Effects of age on pulmonary perfusion heterogeneity measured by magnetic resonance imaging

David L. Levin,¹ Richard B. Buxton,¹ James P. Spiess,² Tatsuya Arai,² Jamal Balouch,² and Susan R. Hopkins¹,²
¹Department of Radiology and ²Division of Physiology, Department of Medicine, University of California, San Diego, La Jolla, California

Submitted 5 May 2006; accepted in final form 26 January 2007

Physiological Imaging of the Lung


Normal aging is associated with a decline in pulmonary function and efficiency of gas exchange, although the effects on the spatial distribution of pulmonary perfusion are poorly understood. We hypothesized that spatial pulmonary perfusion heterogeneity would increase with increasing age. Fifty-six healthy, nonsmoking subjects (ages 21–76 yr) underwent magnetic resonance imaging with arterial spin labeling (ASL) using a Vision 1.5-T whole body scanner (Siemens Medical Systems, Erlangen, Germany). ASL uses a magnetically tagged bolus to generate perfusion maps where signal intensity is proportional to regional pulmonary perfusion. The spatial heterogeneity of pulmonary blood flow was quantified by the relative dispersion (RD = SD/mean, a global index of heterogeneity) of signal intensity for voxels within the right lung and by the fractal dimension of pulmonary blood flow was quantified by the relative dispersion (RD = SD/mean, a global index of heterogeneity) of signal intensity for voxels within the right lung and by the fractal dimension of pulmonary vascular branching with age as being responsible for the observed increase in global spatial pulmonary perfusion heterogeneity measured by the RD.

arterial spin labeling; pulmonary function; fractal dimension; relative dispersion

PULMONARY FUNCTION IS HIGHLY variable, even among subjects of the same age, race, and body habitus (13), posing a challenge for disease detection at the earliest stage. In addition, normal aging is associated with an overall decline in pulmonary function (see Ref. 31 for a recent detailed review). For example, there are well-documented changes in chest wall compliance (14) and elastic recoil of the lung (11). Expiratory flow rates and vital capacity are reduced (32), and functional residual capacity and residual volume are increased (13), as is work of breathing (31). Resting pulmonary gas exchange is impaired in older individuals, as evidenced by an increase in the alveolar-arterial difference for oxygen (26) and a reduction in the partial pressure of oxygen (24, 42). This increase in alveolar-arterial difference for oxygen has been shown to be a result of increasing ventilation-perfusion heterogeneity, reflecting a decrease in gas-exchange efficiency with increasing age (8). Increasing age is also associated with increases in closing volume (5) and alterations in the distribution of ventilation (17, 29). An increase in the apparent diffusion coefficient of 3He is also observed, suggesting increased alveolar size, particularly in the lung apices (15). The effects of normal aging on the spatial heterogeneity of pulmonary perfusion are not well understood. In addition, because many individuals with chronic disease, such as chronic obstructive pulmonary disease, are frequently middle aged or older, it is important to define any changes associated with aging in normal subject, before probing alterations with disease using new technologies that have the ability to provide spatial data.

Arterial spin labeling (ASL) magnetic resonance imaging (MRI) techniques have been used to quantify regional perfusion in many organ systems (16, 35, 38, 40, 46). We have modified the general kinetic model originally developed for analyzing the ASL signal in the brain (46) to collect data in the lung within a single breath hold (3). This technique allows quantification of regional pulmonary perfusion using a specific MRI technique known as ASL-FAIRER (FAIRER stands for flow-sensitive alternating inversion recovery with an extra radio-frequency pulse, described below). While functional MRI techniques are more commonly used in the evaluation of perfusion in the brain (7), we have used ASL-FAIRER in the lung to identify changes in the global changes in spatial perfusion heterogeneity in response to physiological stimuli, such as acute hypoxia (30) and steep head-down tilt (28).

In this study, we used ASL-FAIRER to measure spatial perfusion heterogeneity in healthy, nonsmoking subjects who were of different ages. We hypothesized that spatial perfusion heterogeneity would increase with increasing age, consistent with the changes in ventilation and gas exchange observed with normal aging (8, 17).
METHODS

The Human Subjects Research Protection Program of the University of California San Diego approved this study, and the procedures followed conformed with this institution’s guidelines. Healthy, non-smoking subjects were recruited by advertisement, informed of the risks of the study, and signed informed consent. A clinical history was obtained, with particular reference to smoking and the cardiopulmonary system, and subjects underwent routine spirometry. Subjects were excluded if they had smoked more than 200 cigarettes (10 packs) in their lifetime; however, virtually all the subjects had never smoked. In all, 56 subjects (19 women and 37 men) participated in the study.

MRI of Pulmonary Perfusion

Overview of ASL measurement of pulmonary perfusion. ASL inverts the proton magnetization of blood by applying a radio-frequency pulse, allowing these magnetically tagged protons in blood to act as an endogenous tracer for the evaluation of blood flow. During each measurement, two images are acquired of each section with the signal of blood prepared in a different way. Then the two images are subtracted, canceling the stationary signal within each image voxel and leaving just the signal due to blood delivered to that voxel during a specified time interval (3).

The ASL-FAIRER sequence used in this study was modified in house from one previously reported (33, 35) to allow for a single subtraction (3) and acquisition of data within a single breath hold. As stated, two images are acquired. The sequence is cardiac gated such that both images are acquired during diastole (while flow is minimal), and one complete systole interval occurs during the time between the labeling of the blood and the measurement of the delivery of the tagged blood to the imaged section. In the first image, termed the “tag” image, the magnetization of the blood is inverted at the beginning of the experiment with a preparatory inversion (180°) pulse applied to the whole lung (a spatially nonselective inversion). In the second “control” image, a preparatory inversion (180°) pulse is applied to only the section being imaged (a spatially selective inversion). For each image, a spatially selective 90° pulse is applied to the imaged section immediately after the preparatory inversion pulse. The effect of these radio-frequency pulses during the preparation phase is that the static magnetization within each voxel is reduced to zero in both experiments. The blood magnetization is fully inverted before the tag image, but it is fully relaxed before the control image. After a delay (TI), encompassing one R-R interval, the image is acquired. During this delay, blood flows into each voxel of the imaged section, and there is also relaxation of the magnetization. The static magnetization relaxes identically in both experiments, so when the two images are subtracted this signal is cancelled. In the tag image, the inverted magnetization of blood has relaxed part way to equilibrium, whereas for the control image the magnetization of blood remains fully relaxed. The difference signal (control − tag) measured for each voxel then reflects the amount of blood delivered, weighted with a decay factor due to the relaxation of the blood magnetization during the interval TI. Note that with TI chosen to approximate the R-R interval, the tagged blood signal is near its null point (zero signal) when the tag image is acquired, so a characteristic feature of these images is that vessels tend to be bright on the control image and dark on the tag image. In the ASL difference image (control − tag), the signal intensity for each voxel is proportional to the amount of blood delivered during one cardiac cycle (TI), and so is proportional to the local pulmonary blood flow expressed as volume of blood per volume of lung per minute.

The imaging scheme used for the ASL-FAIRER sequence was a half-Fourier acquisition single-shot turbo spin-echo (HASTE) acquisition (33). The HASTE imaging acquisition reduces susceptibility effects caused by inhomogeneous magnetic fields (10), maximizes the intrinsically low lung signal by allowing recovery of T2 signal loss (23), and reduces artifacts caused by respiratory and cardiac motion (27). The half-Fourier acquisition provides a twofold decrease in imaging time, allowing subsecond image acquisition. The application of this sequence to measuring pulmonary perfusion has been previously described in detail (3, 28, 30).

Data collection. Subjects were imaged in the supine position using ASL-FAIRER along with a HASTE technique as described above. A phased-array torso coil was used. Imaging was performed at functional residual capacity, improving the signal-to-noise characteristics of the image by increasing the amount of tissue relative to air within the lungs (34). Following a minor amount of training, subjects were able to consistently breath hold at this level, as documented by the consistent position of the diaphragm on the nonsubtracted images. The imaging plane was a single, 15-mm-thick, coronal slice, chosen from an initial series of scout images, located within the posterior one-half of the lung in line with the posterior descending aorta. The position was chosen to avoid the heart and large central vessels. A TI of 700–800 ms was used. This was ~80% of the R–R interval and was kept constant for each subject. Additional magnetic resonance parameters were the following: echo time = 36 ms, flip angle = 30°, number of excitations = 1, image matrix = 128 × 256, and field of view = 400 mm. Thus each voxel had a fixed dimension of ~1.5 × 3 × 15 mm (~70 mm2). All sequence parameters were kept within the established Food and Drug Administration safety guidelines for routine clinical magnetic resonance examinations. Three to five perfusion-weighted image maps were obtained for each subject, and the resultant data were averaged.

Quantification of perfusion heterogeneity. MRI data were analyzed using in-house software developed in the MATLAB programming environment (The Mathworks, Natick, MA). For this study, image data from the right lung was used as a single, large, region of interest. The contour of the right lung was manually outlined on a nonsubtracted image, and this was used to define an image mask for the subtracted image. The mean signal intensity and SD were measured for all voxels within this region of interest, and the relative dispersion was calculated (19). The relative dispersion (also known as the coefficient of variation) of blood flow is defined as the SD of signal intensity divided by the mean signal. This provides a global index of spatial heterogeneity without considering the specific anatomic location of the heterogeneous flow. A second measure of perfusion heterogeneity, the fractal dimension, was calculated by calculating the relative dispersion of the image in progressively larger blocks centered on each voxel (19, 21). For blocks that fall partially outside the mask, the weights are adjusted to exclude the effect of the masked-out portions. The slope of the relationship, representing the fractal dimension, is obtained from the plot of log relative dispersion vs. log number of voxels averaged (19, 21). The fractal dimension is therefore a measure of the scale-independent perfusion heterogeneity (19) and indicative of pulmonary vascular branching structure (20). A fractal dimension of 1 represents a uniform distribution, whereas a fractal dimension of 1.5 represents a random distribution.

Data analysis. Data were first analyzed using analysis of covariance (Statview 4.1, SAS Institute, Cary, NC) to determine the effect of any potential gender differences, with age as a covariate for perfusion heterogeneity. Subjects were also grouped by 10-yr intervals (age 20–29, 30–39, 40–49, 50–59, and 60+ yr), and the data were analyzed using ANOVA (Statview 4.1, SAS Institute, Cary, NC) with one grouping variable (age, 5 levels). Where overall significance was established, post hoc testing was applied to determine where the differences occurred. Linear regression was used to relate the change in blood flow heterogeneity to age and physiological variables. Significance was accepted at P < 0.05 (2 tailed). All data shown are means (SD).

RESULTS

Descriptive data for all subjects are given in Table 1. Of the 56 subjects, spirometry was obtained on 47. All pulmonary
Function data were within normal limits as evidenced by forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) being above 80% of predicted and the FEV₁/FVC ratio being >70%. The overall quality of the MRI perfusion maps was excellent and the measurements of perfusion were highly reproducible within an individual (Fig. 1; $R = 0.95$, between images for relative dispersion, $R = 0.92$ for fractal dimension). The reliability data for some of these subjects for relative dispersion have been previously reported (30). In addition, mean signal-to-noise ratio was 29:1, indicating excellent technical quality of the images. The signal-to-noise ratio did not change with increasing age ($P = 0.21$). There was no significant difference in arterial oxygen saturation over the five age groups ($P = 0.14$), and average saturation for all subjects was 97%. However, when data from all subjects were analyzed using linear regression, there was a small, but statistically significant, negative relationship between arterial oxygen saturation and age ($R = 0.30$, $P = 0.05$; Fig. 2) in keeping with the previously reported deterioration in pulmonary gas exchange with increasing age.

**Effect of sex.** There were no significant differences between male and female subjects for heterogeneity of pulmonary blood flow as measured by the relative dispersion ($P = 0.81$), or fractal dimension ($P = 0.43$) when age was considered as a covariate. Thus data from both men and women were pooled to examine the effects of age on perfusion heterogeneity.

### Table 1. Subject descriptive characteristics

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age, yr</th>
<th>$n$</th>
<th>Height, cm</th>
<th>FVC (Liters)</th>
<th>%</th>
<th>FEV₁ (Liters)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29 male</td>
<td>23.8 (1.9)</td>
<td>6</td>
<td>170 (3)</td>
<td>4.76 (0.68)</td>
<td>94 (11)</td>
<td>3.93 (0.50)</td>
<td>93 (10)</td>
</tr>
<tr>
<td>20–29 female</td>
<td>23.8 (1.3)</td>
<td>6</td>
<td>169 (7)</td>
<td>4.99 (0.66)</td>
<td>119 (9)</td>
<td>4.24 (0.36)</td>
<td>118 (3)</td>
</tr>
<tr>
<td>Mean 20–29</td>
<td>23.8 (1.6)</td>
<td>12</td>
<td>169 (5)</td>
<td>4.86 (0.65)</td>
<td>106 (16)</td>
<td>4.10 (0.45)</td>
<td>105 (15)</td>
</tr>
<tr>
<td>30–39 male</td>
<td>32.6 (1.0)</td>
<td>8</td>
<td>181 (6)</td>
<td>5.83 (0.46)</td>
<td>105 (7)</td>
<td>4.76 (0.68)</td>
<td>104 (14)</td>
</tr>
<tr>
<td>30–39 female</td>
<td>33 (2.4)</td>
<td>4</td>
<td>168 (5)</td>
<td>4.35 (0.53)</td>
<td>111 (14)</td>
<td>3.67 (0.38)</td>
<td>111 (13)</td>
</tr>
<tr>
<td>Mean 30–39</td>
<td>32.7 (1.5)</td>
<td>12</td>
<td>177 (9)</td>
<td>5.34 (0.86)</td>
<td>107 (9)</td>
<td>4.40 (0.79)</td>
<td>107 (13)</td>
</tr>
<tr>
<td>40–49 male</td>
<td>42.8 (3.7)</td>
<td>9</td>
<td>181 (5)</td>
<td>5.82 (0.85)</td>
<td>110 (13)</td>
<td>4.58 (0.49)</td>
<td>108 (8)</td>
</tr>
<tr>
<td>40–49 female</td>
<td>44 (2.8)</td>
<td>2</td>
<td>165*</td>
<td>3.81*</td>
<td>106*</td>
<td>3.36*</td>
<td>112*</td>
</tr>
<tr>
<td>Mean 40–49</td>
<td>43.0 (3.5)</td>
<td>11</td>
<td>179 (7)</td>
<td>5.57 (1.06)</td>
<td>109 (3)</td>
<td>4.43 (0.63)</td>
<td>108 (7.6)</td>
</tr>
<tr>
<td>50–59 male</td>
<td>52.6 (3.0)</td>
<td>8</td>
<td>177 (4)</td>
<td>4.95 (0.33)</td>
<td>102 (8)</td>
<td>3.99 (0.39)</td>
<td>103 (9)</td>
</tr>
<tr>
<td>50–59 female</td>
<td>55.0 (5.7)</td>
<td>2</td>
<td>161 (2)</td>
<td>3.99 (0.29)</td>
<td>127 (8)</td>
<td>3.13 (0.12)</td>
<td>123 (1)</td>
</tr>
<tr>
<td>Mean 50–59</td>
<td>53.1 (3.4)</td>
<td>10</td>
<td>174 (8)</td>
<td>4.74 (0.52)</td>
<td>107 (4)</td>
<td>3.80 (0.51)</td>
<td>107 (12)</td>
</tr>
<tr>
<td>60+ male</td>
<td>65.1 (2.8)</td>
<td>6</td>
<td>173 (6)</td>
<td>4.25 (0.53)</td>
<td>97 (4)</td>
<td>3.20 (0.38)</td>
<td>94 (4)</td>
</tr>
<tr>
<td>60+ female</td>
<td>65.4 (6.21)</td>
<td>5</td>
<td>160 (9)</td>
<td>3.16 (0.36)</td>
<td>108 (7)</td>
<td>2.39 (0.23)</td>
<td>104 (12)</td>
</tr>
<tr>
<td>Mean 60+</td>
<td>65.2 (4.4)</td>
<td>11</td>
<td>167 (10)</td>
<td>3.78 (0.72)</td>
<td>102 (7)</td>
<td>2.86 (0.52)</td>
<td>98 (5)</td>
</tr>
<tr>
<td>Mean of all</td>
<td>42.9 (15.2)</td>
<td>56</td>
<td>174 (9)</td>
<td>3.99 (0.75)</td>
<td>105 (12)</td>
<td>4.92 (0.94)</td>
<td>106 (12)</td>
</tr>
</tbody>
</table>

Values are means (SD); $n$, no. of subjects. FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s. *Pulmonary function data available for one subject only.
Effect of age, height, body mass index, pulmonary function, and arterial oxygen saturation. The mean perfusion heterogeneity, as measured using relative dispersion, was 1.00 (SD 0.18) averaged over all subjects. It was lowest in the subjects aged 20–29 yr (0.85 (SD 0.10)) and increased significantly with increasing age (Fig. 3; 0.005) by ~0.1 per decade of age until age 50–59 yr. Using linear regression, there was a significant positive relationship between relative dispersion and age (Fig. 4; R = 0.48, P < 0.0005). Interestingly, there was also a significant positive relationship between relative dispersion and height (Fig. 5; R = 0.39, P < 0.01), and when age and height were combined in a multiple regression these two variables were highly significant (R = 0.66, P < 0.0001).

DISCUSSION

The main findings in this study are first that the spatial heterogeneity of pulmonary blood flow as measured by the relative dispersion was increased with increasing age; however, the fractal dimension statistic was not. Second, unlike some other measurements of lung function, there were no significant differences in pulmonary blood flow heterogeneity between male and female subjects when age was considered as a covariate. Third, the greater perfusion heterogeneity with increasing age as measured by the relative dispersion was not
related to pulmonary function variables measured by spirometry, or body mass index, but it was positively related to height. Finally, although highly significant statistically, age explains only 23% of the variance in pulmonary blood flow heterogeneity between subjects, and when combined with height 40%, leaving 60% of the overall variance unaccounted for.

Aging and changes in pulmonary perfusion and ventilation-perfusion inequality. Very little is known about the spatial changes in pulmonary blood flow that accompany normal aging. Holland and colleagues (29) evaluated the regional distribution of pulmonary blood flow in six male subjects between the ages of 65 and 75 yr using an intravenous injection of $^{133}$Xe dissolved in saline. They found a relative increase in blood flow to the upper lungs while the subjects were upright, compared with similar measures made in younger men. However, pulmonary arterial pressure increases with increasing age (36); thus these findings may be explained partly on the basis of increased pulmonary vascular pressure leading to increased perfusion of zone 1 in the lung (2, 45). In addition, four of the six subjects had significant smoking histories, averaging 35 pack-years, and thus the significance of these findings is uncertain.

More data are available describing the changes in ventilation-perfusion inequality associated with aging. Using various imaging techniques, ventilation-perfusion inequality has been variably reported to be increased in older subjects compared with younger ones (29, 37) or to be unchanged (25). Using the multiple inert gas technique, considered to be the gold standard for measuring ventilation-perfusion inequality, Cardus et al. (8) found an increase in ventilation-perfusion inequality of $\sim 5$–6% per decade in 64 normal subjects aged 18–71 yr, similar to the decreases found in spirometric data with increasing age (13). This increase was not related to lung volumes measured with spirometry or to other physiological variables such as height or weight of the subjects.

In our study, we found a similar increase in perfusion heterogeneity as measured by the relative dispersion, which is a global index of the degree of spatial heterogeneity that provides an overall index of spatial heterogeneity without considering the specific anatomic location of the heterogeneous flow. The increase in relative dispersion with increasing age of $\sim 5\%$ per decade of age is similar to the magnitude of the change in ventilation-perfusion heterogeneity with age (8). Also similar to the study of Cardus et al. (8), the increase in perfusion heterogeneity we observed with age was not related to lung volumes measured with spirometry. One possible explanation for this may be that spirometry measures variables related to pulmonary ventilation rather than perfusion per se. Surprisingly, we found a positive relationship between pulmonary blood flow heterogeneity and height, such that taller individuals had greater pulmonary blood flow heterogeneity, a result not found by Cardus et al. Although it is possible that this may be explained partly on the basis of lung size, this would appear unlikely because of a lack of relationship between spirometric data and perfusion heterogeneity. However, although an individual with larger lungs by spirometry would be expected to have a larger pulmonary blood volume, the scaling of the two variables with body size may not exactly correspond, and thus it may be possible that perfusion heterogeneity would correlate with measures of pulmonary blood volume or diffusing capacity, which were not measured in the present study.

In simple terms, a fractal structure is one that is composed of pieces that are similar to the structure as a whole. The pattern of blood flow in the lung has been described as fractal in nature, and the fractal dimension of pulmonary blood flow has been reported for several mammals, dogs, sheep, and horses, (9, 21, 41), ranging from 1.09 to 1.17. Our value of 1.18 (SD 0.03) for healthy normal humans is therefore very similar. Interestingly, we did not find a relationship between fractal dimension and age. The implication of this finding is that the overall anatomic vascular structure in the lung is retained with increasing age in the healthy human lung, despite the global increase in spatial heterogeneity of pulmonary blood flow.

The reason for the increase in perfusion heterogeneity with increasing age is uncertain. One possibility is that this represents an intrinsic alteration in the pulmonary vasculature with aging due to diffusing capacity for carbon monoxide (12), pulmonary capillary blood volume (22), and capillary density are known to decrease with age (6). However, the finding of the unchanged fractal dimension with age argues against the possibility of an alteration in branching structure, at least at the level of resolution of our technique. Alternatively, because closing volume increases with aging (5), this may represent local hypoxic pulmonary vasoconstriction in response to regional alveolar hypoxia. However, 100% oxygen breathing does not alter areas of low ventilation-perfusion ratio present in the lung bases in elderly subjects (25), arguing against this idea. The lack of a change in fractal dimension does not rule this possibility out because the level of resolution of our measurements is not at a level to image blood flow in very small arterioles. As mentioned earlier, pulmonary arterial pressure increases with increasing age (36). However, our findings cannot represent an effect of increased pulmonary arterial pressure causing increase perfusion to the upper lung zones for two reasons. First, the effect of increased pressure would be expected to make perfusion more uniform rather than less uniform. Second, the imaging in our study was a coronal section of the lung in a supine subject, and thus the data from the image are all in the same gravitational plane, so differences observed between subjects with age cannot reflect gravitationally based changes.

Another possibility that should be considered is that any increases in the heterogeneity of lung density with age would likely be manifest in our study as increases in perfusion heterogeneity, because our technique measures perfusion per unit volume (voxel) rather than per gram of tissue. For example, in a lung in which perfusion per gram of lung tissue was uniform, regions of high or low tissue density would appear as regions of high and low perfusion, respectively, merely because the number of capillaries within a voxel is a function any compression of that voxel. Although data from studies using both computed tomography scanning and positron emission tomography do not support any significant age-related effect on overall lung density (4, 18), the effects on heterogeneity of lung density are not well described. In addition, there is evidence that alveolar size increases with age and that this increase is not uniform across the lung (15); thus alterations lung density heterogeneity may well play a role. Because we do not have regional lung density measurements in our subjects
we cannot address the potential contribution of this mechanism to our observations.

Measurement of Perfusion Heterogeneity With ASL-FAIRER

The techniques used to evaluate pulmonary blood flow heterogeneity are an important feature of this study and have been recently described (3). MRI using ASL techniques has been widely used to determine regional blood flow in other organ systems, such as brain (7). The technique has been validated in tube-flow models (1), heart (38), brain (44), and skeletal muscle (39). There are a number of potential methods to evaluate the spatial heterogeneity of blood flow (reviewed in Ref. 19). Each coronal image generates roughly 15,000 voxels of data using this technique. A significant issue, then, is how to evaluate and express this large data set to compare among subjects. The simplest measurement of heterogeneity is relative dispersion, the SD of the image signal divided by the mean. The advantages of the relative dispersion are that it is robust and reliable (~4% variation over repeated measures as seen in Fig. 1), it is independent of changes in absolute signal intensity that might occur between subjects, and it is largely unaffected by small changes in body position or depth of inspiration. Also, because of these factors, it has the advantage that data can be compared between different imaging centers and allows the establishment of normative values for healthy subjects. The obvious disadvantage of the relative dispersion is the loss of specific anatomic information. Nonetheless, the ability to quantitatively characterize one subject as having a different heterogeneity than another has been shown to be a useful tool in previous studies using this technique (28, 30). In addition, we reported an additional measure of perfusion heterogeneity, the fractal dimension, which was unchanged with increasing age. Like relative dispersion, it is also a highly reliable measure. The nature of data in the present study differs from that previously reported in animals, since they are derived from a single coronal slice of lung and not from a three-dimensional data set. This means that lung voxels in a three-dimensional data set that would normally contribute to the calculation of the fractal dimension at a particular distance contribute to the calculation of the two-dimensional data set only if they fall within the imaging plane. However, fractal analysis of data from dog lung suggests that the heterogeneity of a single slice gives similar results to the analysis of the lung as a whole (43).

Limitations

There are some limitations to the study that should be considered. We imaged a coronal slice of the right lung that encompassed a sample of the lung field, and therefore changes in pulmonary blood flow heterogeneity we observed with increasing age could have been more or less pronounced in regions of the lung that were not assessed. Also, ASL-FAIRER provides an image map of all tagged protons move into the imaging slice during the delay between tagging and image acquisition, and thus components of both pulmonary arterial and venous blood flow are likely present, the significance of which is unclear (3). Nevertheless, this limitation applies to all of our subjects irrespective of age and thus should not affect our conclusions. Finally, we did not perform absolute quantification of pulmonary perfusion. However, because in healthy subjects the lungs receive virtually the entire cardiac output, which is readily measured using a variety of well-established techniques, the relative distribution of perfusion in the lung is the much more interesting data.

In conclusion, understanding the physiological changes that occur with healthy aging is important in the detection of early pathology, in the evaluation of disease progression, and in assessing the effects of therapy. In particular, with the development of new diagnostic techniques such as functional MRI of the lung, it is important to document any age-related changes in healthy subjects, because many patients with diseases such as chronic obstructive lung disease are elderly. If these techniques are to be used to probe pulmonary function in disease, the effects of disease need to be distinguished from the effects of normal aging. We have demonstrated an increase in a global measure of spatial pulmonary blood flow heterogeneity, the relative dispersion with aging among healthy, non-smoking subjects using ASL-FAIRER MRI and established normative data for this measure. The possibility of age related changes in lung density heterogeneity as an explanation for our findings cannot be ruled out. However, the lack of a change in the fractal dimension with aging suggests that the overall pulmonary vascular structure is retained in normal aging.

ACKNOWLEDGMENTS

We thank our subjects for enthusiastic participation. We also thank Kim Prisk and Cortney Henderson for discussions regarding the MRI ASL-FAIRER measurements of regional pulmonary blood flow.

GRANTS

This work was supported by American Heart Association Grant 054002N and National Institutes of Health Grants HL-081171 and M01RR-00827.

REFERENCES