 ± 0.09 across all of their experimental measurements. Glenney *et al.*¹⁵ calculated a similar fractal dimension of 1.09 in supine dogs; we calculate a very similar fractal dimension to these two studies of 1.16 in the ovine model and a slightly higher value of 1.30 in human which is consistent with human measurements.³² This suggests that the distribution of blood in the supine models has a realistic spatial correlation.

Differences Prone and Supine in Sheep

Gravity causes an increase in perfusion in the dependent region (even though tissue deformation is excluded in the current model) because of increased transmural pressure and vessel distension. Inversion of posture does not result in an inversion of the flow distribution. Prone gradients in the human lung are consistently steeper than supine.

Many experimental studies report significant differences in the perfusion gradient in animals between supine and prone, with prone typically reported as having a far smaller—or zero—gradient.^{40,42} Chon *et al.*⁶ measured a moderate reduction in the prone perfusion gradient in dogs, with the greatest reduction from supine to prone in the right lung. Their measurement of a supine perfusion gradient that is moderately reduced by inversion of posture is more consistent with our results. That is, we do not predict a zero prone perfusion gradient in the ovine model, with the distribution of perfusion in Fig. 3a changing only slightly when inverting gravity from supine to prone. Model predictions of only a modest change in flow gradient with posture, similar to measurements from Glenney *et al.*¹⁵ suggest that the arterial structure has a persistent effect on regional perfusion that is only slightly altered by the direction of gravity via the transmural pressure. Petersson *et al.*³⁵ have demonstrated using SPECT imaging that posture primarily alters perfusion gradients via tissue deformation (the slinky effect²²) with only minor flow alterations within the vasculature itself. We currently neglect the effect of tissue deformation and assume a linear variation in pleural pressure—of equal magnitude in the prone and supine postures. The model predictions for postural effects could change if the model were extended to include tissue deformation and movement of the chest wall and diaphragm with posture. Inclusion of these other factors would enable a study of their relative contribution to regional perfusion, whether their relative contribution changes from supine to prone, and which—if any—factors are most important in determining intersubject variability.

Ovine and Human Differences

We have previously compared simulated flow distributions in a symmetric vascular model and an anatomically based model of the human pulmonary arterial tree.³ This study showed the emergence of a reduced flow region in the most gravitationally dependent area, typical of zone 4 flow, purely as a function of the difference in arterial vascular branching structure. Here, we have compared results for only a single sheep and a single human lung. If this were an experimental study then repeating our analysis on more subjects would be essential. However, in the current work we know precisely what the differences are between the two species models, and there is no experimental error (as opposed to numerical error or errors in our assumptions). The model predicts a smaller region of zone 4 in the supine human arteries because the path lengths in the dorsal tissue are less exaggerated than in the sheep. The path lengths from the pulmonary trunk to the terminal arteries are on average longer in the human than in the sheep. In both cases, path lengths are longest in the dorsal region, however the relative increase in path length to the dorsal region compared to path lengths in the ventral region is greatest in the ovine model. The diameter profile along different paths will also contribute to the differences in flow rates predicted across paths. This means that when the ovine lung is supine there is large flow resistance in the dorsal pathways that acts

to reduce the flow in this region; the human dorsal pathways provide relatively less resistance (compared to the ventral tissue in human), therefore there is a smaller reduction in flow. It is not clear whether experimental measurements support a species difference in zone 4, because while some studies report reduced flow in the dependent tissue for animals and human,^{15,22,42} others do not specify whether this zone was present. Zone 4 may be obscured due to higher tissue density in this region, or because of heterogeneity in relatively high resolution data.

Depending on the criteria used for linear regression [i.e., (i), (ii), or (iii) in Figs. 3 and 4], a large range of gradients were determined within the ovine and human model. Comparison of the human and ovine gradients (using criteria (i) all slice data) showed that the gradients did not differ significantly for the various conditions (prone, supine, 0G). This indicates that gravity acts in a similar proportion in both models under the current assumptions. But it also highlights the detail that can be lost when fitting a straight line to flow measurement data. Despite the similarities in linear gradients, Fig. 6 does show a distinct difference in the characteristic flow distributions between human and sheep due to arterial branching structure as a function of vertical height (dorsoventral axis). The effect of gravity in both models is fairly small and if we were presenting experimental data it unlikely that it would be significant. However, the fact that this is model data—and we can effectively switch gravity on and off without affecting anything else—means that these results are not affected by experimental error or noise and therefore shows that gravity does play a role, albeit a minor one, in flow distribution. By comparing gradients predicted using criteria (iii)—exclusion of zone 4—we see a greater change in value from 0G to 1G (prone or supine) than we do using gradients containing all data [criteria (i)].

Humans and animals may have differences in parenchymal and vascular tissue properties and/or cell reactivity that would impact on the balance of mechanical forces and arterial radii.^{27,29} Our results suggest that these species differences are not necessary to predict a different regional distribution of blood flow in the ovine and human lung. This is not meant to imply that such species differences do not exist or are not important, but rather that the fluid dynamics in these different branching structures produces intrinsically different distributions of perfusion that will be further modified by other species differences. The arterial vascular structure makes a fundamental contribution to the distribution of perfusion that differs between human and quadrupeds, and other factors will serve to modify its underlying effect. This study is one such application that highlights the role of computational models in studying the different factors that contribute to functional outcomes. The ability to analyze the effect of individual factors on function means that as this model is advanced we will be able to understand more about the contribution of individual components to flow gradients under various conditions, such as tissue deformation and vasoconstriction.

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FIGURE 1.

Finite element models of the ovine left and right lungs and pulmonary arterial tree. (a) Volumetric meshes of the left and right lung geometry fitted to surface data, (b) front view, and (c) side view of the MDCT-derived arterial vessels (*yellow*) plus branches generated into the lung volume using a volume-filling method (shown in *red*) initiating from the MDCT vessel end points.

FIGURE 2.

Pressure distributions within the sheep arterial model: (a, b) with normal gravity (1G) in the prone and supine postures, respectively, (c) without gravity (0G). Solution spectrum ranges from 0.13 (*dark blue*) to 3.16 (*red*) kPa.

FIGURE 3.

Mean and median flow values per terminal artery (normalized to mean flow value across all terminal arteries) in the ovine model—averaged within 15 mm iso-gravitational slices plotted with respect to vertical (gravitationally dependent) height (dorsoventral axis, %). (a) Prone (0% = ventral, 100% = dorsal), (b) supine, and (c) 0G (0% = dorsal, 100% = ventral). Linear regression was used to characterize flow as a function of height (gradients in %/cm height) using (i) all slice data, (ii) excluding two most dependent slices, (iii) excluding all “zone 4” data (gradient values listed in Table 1). Error bars represent sample minimum to lower quartile and upper quartile to sample maximum. Outliers with values greater than 1.5 times the interquartile range are excluded.

FIGURE 4.

Mean and median flow values per terminal artery (normalized to mean flow value across all terminal arteries) in the human model—averaged within 15 mm iso-gravitational slices plotted with respect to vertical (gravitationally dependent) height (dorsoventral axis, %). (a) Prone (0% = ventral, 100% = dorsal), (b) supine, and (c) 0G (0% = dorsal, 100% = ventral). Linear regression was used to characterize flow as a function of height (gradients in %/cm height) using (i) all slice data, (ii) excluding two most dependent slices. Error bars represent sample minimum to lower quartile and upper quartile to sample maximum. Outliers with values greater than 1.5 times the interquartile range are excluded.

FIGURE 5.

Terminal artery flow (relative to the mean) in the supine ovine model compared with experimental measurements in the supine pig¹⁵ and supine dog²¹ lungs (measured via microsphere dispersion) plotted with respect to vertical height (dorsoventral axis): dorsal (0%) to ventral (100%) direction. Model flows are shown as average values within 5 mm slices.

FIGURE 6.

Comparison between human and ovine arterial models: (a) Terminal artery flows relative to the mean in the supine posture, shown as 5 and 30 mm slice averages, (b) arterial path lengths from pulmonary trunk inlet to terminal locations. Both sub figures plot results with respect to vertical height (dorsoventral axis), where 0% height corresponds to the dorsal surface and 100% to the ventral surface.

FIGURE 7.

Ovine and human model results: (a) plot to determine fractal dimensions (D_s)—normalized relative dispersion ($\log(RD/RD_{ref})$) vs. sample volume size ($\log(V/V_{ref})$) where the reference volume $V_{ref} = 1 \text{ cm}^3$; (b) probability density function of flow per voxel (1 cm^3) relative to mean flow vs. the probability of flow.

TABLE 1
Perfusion gradient (%/cm height) in the ovine and human (H) models (supine, prone, 0G)

	All data	Excluding two dependent slices	Excluding all 'zone 4' data
Supine	-1.63 ($r^2 = 0.055$) [-3.4 dog, ¹⁴ -7.8 sheep, ⁴¹ -9.55 ⁴⁰ and -13.67 FRC, dog]	-5.95 ($r^2 = 0.55$) [-5.0 dog ¹⁴]	-11.98 ($r^2 = 0.94$) [-12.4 and -10.9 pig, ¹⁵ -14.0 sheep ⁴²]
Prone	-1.12 ($r^2 = 0.027$) [-1.4 dog ¹⁴]	-4.89 ($r^2 = 0.43$) [-2.0 dog ¹⁴]	-13.67 ($r^2 = 0.98$) [-13.8 pig ¹⁵]
0G	-0.30 ($r^2 = 0.019$)	N/A	-10.89 ($r^2 = 0.89$) [-12.0 and -8.6 pig ¹⁵]
Supine (H)	-1.75 ($r^2 = 0.25$) [-3.0, ²² -4.4, ³³ -11.0 ¹ all FRC, -2.6 ~ TLC ⁷]	-3.77 ($r^2 = 0.71$)	N/A
Prone (H)	-2.55 ($r^2 = 0.40$)	-4.63 ($r^2 = 0.84$)	N/A
0G (H)	0.28 ($r^2 = 0.0083$)	N/A	N/A

Gradients calculated using mean flow values (normalized to mean flow rate) per 15 mm iso-gravitational slice. Linear regression gradient values, including r^2 values. NB: For 0G the dorsal region points were excluded in the exclusion of zone 4 data. All experimental data mentioned in the text is included in this table.