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Characterizing pulmonary blood flow distribution measured using arterial spin labeling

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Abstract

The arterial spin labeling (ASL) method provides images in which, ideally, the signal intensity of each image voxel is proportional to the local perfusion. For studies of pulmonary perfusion, the relative dispersion (RD, standard deviation/mean) of the ASL signal across a lung section is used as a reliable measure of flow heterogeneity. However, the RD of the ASL signals within the lung may systematically differ from the true RD of perfusion because the ASL image also includes signals from larger vessels, which can reflect the blood volume rather than blood flow if the vessels are filled with tagged blood during the imaging time. Theoretical studies suggest that the pulmonary vasculature exhibits a lognormal distribution for blood flow and thus an appropriate measure of heterogeneity is the geometric standard deviation (GSD). To test whether the ASL signal exhibits a lognormal distribution for pulmonary blood flow, determine whether larger vessels play an important role in the distribution, and extract physiologically relevant measures of heterogeneity from the ASL signal, we quantified the ASL signal before and after an intervention (head-down tilt) in six subjects. The distribution of ASL signal was better characterized by a lognormal distribution than a normal distribution, reducing the mean squared error by 72% ($p < 0.005$). Head-down tilt significantly reduced the lognormal scale parameter ($p = 0.01$) but not the shape parameter or GSD. The RD increased post-tilt and remained significantly elevated (by 17%, $p < 0.05$). Test case results and mathematical simulations suggest that RD is more sensitive than the GSD to ASL signal from tagged blood in larger vessels, a probable explanation of the change in RD without a statistically significant change in GSD. This suggests that the GSD is a useful measure of pulmonary blood flow heterogeneity with the advantage of being less affected by the ASL signal from tagged blood in larger vessels.

Keywords

arterial spin labeling; relative dispersion; pulmonary blood flow; lognormal

INTRODUCTION

Regional pulmonary blood flow may be significantly altered by cardiovascular or pulmonary disease. Focal lung disease may cause local abnormalities in blood flow without necessarily altering the total blood flow, leading to ventilation-perfusion mismatch and inefficient gas exchange (1,2). For example, regional alveolar destruction as would occur in chronic obstructive pulmonary disease would be expected to alter the regional blood flow, although it may not necessarily alter the cardiac output. Therefore, the ability to quantitatively evaluate alterations in the distribution of pulmonary blood flow with indices of pulmonary blood flow heterogeneity may provide insight into how pulmonary diseases affect lung function.

Arterial spin labeling (ASL) is a magnetic resonance imaging (MRI) technique which can be used for imaging non-invasively the pulmonary blood flow and its inherent heterogeneity (3–6). At the time of each measurement, two images are acquired during a single breath-hold with the signal of arterial blood prepared differently for the two images, whereas the signal from stationary tissues is prepared the same for both images. The two images are subtracted, canceling the stationary signal, to give the ASL image, in which the ASL signal of an image voxel is proportional to the amount of blood delivered to that voxel (3). In our approach, we use a cardiac gated flow sensitive alternating inversion recovery with an extra radiofrequency pulse (FAIRER) method (3,5), with inversion recovery images in which the 180° inversion pulse is either slice selective or non-selective while measuring the arterial blood delivered after one systolic period. Conceptually, the ASL approach is similar to a microsphere study in that the labeled spins delivered by blood flow remain in the tissue because the time interval for delivery is too short to allow full passage through the capillary and venous branches (7).

Studies by our group and others (8–15) have used the relative dispersion (RD), also known as the coefficient of variation, of signal intensity for all voxels within the right lung of the ASL image as a reliable measure of pulmonary blood flow heterogeneity. RD is a simple, empirical measure which is calculated as the ratio of the standard deviation to the mean signal intensity. It is typically used as a measure of dispersion of normally distributed data; however, other indices of dispersion may be more appropriate for characterizing distributions which are not normally distributed.

Theoretical studies on the fractal nature of the pulmonary vasculature suggest that the distribution of flow rates in the pulmonary vasculature is lognormally distributed (8,16). In fact, it is the logarithm of flow, rather than the flow itself, which is the natural variable in tree models. This is because the bifurcating tree structure of the pulmonary vasculature has successive branching which results in multiplicative reductions in the flow (3). Mathematical modeling of the pulmonary vasculature has shown explicitly that a vascular network with asymmetric branching and random variation incorporated into each bifurcation results in a lognormal flow distribution (17). For a lognormal distribution, the geometric standard deviation (GSD) is the most appropriate measure of dispersion because of the multiplicative nature of variables which determine the distribution (18).

To date, there has been no systematic study of the distribution of the ASL signal in the lung to test whether it follows the expected lognormal distribution. In addition, although the ASL experiment is similar to a microsphere experiment, in practice there are two effects that cause the ASL experiment to depart from this ideal case and that could cause the ASL signal distribution to differ from the true blood flow distribution. The first effect is due to imperfect slice profiles (19). The spatial width of the selective inversion pulse is wider than the slice thickness of the image in order to ensure an accurate inversion across the full slice width. This creates a gap between the tagging region and the imaging slice, henceforth referred to as the inversion gap, so that the initial blood delivered to the image slice is not fully labeled. The

second is the contribution of signal from blood flow in larger vessels, where flow is sufficiently fast that some of the delivered tagged spins would have cleared by the time of the measurement. Because these large vessels are essentially filled with tagged blood, the ASL difference signal in these vessels reflects blood volume, rather than blood flow. The ASL signal from larger vessels could be removed by applying a threshold technique to remove higher signal intensity voxels; however, selection of a threshold would be somewhat arbitrary. In addition, small vessels with high flow may be eliminated by using this type of approach and thus a bias would be introduced into the data.

In this study, we examined the distribution of the quantified ASL signal and evaluated how that distribution changes with a simple intervention (head-down tilt). This intervention was chosen because it provided a test case where blood volume in the larger vessels could reasonably be expected to be altered, because of redistribution of body fluid from caudal to cephalic regions (20). Thus, this allowed comparison between lognormal and normal fits in the presence of potential large vessel changes. Our goals were to test whether the ASL signal exhibits a lognormal distribution as would be expected for pulmonary blood flow for the entire vascular tree, to determine whether ASL artifacts such as the inversion gap and larger vessels play an important role in the distribution, and extract physiologically relevant measures of heterogeneity from the ASL signal.

METHODS

Using ASL to image pulmonary blood flow

Each subject underwent MRI scanning by a Vision 1.5 T whole-body MR Scanner (Siemens Medical Systems, Erlangen, Germany). All pulse sequence parameters were kept within U.S. Food and Drug Administration guidelines for clinical magnetic resonance examinations. Each subject was oriented head-first and supine in the scanner, with a four-element phased-array torso coil positioned over the thorax. The superior end of the coil was placed directly under the chin to minimize the magnetic field drop off in the apical sections of the lung. Arterial oxygen saturation and heart rate were monitored (3150 MR Monitor; Invivo Research Inc, Orlando, FL) while the subject was in the scanner. All images were collected during a breath-hold at functional residual capacity. A short gradient-echo scout image ($TR = 8.5$ ms, $TE = 4$ ms, field of view = 450 mm, slice thickness = 8 mm, flip angle = 15° , image matrix size 128×128) was acquired to select a 15 mm-thick image slice in the coronal plane in the posterior one-third of the lung. The posterior edge of the descending aorta was located in the scout image and used as a reference point for selecting the coronal slice to be imaged. Each slice was 40×40 cm² and imaged at a resolution of 256×128 pixels, therefore voxels of approximately $1.5 \times 3 \times 15$ mm³ (~ 70 mm³) were imaged. Three pairs of images (selective and non-selective) were collected at each time point. The resulting quantitative data were averaged for each subject at each time point for statistical purposes.

ASL exploits the capability of MRI to invert the magnetization of protons (primarily in water molecules) in a spatially selective way using a combination of radiofrequency pulses and spatial magnetic field gradient pulses (3–5). By inverting the magnetization of arterial blood, these ‘tagged’ protons in blood act as an endogenous tracer. At the time of each measurement, two images are acquired during a single breath-hold of each lung slice with the signal of blood prepared differently in the two images. In the first ‘control’ image, an inversion (180°) pulse is applied to the section being imaged (a spatially selective inversion), leaving the arterial blood outside the imaged section undisturbed. To ensure an accurate inversion over the imaged slice, the spatial thickness of the 180° pulse is three times the slice thickness (3). In the second image, termed the ‘tag’ image, the magnetization of the arterial blood both inside and outside the imaged section is inverted at the beginning of the experiment with an inversion (180°) pulse applied to the whole lung (a spatially non-selective inversion). Both images are acquired after

a delay TI chosen to be approximately 80% of one R-R interval. During this delay, blood flows into each voxel of the imaged slice and there is relaxation of the magnetization. The difference or ASL signal (control-tag) measured for each voxel then reflects the amount of blood delivered during the inversion time (TI) interval, weighted with a decay factor due to the relaxation of the blood magnetization during that interval.

An ASL-FAIRER pulse sequence with a HASTE (half-Fourier acquisition single-shot turbo spin-echo) imaging scheme was used for data collection (3,5). Imaging parameters were as follows: TI = 600–800 ms, TE = 36 ms, field of view = 400 mm, slice thickness = 15 mm, image matrix size = 128×256 . The HASTE imaging sequence had an inter-echo time of 4.5 ms and 72 lines of phase encoding, resulting in a data acquisition time of 324 ms. The total scan time was approximately 8–10 s.

The ASL signal largely represents pulmonary blood flow, so a useful measure of the spatial heterogeneity of pulmonary blood flow is simply the RD of the ASL signal (15), which is independent of the absolute scaling of the signal. The absolute quantitative signal depends on the details of the image acquisition, including the size of the inversion gap, RF coil sensitivity, timing parameters and relaxation times. A derivation of the ASL signal is included in the Appendix. Based on this formulation, a calibration factor converting the ASL signal to absolute pulmonary blood flow can be estimated (using eqn (A13)) by including a reference phantom in the imaging field and making appropriate assumptions about the relaxation times (13,14). Therefore, a water phantom doped with gadolinium (Berlex Imaging, Magnevist® with 469 mg/mL gadopentetate dimeglumine) with a longitudinal relaxation time (T_1) of 1650 ms and spin-spin relaxation time (T_2) of 976 ms was included in the field of view for calibration. In order to quantify blood flow in mL/min per cm³ of lung, we assumed a T_1 of 1430 ms and T_2 of 117 ms for human pulmonary arterial (mixed venous) blood under normal *in vivo* conditions (hematocrit ~0.4 and oxygen saturation ~75%) (21). The doped water phantom was used to represent a voxel filled with fluid and thus the maximum flow that can be measured using ASL. Pulmonary blood flow in units of mL/min per cm³ of lung (averaged over a cardiac cycle) was calculated as described in the Appendix with the additional assumption that the inversion gap was zero. Analysis of the distribution of the ASL signal was then performed in terms of the calculated absolute blood flow values.

Test case protocol: 30° head-down tilt

As a test case, we applied the techniques developed in this study to evaluate how the distribution of pulmonary blood flow was altered as a result of a 30° head-down tilt for 1 h. Six subjects were included in this study, four of them had already been imaged previously for a study we recently reported regarding the effects of a 30° head-down tilt for 1 h on the heterogeneity of pulmonary blood flow (15) measured by RD. This intervention was chosen because it provided a test case where blood volume in the larger vessels could reasonably be expected to be altered, because of the redistribution of the body fluid from caudal to cephalic regions (21). Thus, this allowed a comparison between lognormal and normal fits in the presence of potential large vessel changes. Briefly, we acquired three images at the baseline while the subject was supine in the scanner; then the subject was placed in a steep (30°) head-down tilt position for 1 h outside the scanner room. At the end of the 1 h tilt period, the subject was returned to the supine position and transported via gurney to the scanner. Post-tilt images were acquired in triplicate at approximately 10, 20, 30, 40, 50, and 60 min after the tilt.

Application of the lognormal model to probability histograms of pulmonary blood flow

A histogram analysis was performed to characterize the distribution of pulmonary blood flow. The images were displayed as a histogram of quantified pulmonary blood flow in mL/min per cm³ of lung calculated from ASL signal intensities (see the Appendix). The histogram was

expressed as a probability distribution and thus was normalized to the area under the curve. The Freedman–Diaconis rule was used to calculate an appropriate bin width in order to smoothen the data (22).

As the subjects were stationary during image acquisition, negative value voxels that result from the subtraction of the two primary ASL images should have only occurred in circumstances in which noise contributes to the image (there should not be any ‘negative’ blood flow). A small number of voxels in this category provides a reliability measure of the ASL image, and we used this as an internal quality control criterion. We rejected any image that had more than 5% of voxels with an ASL signal less than zero. In order to minimize the contribution of noise to the probability histogram, we assumed that the observed net probability distribution calculated from the image data is the sum of two distributions: a lognormal distribution resulting from blood flow (only positive values) and a Gaussian distribution with a mean of zero resulting from the noise (positive and negative values). A Gaussian function with a mean fixed at zero was fit to all negative value voxels to estimate the noise distribution. Next, the fitted Gaussian distribution representing the noise (positive and negative values) was subtracted from the observed net probability distribution to give only a lognormal distribution representing blood flow.

A lognormal model distribution which included a scale and shape parameter was fit to the probability histogram data using an algorithm which minimized the sum of the squares of an objective function (defined to be the difference between the data and model predicted values) (23,24). Statistical distribution models of this type typically utilize either two or three parameters that characterize the location, scale, and shape of the distribution. The location parameter defines the location of the origin of a distribution and is used to shift a distribution in either the positive or negative direction. Assuming that noise contributions have been effectively removed using the technique described above, the location of the origin of the pulmonary blood flow distribution should be zero since there should be only positive flow values. Therefore, the location parameter was set to zero and was not incorporated into the model. The scale parameter defines where the bulk of the distribution lies, or how stretched out is the distribution. The shape parameter, as the name implies, helps to define the shape of a distribution. If a variable x is lognormally distributed with scale parameter μ and shape parameter σ ($\sigma > 0$), then $\ln(x)$ is normally distributed with mean μ and standard deviation σ . The lognormal distribution model is

$$p(x) = \frac{1}{x \cdot \sigma \sqrt{2\pi}} e^{-\frac{[\ln(x)-\mu]^2}{2\sigma^2}} \quad (1)$$

where x is the quantified blood flow value for a given voxel.

For the head-down tilt test case, probability histograms of pulmonary blood flow (mL/min per cm³ of lung) for voxels within the right lung were generated for each time point. The mean, standard deviation, and RD of the data were calculated to evaluate the global heterogeneity of perfusion. The GSD was also calculated for each time point as $GSD = \exp(\sigma)$ and compared to RD results (see the Appendix for details on the mathematical relationship between RD, σ , and GSD) (18).

Larger vessels contain higher blood flow and therefore they primarily contribute to the right end or tail of the probability histogram. In order to examine the effects of larger vessels on the measures of heterogeneity used in this study (RD and GSD), the lognormal model was fit to an example probability histogram before and after the removal of flow above the flow cutoff values of 10, 5, and 2.5 L/min per cm³ of lung.

Statistics

Data were analyzed by using the analysis of variance (ANOVA, Statview 5.0.1, SAS Institute Inc., Cary, NC) with one repeated measure (time post-tilt, seven levels: $t = 0, 70, 80, 90, 100, 110, 120$) (25)., Student–Neuman–Keuls' *post hoc* analysis of variance testing was applied to determine the overall significance and where significant differences occurred. The null-hypothesis (no effect) was rejected for $p < 0.05$, two tailed. All data are shown as mean $\pm$ standard deviation.

RESULTS

Four male subjects and two female subjects participated in the head-down tilt experiment ($n = 6$). All subjects had a normal lung function with a forced expiratory volume in one second of $107 \pm 4\%$ predicted (based on gender, age, and height) and a forced vital capacity of $109 \pm 4\%$ predicted. Figure 1 shows quantitative images of pulmonary blood flow at baseline and post-head-down tilt for a typical subject, as well as the corresponding probability histograms. The probability histogram shifted to the left as a result of the 30° head-down tilt for 1 h, and displayed a higher peak.

A probability histogram analysis of the images of pulmonary blood flow showed that after removal of the noise, a lognormal model distribution described the data well. The average mean squared error resulting from fitting a lognormal model to the data was $\sim 28\%$ of the average mean-squared error that resulted from fitting a normal distribution ($p < 0.005$). Since the probability histogram of pulmonary blood flow exhibited a long tail to the right of the distribution, we also plotted the same data on a log–log scale as a cumulative distribution, or 'rank/frequency plot', to evaluate whether it exhibited power law behavior (26). We found that although the cumulative distribution of pulmonary blood flow spanned a few orders of magnitude, it was only linear for about one decade, and therefore did not exhibit power law behavior.

Figure 2 shows how the mean, standard deviation, and RD of pulmonary blood flow changed as a result of the 1 h long 30° head-down tilt. RD increased from 0.81 ± 0.10 to a maximum value at 30 min post-head-down tilt of 0.98 ± 0.20 , and was significantly elevated for all time points measured post-head-down tilt by 17% on average (Fig. 2C, $p < 0.05$).

The average scale parameter μ and shape parameter σ resulting from fitting the lognormal model distribution to pulmonary blood flow data for all six subjects at baseline and every 10 min up to 1 h following tilt are shown in Fig. 3. After 1 h of 30° head-down tilt, the scale parameter μ decreased from 1.2 ± 0.6 to a minimum of 0.6 ± 0.4 at 30 min post-head-down tilt (Fig. 3A, $p < 0.05$) and was decreased for all time points measured post-head-down tilt by 41% on average ($p < 0.05$). The shape parameter σ and GSD (e^σ), however, were not significantly different for any of the time points post-head-down tilt when compared to baseline (Figs 3B and 3C, respectively).

The lognormal model fits generated from the average scale and shape parameters calculated from the six healthy subjects at baseline ($\mu = 1.2$, $\sigma = 0.68$) and at the time point post-head-down tilt which showed the greatest average change in RD (30 min post-head-down tilt: $\mu = 0.65$, $\sigma = 0.72$) are shown in Fig. 4, providing a descriptive view of the average changes in the ASL signal resulting from head-down tilt. Again note that the probability histogram shifted to the left and displayed a higher peak as a result of head-down tilt.

We applied a threshold to a sample data set to examine the effects of ASL signal contributions from larger vessels on heterogeneity measures such as the RD and GSD (Fig. 5). When no larger vessels were removed and the lognormal model was fit to the sample data set, we obtained

RD = 0.81 and GSD = 2.0. When vessels with an ASL signal greater than 10 mL/min per cm³ of lung were removed, RD = 0.53 and GSD = 2.0 (Fig. 5A). The corresponding image is shown on a color scale with removed voxels within the lung shown in black (Fig. 5B). As the cutoff threshold was set to a lower ASL signal value of 5 mL/min per cm³ of lung, we obtained RD = 0.45 and GSD = 2.0 (histogram shown in Fig. 5C and corresponding image in Fig. 5D). The GSD was not affected until the threshold value was set below the peak value. When all ASL signal values above 2.5 mL/min per cm³ of lung were removed, we obtained RD = 0.57 and GSD = 2.2 (histogram shown in Fig. 5E and the corresponding image shown in Fig. 5F). Note that, in the corresponding images, higher ASL signal values that were removed appear to be located in larger vessels. These data suggest that the GSD is less sensitive to the ASL signal resulting from the larger vessels than is RD.

DISCUSSION

The 'gold standard' for measuring blood flow to tissues uses microspheres, or labeled particles that are too large to fit through capillaries. Once microspheres are injected into the arteries, they are delivered to each tissue element in proportion to the local blood flow. They remain trapped in this location and are subsequently counted to quantify the blood flow. Microsphere studies are highly invasive and therefore not feasible for human studies. In addition, in the lung, post-mortem tissue processing may significantly distort the normal lung architecture (13) leading to different interpretations of data. ASL techniques provide an alternative means of measuring blood flow by manipulating the magnetization of the arterial blood before it reaches the imaging slice in a non-invasive way. In ASL, two images are acquired such that signal from static tissues is the same in both images. The difference between the two images results in an image of signal that is proportional to the amount of blood delivered during the interval TI. In the ideal case, this method is conceptually similar to a microsphere study (7). Although the tagged spins are not trapped in the tissue as in a microsphere study, the timing delay TI between tagging and imaging is too short for spins to pass through the vasculature and exit the tissue. In practice, however, there are two potential technical limitations with the ASL experiment in the lung that could cause the ASL signal to differ from the true pulmonary blood flow. The first is the required inversion gap between the arterial tagging region and the imaging slice, and the second is the contribution of signal from larger vessels (described more fully below).

Technical limitations of the ASL method

Some aspects of the experimental procedure cause the ASL signal to not be a pure measure of pulmonary blood flow. In the selective inversion image, an inversion pulse is applied to a wider band than the image slice thickness in order to avoid slice profile imperfections. This ensures that all signals in the image plane are completely inverted; however, it introduces a 'gap' just outside the image plane in which the magnetization of arterial blood is not fully relaxed in the slice selective experiment. Consequently, in the ASL difference image the first amount of blood that is delivered to the imaged section is not fully labeled because it was in the inversion gap when the inversion pulses were applied. Therefore, this delivered blood does not contribute fully to the ASL signal, resulting in an underestimation of blood flow (3).

A second factor that affects the interpretation of the ASL signal is the larger vessels. For larger vessels, the flow rate can be sufficiently high that a voxel is filled with blood during the time interval between the application of the inversion pulse and image acquisition. In this case, the ASL signal is actually measuring the blood volume instead of the flow (27). The ASL signal from a voxel will then vary between two extremes: (a) for voxels containing larger vessels the ASL signal will saturate at a maximum value corresponding to a complete filling of the vessel volume within the voxel with tagged blood; and (b) for voxels containing only smaller vessels

the ASL signal reflects signal from tagged blood that is delivered, but not cleared, during the experiment.

Test case

In this study, we investigated the distribution of the ASL signal and how it was modified by 1 h of 30° head-down tilt. Our primary finding was that the distribution of pulmonary blood flow measured using ASL can be described by a lognormal distribution with a scale parameter and a shape parameter. These results are consistent with theoretical studies on the fractal nature of the pulmonary vasculature which suggest that the distribution of flow rates in the pulmonary vasculature is lognormally distributed (8,16). Our results are also consistent with mathematical modeling studies of the pulmonary vasculature showing explicitly that a vascular network with asymmetric branching and random variation incorporated into each bifurcation results in a lognormal flow distribution (17).

We found that although RD increased as a result of head-down tilt (Fig. 2), there was no significant change in the shape parameter or the $GSD = e^{\sigma}$ (18) (Fig. 3). This is contrary to what one would expect, because for a truly lognormal distribution, RD mathematically depends only on the shape parameter (see the Appendix for details on the mathematical relationship between RD, σ , and GSD). If only the scaling parameter is changed, implying only a rescaling of the data, the mean and the standard deviation of the data should both change by the same amount and in the same direction. Therefore, the RD, calculated as the standard deviation divided by the mean, should not change. Since RD increased as a result of tilt, one would expect a change in the shape parameter not simply a change in only the scaling parameter. Although not statistically significant, the changes in the shape parameter and GSD from baseline to 30 min post-tilt were from 0.68 to 0.72 (6% increase) and 1.5 to 1.9 (27% increase), respectively. From eqn (A17) (see the Appendix), this should have produced a change in RD from baseline to 30 min post-tilt of 0.77–0.82 (6% increase), much less than what was observed (0.81–0.98, or 21% increase). This suggested that the distribution was not purely lognormal, and that the influence of larger vessels and the inversion gap may be important.

Simulation studies

In order to investigate why there was a significant change in RD but not the shape parameter or GSD, numerical simulations were performed to evaluate the effect of flow in larger vessels (Fig. 6). A model pre-head-down tilt histogram was generated with the scale ($\mu = 1.2$) and shape ($\sigma = 0.68$) parameters taken as the average for the six subjects at baseline (Fig. 4). Similarly, a model post-head-down tilt histogram was also generated with scale ($\mu = 0.65$) and shape ($\sigma = 0.72$) parameters corresponding to 30 min post-head-down tilt (Fig. 4). As expected, both RD and GSD changed by a small percentage with tilt when no modifications to the probability histogram were made to account for larger vessels (Fig. 6A).

To simulate the effect of larger vessels, we assumed that voxels dominated by larger vessels contribute a small bump to the tail of the lognormal distribution, and that this contribution does not change significantly as a result of tilt post-tilt because in both cases the larger vessels are assumed to be filled with tagged blood. With a normal distribution added at 8 mL/min per cm^3 of lung (mean = 8, SD = 1) to represent the signal from larger vessels, RD changes more than the GSD with tilt (11% vs. 6%, Fig. 6B). A larger effect is seen when a normal distribution is added at 30 mL/min per cm^3 of lung (mean = 30, SD = 1) when RD changes by 45% while the GSD changes by a modest 5% (Fig. 6C). These simulations suggest that RD is more sensitive to signal from larger vessels than is the shape parameter of the fitted lognormal distribution, and thus GSD. Our finding of a change in RD, but no corresponding change in the shape parameter of the lognormal fit, is thus consistent with the ASL signal distribution being primarily a lognormal distribution reflecting pulmonary blood flow with an added

component in the tail due to larger vessels. Because the lognormal fitting is relatively insensitive to this added component, the GSD would be expected to provide a robust characterization of the heterogeneity of the flow distribution. The raw RD, however, is more sensitive to the larger vessel component. Although this suggests that RD of the ASL signal distribution may exaggerate the true RD of the flow, it also suggests that RD remains a sensitive probe to changes in the distribution.

Test case results in the light of the ASL experimental limitations

The head-down tilt test case results are consistent with a simple conclusion: more tagged blood is delivered to the voxels pre-head-down tilt than post-head-down tilt. Qualitatively, from the images in Fig. 1 it appears that more voxels have approached a saturation condition pre-head-down tilt, consistent with how the ASL signal varies with delivery in voxels containing larger vessels. This would make the small bump added to the tail of the distribution in the simulation studies larger; however, it would not necessarily change its location. The blue blush in the images that dominates the left side of the probability histogram appears to be scaled down proportionately in each voxel as a result of head-down tilt. This is consistent with the behavior of voxels that lack larger vessels, where delivery is not near saturation. This qualitative picture is consistent with the quantitative fits of the distribution to the lognormal model, showing the primary effect of a reduction of the scale parameter.

What would cause less tagged blood to be delivered to the imaged voxels post-head-down tilt? Post-head-down tilt, stroke volume may have decreased or a larger fraction of the tagged blood may have remained in the inversion gap and was not delivered to the voxel. We consider it unlikely that there was a significant change in stroke volume as a result of head-down tilt because a previous study (28) similar to the head-down tilt protocol used in this study found that 45 min of 30° head-down tilt did not significantly alter the stroke volume. Furthermore, all images were taken supine and so any change in stroke volume that may have occurred during the head-down tilt would likely have diminished following the return to the supine posture prior to imaging. Therefore, the most likely explanation is that the volume of blood in the inversion gap was larger post-tilt. If pulmonary vascular resistance had increased at the capillary level post-head-down tilt, there would be an increased volume of blood in the larger vessels. If this is indeed the case, a larger fraction of the initial delivery of blood would be untagged, reducing the ASL signal. Further experiments are needed to identify the mechanisms responsible for these results of this particular test case.

Advantages and limitations of pulmonary blood flow quantification

The obtained data highlight the importance of quantifying the heterogeneity of pulmonary blood flow using lognormal analyses. Changes in the distribution of blood flow should still be assessed using RD and measures that do not depend on the absolute scaling. The advantage of the RD parameter is that it has been shown to be highly reliable (11). There are many interventions where one would not expect such a dramatic change in the behavior of larger vessels as we observed with head-down tilt, thus this can be thought of as a ‘worst case scenario’ for the use of RD to describe change in pulmonary blood flow heterogeneity. Nevertheless, using RD alone would not have allowed for the detection of a change in the scaling parameter. In fact, since RD changed as a result of the head-down tilt yet the shape parameter of the lognormal model did not significantly change, we questioned whether there was some systematic error in the absolute calibration. Quantification of blood flow in units of mL/min per cm³ of lung was calculated using the parameters associated with each image (see the Appendix). The scaling factors associated with quantification were not significantly different as a result of tilt; therefore it is unlikely that the data were systematically scaled differently before and after the tilt.

Images collected with a surface coil (such as those collected for the test case in this study) have a significantly higher signal to noise ratio than images collected with the body coil which is built into the scanner; however, surface coil images are corrupted by coil inhomogeneity because the sensitivity of the coils falls off rapidly with distance. The resulting surface coil image is a product of the magnetic resonance signal from the sample and the surface coil sensitivity (see the Appendix). Although we did not correct for this effect in these studies, it is reasonable to assume that the coil sensitivity profile did not significantly change as a result of head-down tilt; therefore, the relative changes in RD and the GSD were not affected.

The doped water phantom that was included in the field of view for calibration purposes had a T_1 of 1650 ms and T_2 of 976 ms. In order to quantify the blood flow in mL/min per cm³ of lung, we assumed a T_1 of 1430 ms and T_2 of 117 ms for human pulmonary arterial (mixed venous) blood under normal *in vivo* conditions (hematocrit ~0.4 and oxygen saturation ~75%) (29). Although the T_2 of the water phantom was much larger than the T_2 of pulmonary arterial blood, we corrected for this in our calculations (by using the Appendix eqn (A12)). In future studies, if the T_1 and T_2 of the doped water phantom are matched to that of pulmonary arterial blood, the equation for quantifying perfusion simplifies (see Appendix eqn (A12) and (A13)).

CONCLUSIONS

We found that the distributions of ASL signal values both pre-tilt and post-tilt were well-characterized as lognormal. The change in the distribution post-tilt was essentially a reduction of the scale parameter with no significant change in the shape parameter, but in contrast, the RD of the distribution was increased. This unexpected behavior is consistent with the presence of ASL signal from larger vessels, which reflects blood volume rather than blood flow. Simulation studies demonstrate that RD is more sensitive than the lognormal shape parameter to signal from flow in larger vessels than the GSD, likely explaining why head-down tilt resulted in a significant change in RD but not in the shape parameter or GSD. The results of this study suggest that the GSD provides useful additional information to RD about the heterogeneity of pulmonary blood flow since it is less affected by the ASL signal resulting from larger vessels.

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Abbreviations used

ASL	arterial spin labeling
FAIRER	flow sensitive alternating inversion recovery with an extra radiofrequency pulse
GSD	geometric standard deviation
HASTE	half-Fourier acquisition single-shot turbo spin-echo

RD	relative dispersion
TI	inversion time

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APPENDIX

Modeling the ASL signal and quantification of pulmonary blood flow (mL/min per cm³ of lung)

The ASL acquisition involves the subtraction of two images acquired with selective and non-selective tags (3). A doped water phantom with known T_1 and T_2 was included in the images. The volume of blood delivered to a voxel in one cardiac cycle depends on the blood flow F , which is the volume of blood delivered to a volume of tissue per unit time (the pulmonary blood flow signal we wish to quantify), the voxel volume (V_{voxel}), and the RR interval (T_{RR}):

$$V = F V_{\text{voxel}} T_{\text{RR}} \quad (\text{A1})$$

If we define V_{gap} as the volume of blood within the inversion gap that will ultimately be delivered to a voxel, then the volume of tagged blood (V_{ASL}) that was delivered to the voxel during the TI is:

$$V_{\text{ASL}} = V - V_{\text{gap}} \quad (\text{A2})$$

The measured ASL signal, ΔS , is a function of the signal that would be expected to result from a voxel completely filled with tagged blood modified by the fractional filling of the voxel we image:

$$\Delta S = \frac{V_{\text{ASL}}}{V_{\text{voxel}}} \Delta S_{\text{B}} \quad (\text{A3})$$

where ΔS_{B} is the ASL signal that would result if a voxel is 100% filled with tagged blood (3), which is the difference between the blood magnetization in the selective and non-selective images. In the selective image, the blood outside the slice is completely relaxed. In the non-selective image, the magnetization of blood outside the slice can be described by an inversion recovery (growing from $-M_{\text{oB}}$, the inverted initial longitudinal magnetization of blood, with time constant $T_{1\text{B}}$). In both images, there is some loss of transverse magnetization ($T_{2\text{B}}$ decay) which occurs during image acquisition and both are scaled by the scanner receiver gain k :

$$\begin{aligned} \Delta S_{\text{B}} &= S_{\text{B}}^{\text{S}} - S_{\text{B}}^{\text{NS}} \\ &= \left[M_{\text{oB}} - M_{\text{oB}} \left(1 - 2e^{-\frac{\text{TI}}{T_{1\text{B}}}} \right) \right] e^{-\frac{\text{TE}}{T_{2\text{B}}}} C_{\text{torso}}(x, y)k \end{aligned} \quad (\text{A4})$$

Simplification gives:

$$\Delta S_{\text{B}} = 2M_{\text{oB}} e^{-\frac{\text{TI}}{T_{1\text{B}}}} e^{-\frac{\text{TE}}{T_{2\text{B}}}} C_{\text{torso}}(x, y)k \quad (\text{A5})$$

where S_{B}^{S} and S_{B}^{NS} are the blood signals in the selective and non-selective images, respectively at the time of image acquisition, M_{oB} is the initial longitudinal magnetization of blood, TI is the time between the application of the tag and image acquisition which is set to be ~0.8 of the R-R interval, TE is the echo delay time, $T_{1\text{B}}$ and $T_{2\text{B}}$ are the T_1 and T_2 of blood respectively, and $C_{\text{torso}}(x, y)$ is the sensitivity profile of the torso coil.

The signal of the phantom in either the selective or non-selective inversion image grows from zero with time constant $T_{1\text{P}}$ with some loss of transverse magnetization ($T_{2\text{P}}$ decay) occurring during image acquisition, and is also scaled by the scanner receiver gain k :

$$S_{\text{P}} = M_{\text{oP}} \left(1 - e^{-\frac{\text{TI}}{T_{1\text{P}}}} \right) e^{-\frac{\text{TE}}{T_{2\text{P}}}} C_{\text{torso}}(x_{\text{P}}, y_{\text{P}})k \quad (\text{A6})$$

where M_{oP} is the initial longitudinal magnetization of the phantom, $T_{1\text{P}}$ and $T_{2\text{P}}$ are the T_1 and T_2 of the phantom respectively, and $C_{\text{torso}}(x_{\text{P}}, y_{\text{P}})$ is the sensitivity profile of the torso coil in the region of the phantom. The initial magnetization of blood and the phantom can be related by:

$$M_{\text{oB}} = RM_{\text{oP}} \quad (\text{A7})$$

where R is the measured ratio of the proton density of blood to the water phantom. This value has been previously reported to be 0.76 (30) and was subsequently measured by our collaborators using a proton density weighted gradient-echo imaging sequence (TE = 5 ms, TR = 1000 ms, $\alpha = 10^\circ$) (31) and found to be 0.72 (J Perthen and TT Liu, unpublished observations). For our study, we used $R = 0.72$.

Substituting into eqn (A5) for M_{oB} using A7:

$$\Delta S_B = 2RM_{OP} e^{\frac{-T_1}{T_{1B}}} e^{\frac{-T_2}{T_{2B}}} C_{\text{torso}}(x, y)k \quad (\text{A8})$$

Substituting for M_{OP} using A6:

$$\Delta S_B = 2R \left[\frac{S_P}{\left(1 - e^{\frac{-T_1}{T_{1P}}}\right) e^{\frac{-T_2}{T_{2P}}} C_{\text{torso}}(x_P, y_P)} \right] e^{\frac{-T_1}{T_{1B}}} e^{\frac{-T_2}{T_{2B}}} C_{\text{torso}}(x, y) \quad (\text{A9})$$

Using A1, A2, and A3 to solve for flow as a function of ΔS_B :

$$\begin{aligned} F &= \frac{V}{V_{\text{voxel}} T_{\text{RR}}} \\ &= \frac{V_{\text{ASL}} + V_{\text{gap}}}{V_{\text{voxel}} T_{\text{RR}}} \\ &= \frac{\Delta S}{\Delta S_B T_{\text{RR}}} + \frac{V_{\text{gap}}}{V_{\text{voxel}} T_{\text{RR}}} \end{aligned} \quad (\text{A10})$$

Substituting for ΔS_B using A9:

$$\begin{aligned} F &= \frac{\Delta S}{T_{\text{RR}}} \left[\frac{\left(1 - e^{\frac{-T_1}{T_{1P}}}\right) e^{\frac{-T_2}{T_{2P}}}}{2RS_P e^{\frac{-T_1}{T_{1B}}} e^{\frac{-T_2}{T_{2B}}}} \right] \frac{C_{\text{torso}}(x_P, y_P)}{C_{\text{torso}}(x, y)} \\ &\quad + \frac{V_{\text{gap}}}{V_{\text{voxel}} T_{\text{RR}}} \end{aligned} \quad (\text{A11})$$

When V_{gap} is small relative to V , $V_{\text{ASL}} \approx V$ and the V_{gap} term in eqn (A11) may be neglected (see eqn (A2) and (A10)):

$$F = \frac{\Delta S}{T_{\text{RR}}} \left[\frac{\left(1 - e^{\frac{-T_1}{T_{1P}}}\right) e^{\frac{-T_2}{T_{2P}}}}{2RS_P e^{\frac{-T_1}{T_{1B}}} e^{\frac{-T_2}{T_{2B}}}} \right] \frac{C_{\text{torso}}(x_P, y_P)}{C_{\text{torso}}(x, y)} \quad (\text{A12})$$

If the phantom is doped such that its T_1 and T_2 equal that of blood, or $T_{1P} \approx T_{1B} = T_1$ and $T_{2P} \approx T_{2B} = T_2$, then

$$F = \frac{\Delta S}{S_P} \left(\frac{e^{\frac{T_1}{T_1}} - 1}{2RT_{\text{RR}}} \right) \frac{C_{\text{torso}}(x_P, y_P)}{C_{\text{torso}}(x, y)} \quad (\text{A13})$$

Thus, flow in units of mL/min per cm^3 of lung (averaged over a cardiac cycle) can be measured from the subtracted ASL signal corrected to the signal resulting from the phantom in either the selective inversion or non-selective inversion images. For this study, we did not calculate the ratio of the coil sensitivity profiles in the region of the phantom and lung, or $C_{\text{torso}}(x_P, y_P)/C_{\text{torso}}(x, y)$. While we did not correct for this coil inhomogeneity effect, it is reasonable to

assume that the coil sensitivity profile did not significantly change as a result of head-down tilt; therefore, it is expected that the relative changes in the flow distribution would not be affected.

Relationship between RD, the lognormal shape parameter, and the GSD

The RD can be expressed mathematically as a function of the shape parameter or GSD. For a lognormal distribution, the mean μ_L and standard deviation σ_L of the distribution can be expressed as

$$\mu_L = e^{\mu + \frac{\sigma^2}{2}} \quad (\text{A14})$$

and

$$\sigma_L = \left[(e^{\sigma^2} - 1) e^{2\mu + \sigma^2} \right]^{\frac{1}{2}} \quad (\text{A15})$$

where μ and σ are the scale and shape parameter of the lognormal distribution, respectively. The RD of the lognormal distribution is

$$RD_L = \frac{\sigma_L}{\mu_L} = \frac{\left[(e^{\sigma^2} - 1) e^{2\mu + \sigma^2} \right]^{\frac{1}{2}}}{e^{\mu + \frac{\sigma^2}{2}}} \quad (\text{A16})$$

Simplifying and using $GSD = \exp(\sigma)$:

$$\begin{aligned} RD_L &= (e^{\sigma^2} - 1)^{\frac{1}{2}} \\ &= \left\{ e^{[\ln(GSD)]^2} - 1 \right\}^{\frac{1}{2}} \end{aligned} \quad (\text{A17})$$

Therefore, the RD of the lognormal distribution can be expressed strictly as a function of the shape parameter or GSD.

Figure 1.

Quantitative images of pulmonary blood flow measured with ASL at baseline (A) and post-head-down tilt (B) for a typical healthy subject, as well as the corresponding probability histograms (C and D, respectively). The mean, standard deviation, and relative dispersion are shown for each histogram. Note that the probability histogram shifted to the left as a result of the 1 h 30° head-down tilt, and displayed a higher peak.

Figure 2.

Mean (A), standard deviation (B), and relative dispersion (C) of pulmonary blood flow (mL/min per cm³) at baseline and at 10 min intervals up to 1 h following a 1 h period of 30° head-down tilt (denoted by bar) for six healthy subjects. Mean pulmonary blood flow was decreased for all time points up to 1 h following tilt, while the standard deviation showed no significant change. Thus, there was a significant increase in the relative dispersion (standard deviation/mean) of pulmonary blood flow for all time points measured during the hour following tilt; *, significantly different from pre-tilt value, $p < 0.05$.

Figure 3.

Scale parameter μ (A), shape parameter σ (B), and GSD calculated from the shape parameter (C) resulting from fitting a lognormal model to probability histograms of pulmonary blood flow at baseline and at 10 min intervals up to 1 h following a 1 h period of 30° head-down tilt (denoted by bar) for six healthy subjects. Lognormal scale parameter μ decreased following a 1 h period of 30° head-down tilt, and remained lower than baseline for the 1 h following tilt, while the lognormal shape parameter σ and GSD (e^σ) showed no significant change; *, significantly different from pre-tilt value, $p < 0.05$.

Figure 4.

Lognormal model fits for probability histograms of pulmonary blood flow generated from the average scale and shape parameters calculated from the six healthy subjects pre-head-down tilt (solid line) and at 30 min post-head-down tilt (dashed line). Note that the probability histogram shifted to the left as a result of the 1 h 30° head-down tilt, and displayed a higher peak.

Figure 5.

A threshold was applied to an example data set to examine the effects of ASL signal contributions from larger vessels on heterogeneity measures such as the RD and GSD. When no voxels were removed and the lognormal model was fit to the example data set, RD = 0.81 and GSD = 2.0. Histograms and images for decreasing thresholds of 10 mL/min per cm³ (A and B, respectively), 5 mL/min per cm³ (C and D), and 2.5 mL/min per cm³ (E and F) are shown. Note that as the threshold value for removing voxels decreases, RD varies substantially while the GSD remains unaffected until the cutoff value was set to below the peak value. Note in the corresponding images, voxels with higher ASL signal that were removed appear to be

located in larger vessels. These data suggest that the GSD is less affected by the ASL signal in larger vessels than RD.

Figure 6.

Numerical simulations demonstrate that the GSD is less affected by signal from larger vessels than RD. Data for pre-head-down tilt histogram were generated using the average scale ($\mu = 1.22$) and shape ($\sigma = 0.68$) parameters for six healthy subjects at baseline. Post-head-down tilt histogram data were generated with the average scale ($\mu = 0.65$) and shape ($\sigma = 0.72$) parameters at 30 min post-head-down tilt. With no larger vessels added, RD and GSD both change by a small percentage with tilt. With a normal distribution added at 8 mL/min per cm³ of lung to represent the signal from larger vessels, RD changes more than GSD with tilt (11% vs. 6%). The greatest effect is seen when a normal distribution is added at 30 mL/min per cm³ of lung, when RD changes by 45% while GSD changes by only a modest 5%.