Transit time dispersion in the pulmonary arterial tree

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1Department of Mathematics, Statistics and Computer Science and 2Biomedical Engineering Department, Marquette University, Milwaukee 53201-1881; Departments of 3Physiology and 4Anesthesiology, Medical College of Wisconsin, Milwaukee 53226; and 5Research Service, Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin 53295

Clough, Anne V., Steven T. Haworth, Christopher C. Hanger, J Erri Wang, David L. Roerig, John H. Linehan, and Christopher A. Dawson. Transit time dispersion in the pulmonary arterial tree. J. Appl. Physiol. 85(2): 565–574, 1998.—Knowledge of the contributions of arterial and venous transit time dispersion to the pulmonary vascular transit time distribution is important for understanding lung function and for interpreting various kinds of data containing information about pulmonary function. Thus, to determine the dispersion of blood transit times occurring within the pulmonary arterial and venous trees, images of a bolus of contrast medium passing through the vasculature of pump-perfused dog lung lobes were acquired by using an X-ray microfocal angiography system. Time-absorbance curves from the lobar artery and vein and from selected locations within the intrapulmonary arterial tree were measured from the images. Overall dispersion within the lung lobe was determined from the difference in the first and second moments (mean transit time and variance, respectively) of the inlet arterial and outlet venous time-absorbance curves. Moments at selected locations within the arterial tree were also calculated and compared with those of the lobar artery curve. Transit times for the arterial pathways upstream from the smallest measured arteries (200-µm diameter) were less than ~20% of the total lobe mean transit time. Transit time variance among these arterial pathways (interpathway dispersion) was less than ~5% of the total variance imparted on the bolus as it passed through the lung lobe. On average, the dispersion that occurred along a given pathway (intrapathway dispersion) was negligible. Similar results were obtained for the venous tree. Taken together, the results suggest that most of the variation in transit time in the intrapulmonary vasculature occurs within the pulmonary capillary bed rather than in conducting arteries or veins.

indicator dilution; pulmonary circulation; bolus dispersion; X-ray; angiography; mean transit time; variance

THE MEAN AND DISTRIBUTION around the mean of blood transit or residence times within the pulmonary vasculature have important implications with regard to lung function (6, 18, 27). Arterial dispersion is an important determinant of the capillary input concentration curve after a pulmonary arterial injection of a tracer bolus. Indicator-dilution studies involving the injection of a tracer bolus have provided the means of determining transit-time dispersion within the whole lung from arterial inlet to venous outlet (2, 3, 23). However, dynamic imaging studies enable access to temporal information from small arteries within the lungs that can be used to estimate dispersion occurring within the arterial portion of the pulmonary vasculature alone.

Knowledge of the input curve presented to the capillaries is required in functional imaging studies designed to quantify capillary transit times, volume, and flow by using an inlet concentration and a tissue residue curve (8, 10, 21, 22, 25), obtained from X-ray angiography, fast-computed tomography, or functional magnetic resonance imaging. However, direct measurement of the inlet curve to the capillaries is not usually possible. Instead, the concentration curve is measured at an upstream location (for the lungs the right ventricle or pulmonary artery), assuming that little bolus dispersion occurs between the upstream measuring site and the entrance to the capillaries. If this assumption is violated, regional capillary mean transit time tends to be overestimated, whereas the corresponding flow is underestimated (10). Thus there is a significant question to be addressed, How much dispersion occurs within the arterial pathways between an upstream measurement site and the entrance to the capillary bed?

Knowledge of the dispersion occurring within the arterial tree is also important for multiple-indicator-dilution studies designed to determine the kinetics of metabolism or receptor binding within an organ (4, 6, 7, 14). In particular, the mathematical model estimates of kinetic parameters from pulmonary indicator-dilution data are substantively dependent on assumptions concerning bolus dispersion. The literature reveals that the whole spectrum of assumptions have been used, from the assumption that all dispersion occurs within the arterial tree so that the capillary transport function takes the form of a delta function (19), i.e., all capillaries have one common transit time, to the assumption that the arterial transport function is a delta function with most of the organ dispersion occurring within the capillary bed (17, 19). Experimental support for one of these alternatives, or a combination thereof, would be directly useful in providing increased confidence in the estimates. Thus the objective of this study was to determine how much of the bolus dispersion occurring within the pulmonary vasculature occurs within the pulmonary arterial tree.

To begin, we consider the overall dispersion of a bolus within an organ to occur via 1) intrapathway effects such as might result from velocity profiles along a given arterial or venous pathway, 2) interpathway effects such as result from heterogeneity of flows and/or lengths among parallel arterial and venous pathways, and 3) the tortuosity of the capillary bed. If, on the one hand, the transit time dispersion were due only to intrapathway dispersion, the bolus would be presented to all the capillaries at the same time but it would be more dispersed than at the arterial input. Alternatively, if
only interpathway effects contributed to the dispersion, each capillary would receive an input concentration curve having no more dispersion than the original arterial input but it would arrive at different capillaries at different times, resulting in an aggregated input to the entire capillary bed being more dispersed than the arterial input curve. Knowledge of the relative contribution of these two effects is important for interpreting indicator-dilution data (1, 2). Therefore, we have attempted to begin to describe intra- and interpathway effects and their relative contributions to dispersion within the pulmonary arterial tree. To begin with a relatively simple system, we have studied the dispersion of a bolus of radiographic contrast medium through the pulmonary arterial tree within the left lower lobe of a dog lung perfused with a steady flow. X-ray absorbance was measured at the arterial inlet, venous outlet, and various vascular locations throughout the lung lobe. Venous dispersion was studied in a similar fashion during retrograde perfusion.

EXPERIMENTAL METHODS

X-ray angiographic image data were obtained from an isolated dog lung lobe preparation \( n = 9 \); body wt, 37.1 ± 5.9 g lung lobe wt), as described previously (13). The lobar artery, vein, and bronchus of the left lower lobe were cannulated. After exsanguination and excision, the lobe was positioned between the X-ray source (Fein Focus FXE-100.20 with a 3-µm focal spot) and the detection system consisting of an image intensifier/CCD camera image train. The orientation of the lobe was with the hilum either at the top (with the lobe beneath the hilum) or at the bottom (with the lobe suspended above the hilum). The perfusion system included a pump that pumped the blood from a reservoir into the lobar artery at a flow of 480 ± 12 ml/min. The blood then drained back through the lobar vein into the reservoir. The inflow tubing included an injection loop that allowed the introduction of a 5-ml bolus of radiopaque contrast material [61% iopamidol (Isovue 300) or 60% diatrizoate meglumine (Reno 60)] into the lobar arterial inflow, without changing the pressure or flow (13). To measure venous transit times in three of the lung lobes, retrograde perfusion was performed subsequently under the same flow conditions. To examine the influence of gravity in two of the lobes, injections were made with the hilum at the top and then again with the hilum at the bottom.

Between measurements, the lobe was ventilated with a gas mixture containing \( \sim 15\% \text{O}_2-5.6\% \text{CO}_2-79.4\% \text{N}_2 \). This resulted in a \( \text{PO}_2 \) of 110 ± 10 Torr, \( \text{PCO}_2 \) of 49 ± 6 Torr, and pH of 7.32 ± 0.04 in the blood. The ventilation was stopped with a transpulmonary pressure of 4.0 ± 1.1 Torr during the passage of a bolus. The lobar artery pressure averaged 15.4 ± 3.7 Torr and the lobar venous pressure 4.8 ± 1.2 Torr.

Video images were recorded at 30 frames/s by using an S-VHS videocassette recorder as the bolus passed through the lobar vasculature. The field of view at the magnification settings used ranged from \( \sim 12 \) cm in diameter at low magnification to 1 cm at high magnification. Examples of low-magnification images acquired at different times during bolus passage through the pulmonary vascular bed are shown in Fig. 1.

The image was displayed, and intensity vs. time curves were measured by positioning regions of interest (ROIs) over individual arteries as well as adjacent regions of the microvasculature as the bolus passed through the field of view. Up to 20 ROIs could be positioned within the field of view at the same time. The arterial ROIs were generally squares, with width equal to one-half of the vessel diameter. Each corresponding microvascular ROI was positioned in a nearby region free of any visible arteries or veins and was the same size as the arterial ROI. An example of a higher magnification image indicating the positions of the arterial and microvascular ROIs is shown in Fig. 2.

The intensity curves were time averaged over three consecutive frames, corresponding to a 0.1-s time interval when using a moving average. The averaged intensity curves were then

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**Fig. 1.** Angiographic images acquired at \( t = 1.4, 2.8, \) and \( 4.9 \) s after bolus injection. Left: arterial tree is filled with contrast medium, but little has yet entered capillaries; middle: contrast medium has exited arteries and resides within the capillaries; right: venous tree filled with contrast medium after most of contrast medium has left capillaries. Regions of interest (ROIs) positioned over the inlet lobar artery (A; diam = 0.65 cm) and outlet lobar vein cannulas (V; diam = 0.63 cm) for acquisition of inlet and outlet absorbance curves.

**Fig. 2.** Angiographic image at higher magnification, indicating positions of the small-artery ROI (a; diam = 520 µm) and an adjacent microvascular ROI (m).
converted to absorbance by using the log transformation

\[
\text{Absorbance}(t) = -\ln \left( \frac{I(t) - I_{\text{max}}}{I(0) - I_{\text{max}}} \right)
\]

where \(I(t)\) is the measured X-ray intensity at time \(t\), \(I(0)\) is the average baseline intensity measured before the arrival of the bolus, and \(I_{\text{max}}\) is the intensity corresponding to maximum intensity (minimum absorbance) within the image (8). Absorbance due only to the artery of interest was obtained by subtracting the absorbance measured at a region of the microvasculature adjacent to the measured artery. This subtraction is based on the assumption that the adjacent microvascular absorbance is representative of the absorbance due to the passage of the bolus through the microvasculature in the X-ray path in front of and behind the artery and thereby contributing to the absorbance curve measured over the artery (8). Occasionally, there were small differences between the microvascular absorbance measured in the arterial ROI and the microvascular absorbance measured in the adjacent microvascular ROI. To compensate for this difference, before subtraction, the adjacent microvascular absorbance curve was scaled in magnitude to match the microvascular absorbance measured in the arterial ROI. The scale factor was chosen to minimize the sum of the squared residuals between the arterial and adjacent microvascular absorbance curves during the downslope portion (between the peak and the first subsequent zero crossing) of the adjacent microvascular curve. Figure 3A shows an example of absorbance curves acquired from an 850-µm-diameter arterial ROI and the adjacent microvascular ROI. The lower panel is the arterial absorbance curve following microvascular subtraction. Figure 4 is an example of subtracted, normalized absorbance curves acquired from the inlet lobar artery (diameter = 0.65 cm) and outlet lobar vein (diameter = 0.63 cm) of the lung lobe shown in the images of Fig. 1.

Time-absorbance curves were measured at up to 40 locations within the arterial tree of each lung lobe. The diameter of each small-artery was measured from the angiographic images by using the cylindrical-model function fit to the arterial cross-section absorbance data, as described previously (9). Each diameter value was then normalized by the inlet lobar artery diameter.

The length of each pathway from the lobar artery to the small-artery ROI was also measured from the angiographic images. Because of the orientation of the lobar arterial tree relative to the X-ray beam, many of the arterial pathways are virtually confined to a plane perpendicular to the beam or to a thin slice of lung parallel to the source and detector planes. In other words, the predominant flow direction of the pathways examined was orthogonal to the X-ray beam. These pathways were identified by almost imperceptible stereoscopic distortion when the lobe was moved across the X-ray beam. Thus length measurement errors due to pathways protruding out of the perpendicular plane were small. To verify this, 90° biplane angiograms of one lung lobe were acquired to compare pathway length measured from a single view with the corrected length derived from the 90° view for 19 representative pathways from the arterial inlet to the periphery of the lung lobe. The corrected pathway lengths were 10.2 ± 1.4% longer than their planar projections. This difference was considered small, and thus the planar projection distance was used. The pathway length measurements were normalized by dividing by the longest arterial pathway length within the lung lobe. The corrected pathway lengths were 12.2 ± 0.7 cm from arterial inlet to the margin of the lobe.

**SIGNAL ANALYSIS**

The measured time-absorbance curves from the lobar artery and vein were used to estimate the total mean transit time and dispersion of transit times through the
lungs lobe. Dispersion of each absorbance curve was characterized by its variance, i.e., second moment about its mean. The moments of the distribution of transit times through the lungs lobe were obtained from the difference between the curves measured from the lobar artery and vein. Thus the inlet lobar arterial [c_A(t)], with first moment µ_A and second moment about the mean σ^2_A, and outlet lobar venous [c_V(t)], with first moment µ_V and second moment about the mean σ^2_V absorbance curves were used to obtain the lobar mean transit time and variance about the mean (µ_lob and σ^2_lob, respectively). That is

\[ µ_lob = µ_V - µ_A = \int_0^T c_V(t) \, dt - \int_0^T c_A(t) \, dt \]

\[ \sigma^2_lob = \sigma^2_V - \sigma^2_A = \int_0^T (t - µ_V)^2 c_V(t) \, dt - \int_0^T (t - µ_A)^2 c_A(t) \, dt \]

where T denotes the first time at which the integrand (i.e., the respective concentration curve) crosses zero after having reached its peak value.

The same approach was used to characterize the passage of the bolus along an individual arterial pathway. The mean (µ_art) and variance about the mean (σ^2_art), were computed from the small-artery [c_A(t)], with first moment µ_A and second moment about the mean σ^2_A, and the inlet lobar artery, c_A(t), absorbance curves by using

\[ µ_art = µ_A - µ_A = \int_0^T t c_A(t) \, dt - \int_0^T c_A(t) \, dt \]

\[ \sigma^2_art = \sigma^2_A - \sigma^2_A = \int_0^T (t - µ_A)^2 c_A(t) \, dt - \int_0^T (t - µ_A)^2 c_A(t) \, dt \]

Finally, µ_art and σ^2_art of each pathway were divided by the respective µ_lob and σ_lob, so that µ_art and σ^2_art for a given arterial pathway could be referenced to the total lobar mean transit time and variance. These fractional arterial pathway mean transit times and variances are defined as fµ_art = µ_art/µ_lob and fσ^2_art = σ^2_art/σ^2_lob, respectively.

RESULTS

The total lung lobe mean transit time, µ_lob, and variance, σ^2_lob, determined from lobar inlet arterial and outlet venous absorbance curves such as those shown in Fig. 4, were determined by using Eq. 2 to be \( 4.28 \pm 0.15 \) s and \( 2.65 \pm 0.24 \) s^2, respectively. The resulting mean value of the lung lobe relative dispersion, \( \sqrt{σ^2_lob/µ_lob} \), was 38%, with an average vascular volume (µ_lob × lobar flow) of \( 39.1 \pm 5.9 \) (SD) ml.

Figure 5 is the compilation of fractional arterial pathway mean transit times and variances from ~10–50 measurements obtained from eight lungs. The arterial diameters ranged from 0.68 ± 0.05 cm for the inlet lobar artery (D_A) down to ~200 µm at lengths up to 11 cm from the inlet measurement site. In Fig. 5, fµ_art and fσ^2_art are plotted as a function of normalized arterial pathway length (Fig. 5A) and logarithm of normalized arterial diameter (Fig. 5B). The fµ_art values increase as a function of both increasing length from the inlet (Fig. 5A) and decreasing arterial diameter (Fig. 5B). However, even the longest measured pathway mean transit time was only ~20% of the total mean transit time of the lung lobe.

The fractional arterial pathway variances, fσ^2_art, also shown in Fig. 5, were at most ~5% of the lung lobe variance, even for the longest pathways to the smallest measured arteries. Unlike the mean transit time, the variance exhibited no significant systematic dependence on either pathway length or arterial diameter in that the slope of the regression line is not significantly different from zero for either length (Fig. 5A) or diameter (Fig. 5B). In fact, the negative fractional variance values indicate that the time-absorbance curves of the small arteries were often less dispersed than those measured at the inlet lobar artery, i.e., σ^2_art < σ^2_A in Eq. 3b.

To examine the inter- and intrapathway contributions to arterial dispersion, transit times and variances between the arterial inlet and representative small arteries were examined. Figure 6, left, shows an example of arterial ROI positions along a single pathway at progressively longer lengths from the inlet lobar artery, with the corresponding normalized arterial absorbance curves shown in Fig. 7A. The arterial mean transit times tended to increase with length along the tree, as indicated by the successively larger positive displacement of the absorbance curves, but there was little bolus dispersion along the arterial pathway. This relatively small increase in variance along the single pathway exemplified in Fig. 6 and 7A, and compilation of all the measured intrapathway variances (Fig. 5), suggests that the arterial intrapathway dispersion makes little contribution to the total dispersion occurring within the lungs lobe.

In comparison, arterial ROI positions on different pathways, both with diameter of ~500 µm but with different pathway lengths (6 and 10 cm), are shown in Fig. 6, right. The corresponding arterial absorbance curves are shown in Fig. 7B. Here again, little disper-
sion was observed along a given pathway ($f_{\text{art}}^{2} \approx 0.03$ for both small arteries). Furthermore, for these example pathways, the difference between the pathway mean transit times was small ($f_{\text{art}} = 0.13$ and 0.12 for the 6- and 10-cm pathway, respectively). This, together with Fig. 5B, suggests that there is proportionately less variation in transit times of pathways to small arteries of a given diameter than predicted by the variation in pathway lengths. Thus interpathway dispersion also appears to be small. Moreover, although pathway length and diameter are correlated, in that longer pathway lengths tend to be associated with smaller arteries, arterial diameter appears to also be a significant predictor of arterial pathway mean transit time, independent of length.

To further examine these interpretations, the interpathway dispersion determined from all of the data was examined by evaluating the variance about the mean transit times among arterial pathways of the same length (Fig. 5A) or to the same diameter (Fig. 5B). The coefficient of variation (CV), assuming both mean transit time and SD about the mean transit time regression line were proportional to length (or log diameter), was 41% for the length regression and 45% for the diameter regression.

To evaluate the relative importance of length vs. diameter in the variation of observed transit times, a multiple-linear-regression model was used, in which the fractional arterial mean transit time, $f_{\text{art}}$, is a function of both arterial pathway length and diameter

$$f_{\text{art}} = a \cdot \text{length} + b \cdot \log \left( \frac{D}{diameter} \right) + \epsilon$$  \hspace{1cm} (4)

where $D$ is the inlet lobar artery diameter. In two reduced models

$$f_{\text{art}} = a \cdot \text{length} + \epsilon$$  \hspace{1cm} (5)

$$f_{\text{art}} = b \cdot \log \left( \frac{D}{diameter} \right) + \epsilon$$  \hspace{1cm} (6)

$f_{\text{art}}$ is a function of only length (Eq. 5) or diameter (Eq. 6). A nested model f-test (5) revealed that the CV associated with either reduced model (Eqs. 5 and 6) is

Fig. 5. A: fractional arterial mean transit time ($f_{\text{art}}$; ○) and variance ($f_{\text{art}}^{2}$; ■) as a function of normalized arterial pathway length. Lines are linear regression fits through the origin: $y = [0.15 \pm 0.06 \text{ (SD)}] \times x$ (○) and $y = [0.01 \pm 0.04 \text{ (SD)}] \times x$ (■). B: $f_{\text{art}}$ (○) and $f_{\text{art}}^{2}$ (■) as a function of ratio of inlet lobar artery diameter ($D_{A}$) to small-artery diameter ($D$). Origin corresponds to the inlet lobar artery, whereas 1.6 corresponds to an ~170-µm artery. Lines are linear regression fits through the origin: $y = [0.11 \pm 0.05 \text{ (SD)}] \times x$ (○) and $y = [0.01 \pm 0.03 \text{ (SD)}] \times x$ (■).

Fig. 6. Arterial tree image indicating positions of inlet lobar artery (A) and small-artery ROIs ($a_{1}$ and $a_{2}$), from which time-absorbance curves were acquired. Left: $a_{1}$ and $a_{2}$ positioned along same arterial pathway. Right: $a_{1}$ and $a_{2}$ positioned on different arterial pathways but both have diameter ~500 µm.
This supports the hypothesis that both length and diameter influence arterial pathway mean transit time independently. Furthermore, an analysis of variance of model Eq. 4 showed that 40% of the variation in the mean transit time data was accounted for by the length and diameter dependence. Thus 60% of the variation must have been due to other factors, such as regional hemodynamic variations, gravitational effects, or measurement error.

The possible contribution of gravitational effects was evaluated in two ways. One was to include vertical height relative to the arterial inlet in the regression analysis. That is, Eq. 4 was modified as follows

\[ f_{\mu_{\text{art}}} = a \cdot \text{length} + b \cdot \log \left( \frac{D_A}{\text{diameter}} \right) + c + d \cdot \text{height} + \epsilon \]  

(7)

The nested model f-test (5) comparing model Eq. 7 with model Eq. 4, did not support the hypothesis that incorporation of vertical height significantly improves the prediction of \( f_{\mu_{\text{art}}} \). However, since all three independent variables tend to be highly correlated, we also carried out an experiment designed to break the correlation between height and length. Time-absorbance curves

were acquired from small arteries in lung lobes positioned with the hilum at the top of the lobe so that the arterial blood flow was generally in the downward direction, and then the lobe was rotated 180° so that the hilum was at the bottom and arterial flow was generally in the upward direction. The moments of the curves were computed as described above, and the vertical distance of each arterial ROI position from the inlet lobar artery ROI was measured from the images. The total vertical length of the lung lobes was 11.6 ± 0.5 cm. Vertical height was normalized by the total vertical length of the lung lobe so that the resulting height measurements ranged from zero, for the inlet lobar artery, to \( -1 \), for arteries at the bottom of the lobe when oriented upright, or \( +1 \), for arteries at the top of the lobe when rotated 180°. Fractional arterial pathway mean transit time is plotted as a function of normalized vertical height in Fig. 8. No significant difference between the absolute values of the slopes of the mean transit time regression lines for the upright vs. rotated lung position was observed. Thus gravity was not a significant factor, relative to length and diameter, in the prediction of arterial pathway transit time.
Measurement error in the fractional arterial pathway moments was evaluated to determine its contribution to the scatter around the regression lines in Fig. 5. The $f_{\mu \text{art}}$ and $f_{s \text{art}}^2$ were computed from absorbance curves acquired from selected arteries (400–4,000 µm in diameter) after six identical bolus injections. The average SD in the repeated calculation of $f_{\mu \text{art}}$ and $f_{s \text{art}}^2$ was $0.010 \pm 0.003$ and $0.006 \pm 0.003$, respectively. Also, to assess the effect of the choice of the measured background microvascular ROI on the resulting arterial absorbance curve, ROIs were positioned over a 1,200-µm artery and 12 nonoverlapping nearby microvascular regions. The SD in the repeated calculation of $f_{\mu \text{art}}$ and $f_{s \text{art}}^2$ with the use of each of the different microvascular ROI curves was $0.011$ and $0.015$, respectively.

To assess the bolus dispersion occurring within the pulmonary venous tree, absorbance curves were obtained from the lobar vein, small veins, and the lobar artery during reverse-flow conditions. Fractional venous pathway mean transit times and variances were computed from these curves by using equations analogous to Eqs. 2 and 3, except for the roles of the lobar artery and lobar vein, which were interchanged. Figure 9 shows the compilation of fractional venous pathway moments.

**DISCUSSION**

The total lobar vascular volume of $\sim 40$ ml, which is the total lobar mean transit time multiplied by the blood flow, is in the range of reported mean values [34–54 ml (11–13, 26)] for left lower lung lobes of dogs of similar size, obtained with various indicator-dilution methods. Similarly, the relative dispersion of 38% is consistent with values reported previously (28–46%).

Calculation of the arterial transport function describing the flow-weighted distribution of transit times through the arterial portion of the vasculature is not directly obtainable from the data presented here. Instead, the small-artery absorbance curves in Fig. 7 provide information pertaining to the transit time and dispersion along individual vascular pathways. To obtain the overall arterial transport function, the individual pathway data would need to be appropriately flow weighted, thus requiring additional information. Nonetheless, we can make some observations that characterize the arterial dispersion.

The data indicate that the arterial transport function is narrow (undispersed) relative to the total lung lobe transport function. Thus most of the bolus dispersion processes within the organ occur downstream from the arteries, presumably mainly in the capillaries. First, the narrowness of the small-artery absorbance curves is quantified by the small fractional variances of Fig. 5. This observation suggests that within individual arterial pathways the dispersion processes such as might be expected to result from the velocity profile in the pathway are small compared with the dispersion occurring within the entire vascular bed. Second, the small variation in mean transit time among the absorbance curves obtained from small arteries with the same diameter (Fig. 5B) and the moderately small variation in the mean transit times of the smallest measured arteries (Fig. 7B) support the concept that the amount of dispersion due to interpathway effects is also small. As both the intra- and interpathway variations appear small, it seems reasonable to infer that the arterial tree

![Fig. 9. A: fractional venous mean transit time ($f_{\mu \text{vein}}$) and variance ($f_{s \text{vein}}^2$) as a function of normalized venous pathway length. Lines are linear regression fitted through the origin: $y = [0.22 \pm 0.07(SD)] \times x (\bullet)$ and $y = [-0.03 \pm 0.06(SD)] \times x (\blacksquare)$. B: $f_{\mu \text{vein}}$ (\bullet) and $f_{s \text{vein}}^2$ (\blacksquare) as a function of logarithm of ratio of inlet lobar vein diameter ($D_A$) to small-vein diameter ($D_v$). Lines are $y = [0.15 \pm 0.05(SD)] \times x (\bullet)$ and $y = [-0.02 \pm 0.04(SD)] \times x (\blacksquare)$.](image-url)
Several aspects of the data, which might be expected to result from, for example, velocity profiles, deserve additional consideration. First, the intrapathway effects appear to be quite small, as indicated by the small fractional pathway variances of Fig. 5. Moreover, for many pathways, the absorbance curve measured at a site downstream from the inlet was even less dispersed than that measured at the inlet lobar artery. Second, the pathway mean transit time was significantly inversely correlated with arterial diameter, independent of the fact that diameter was also inversely correlated with pathway length. Thus there is a tendency for the differences in bolus arrival times in vessels of a given diameter to be smaller than those predicted by their differences in distances from the hilum.

One way to explain these two observations (the small and often negative pathway variances and the significant contribution of diameter to the variance in transit times among parallel pathways) is to visualize the arterial inlet fluid stream as comprising a bundle of a large number of streamtubes (24). Each streamtube extends to a terminal arteriole as a bundle of coherent streamlines, with little molecular diffusion of contrast medium between streamtubes on the time scale of the bolus passage. Because of the blood viscosity, the streamtubes have a range of velocities. When a bolus is introduced into the flow in the manner of these experiments, it becomes a fluid plug in each streamtube at about the same time and axial location within the vessel. However, since the velocity of each streamtube is different, each plug reaches the detection site at a different time. As the different velocity plugs pass through the cross-sectional area of the X-ray detection system, the absorbance record of the individual plugs, now spread out in space, appears as a dispersed bolus, i.e., more dispersed in time than the still-intact plug in an individual streamtube. In contrast, only a small number of the streamtubes extend through any given small artery. Being a subset of the original, each subset of plugs has only a part of the total range of velocities extant in the entire stream passing through the inlet-detection site. Consequently, the cross-sectionally sampled plugs passing through a small arterial detection site could appear more or even less dispersed than the total bolus sampled at the inlet.

In addition, the slower velocity streamtubes will tend to be located closer to the vessel wall. The branching pattern of the arterial tree is such that, at an asymmetric bifurcation, streamtubes passing through the smaller of the two branches are drawn from the streamtubes near the parent vessel wall and, therefore, tend to be weighted in favor of those having slower velocity, whereas the higher velocity streamtubes in the middle of the upstream vessels continue on to subsequent bifurcations. Thus the smaller of the two vessels at a bifurcation tends to begin receiving its portion of the bolus after the bolus front has passed the bifurcation. This results in an apparent relative retardation of distal bolus arrival times, which are inversely related to the distance from the hilum that a given-sized artery bifurcates off the dominant trunk and is a possible explanation for the diameter dependence of the transit times.

Errors in the estimates of the variance of each absorbance curve undoubtedly contribute to the range in the differences between variances measured at the inlet and a given arterial site, i.e., to the “pathway variance.” For example, the CV for measurements of the variance of absorbance curves acquired from a single vessel after repeated bolus injections ranged between 5 and 20% for different bolus injections, whereas CV for measurements of the variance of absorbance curves acquired by using different microvascular background curves was 22%. Thus it is not the negative pathway variances that are the key observation. Instead, it is that the individual pathway variances are very small, regardless of reasonable assumptions about the contribution of measurement errors to the range in pathway variances. Similarly, measurement errors in the pathway mean transit times contribute to the scatter around the regression lines of Fig. 5, A and B, although the CV in the fractional mean transit times obtained from repeated measurements as described above (CV = 16% for repeated injections and 18% for different microvascular background ROIs) was significantly smaller than the CV about the regression line (41%).

X-ray angiographic absorbance imaging of the arteries and veins is cross-sectional sampling, rather than flow-proportional sampling (16). Thus, assuming a more or less distributed velocity profile at the artery ROI, the interpretation of the moments obtained by using cross-sectional and flow-proportional sampling would not be identical (16). Nonetheless, dispersion of the bolus in the arterial tree must be small, since the shape of the absorbance curves does not change significantly when measured at the inlet lobar artery or at the sites down at the smallest measured arteries (≈200 µm). Furthermore, the shapes and parameters of the lobar inlet arterial and outlet venous absorbance curves are reasonably consistent with those measured by using flow-proportional sampling in other studies (2, 7, 13).

The diameters of the smallest arteries studied were limited by the artery-to-microvascular background contrast ratio as the bolus passed through the artery and capillaries. At high magnification, vessels as small as ~50 µm are clearly visible within the field of view. However, the small amount of contrast material arriving at these arteries, in comparison to the background absorbance signal, precludes accurate measurement of the absorbance curves in such small vessels. Injection of a larger bolus can improve the signal-to-noise ratio in the small vessels up to a point, but the trade-off is that the inlet curve is more dispersed. The amount of dispersion occurring within the organ relative to the input is then reduced, reducing the precision in the estimation of the organ and arterial pathway moments. Thus the bolus size we used was a compromise.
To put the portion of the arterial tree under observation in perspective, Fig. 5A shows that the pathways studied included pathway lengths of >90% of the longest pathways in the lobe. Figure 5B provides an estimate of the fractional vascular volume in arteries larger than the smallest of those measured, assuming equivalence of fractional volume and mean transit time. On the basis of the regression line, arteries >200 µm contained ~17% of the lobar volume. This can be compared with other dilution measurements of lobar arterial volumes, which have estimated the arterial volume to be <20% of the lobar volume under similar conditions (13). Thus ~85% of the arterial volume appears to be contained in arteries in which the diameter is >200 µm.

The ultimate objective will be to assess dispersion in the entire pulmonary arterial tree, including vessels smaller than those measured in the present study. However, given the small fraction of the total lobar or arterial transit time, as indicated above, which also reflects the small fraction of the lobar vascular volume in smaller arteries consistent with morphometric measurements (15, 20), it appears unlikely that smaller arteries could contribute substantially to the total bolus dispersion within the lungs. In other words, the small fraction of the mean transit time available would require some transit times to be negative for substantial contribution to the total variance.

One point that may need additional emphasis is that we suspect that transit times through arterial vessels smaller than those from which absorbance curves were measured made little contribution to the total transit time dispersion within the organ. However, it is possible and, perhaps, likely that these small arteries control much of the transit time dispersion within both larger and smaller vessels. One way of visualizing this is to consider the valve controlling the flow through the garden hose. Whether the flow is on high or low, the transit time through the valve is a negligible fraction of the transit time through the hose. Yet, the transit time through the hose depends not only on the length and diameter of the hose but also on the flow through the valve.

Because of the convergence of the venous tree and the fact that the bolus can emerge from the capillaries into small veins at different times, it is not possible to carry out the same analysis of venous dispersion during normal forward perfusion. Therefore, to provide some information about the contribution of the venous tree to the dispersion of lobar transit times, we carried out the analysis of venous dispersion during retrograde perfusion. As discussed by Lee (24), for low Reynolds number flow, flow reversal would be expected to have little effect on the distribution of streamtube velocities producing venous dispersion. The results of Fig. 9 suggest that the amount of bolus dispersion within the venous portion of the pulmonary vasculature accessible to these measurements may have been slightly larger than in the arteries, yet still relatively small as a fraction of the overall dispersion occurring within the lobe.

The arterial and venous trees defined by the present resolution of the methods used here each contributed <20% to the total lobar mean transit time. Their contribution to the total lobar dispersion, as measured by transit time variance, was even smaller, with most of what little dispersion there was due to interpathway, as opposed to intrapathway, dispersion. The correlation of arterial transit times with vessel diameter, independent of pathway length, suggests that the branching pattern of the arterial tree tends to mitigate the potential dispersive effects of a fully developed velocity profile.

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