The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung

A. Cortney Henderson,¹,³ Rui Carlos Sá,¹,³ Rebecca J. Theilmann,²,³ Richard B. Buxton,²,³ G. Kim Prisk,¹,²,³ and Susan R. Hopkins¹,²,³

¹Department of Medicine, University of California, San Diego, La Jolla, California; ²Department of Radiology, University of California, San Diego, La Jolla, California; and ³The Pulmonary Imaging Laboratory, University of California, San Diego, La Jolla, California

Submitted 21 December 2012; accepted in final form 18 April 2013

Henderson AC, Sá RC, Theilmann RJ, Buxton RB, Prisk GK, Hopkins SR. The gravitational distribution of ventilation-perfusion ratio is more uniform in prone than supine posture in the normal human lung. J Appl Physiol 115: 313–324, 2013. First published April 25, 2013; doi:10.1152/japplphysiol.01531.2012.—The gravitational gradient of intrapleural pressure is suggested to be less in prone posture than supine. Thus the gravitational distribution of ventilation is expected to be more uniform prone, potentially affecting regional ventilation-perfusion (VA/Q) ratio. Using a novel functional lung magnetic resonance imaging technique to measure regional VA/Q ratio, the gravitational gradients in proton density, ventilation, perfusion, and VA/Q ratio were measured in prone and supine posture. Data were acquired in seven healthy subjects in a single sagittal slice of the right lung at functional residual capacity. Regional specific ventilation images quantified using specific ventilation imaging and proton density images obtained using a fast gradient-echo sequence were registered and smoothed to calculate regional alveolar ventilation. Perfusion was measured using arterial spin labeling. Ventilation (ml·min⁻¹·ml⁻¹) images were combined on a voxel-by-voxel basis with smoothed perfusion (ml·min⁻¹·ml⁻¹) images to obtain regional VA/Q ratio. Data were averaged for voxels within 1-cm gravitational planes, starting from the most gravitationally dependent lung. The slope of the relationship between alveolar ventilation and vertical height was less prone than supine (−0.17 ± 0.10 ml·min⁻¹·cm⁻¹ supine, −0.040 ± 0.03 prone ml·min⁻¹·cm⁻¹, P = 0.02) as was the slope of the perfusion-height relationship (−0.14 ± 0.05 ml·min⁻¹·cm⁻¹ supine, −0.08 ± 0.09 prone ml·min⁻¹·cm⁻¹, P = 0.02). There was a significant gravitational gradient in VA/Q ratio in both postures (P < 0.05) that was less in prone (0.09 ± 0.08 cm⁻¹ supine, 0.04 ± 0.03 cm⁻¹ prone, P = 0.04). The gravitational gradients in ventilation, perfusion, and regional VA/Q ratio were greater supine than prone, suggesting an interplay between thoracic cavity configuration, airflow and vascular tree anatomy, and the effects of gravity on VA/Q matching.

Passive mechanisms include vascular branching structure and the effect of gravity on ventilation and perfusion (53). Modeling studies suggest that, because of the shape of the lungs within the thorax, the gradient of intrapleural pressures is more uniform in prone posture compared with supine (48). This predicts that the gravitational distribution of ventilation and perhaps VA/Q matching is also expected to be more uniform. This is consistent with animal studies, where prone posture was associated with a reduction in regional VA/Q heterogeneity compared with supine posture, largely because of a reduction in the gravitational gradient of ventilation (35, 50). However, results in human studies have shown inconsistent results, with some studies reporting that the gravitational gradient of ventilation in prone posture was not different from supine (36, 38, 42), thus conflicting with the animal studies. In those prior human studies, a potential confounding issue is that alveolar ventilation (VA) is not measured, but rather is inferred from measures of specific ventilation [local tidal volume-to-functional residual capacity (FRC) ratio] or the distribution of inhaled labeled particles. Since both of these measures are affected by the underlying distribution of the amount of gas resident in the alveolus, estimates of local ventilation may be affected if the gradient of intrapleural pressure changes between postures. In addition, ventilation and perfusion are not quantified in absolute terms, but expressed relative to the mean ventilation and perfusion.

In this paper, we report a new technique for measuring regional VA/Q matching. We have extensively utilized a MRI technique that allows for absolute quantification of regional pulmonary blood flow (6) using arterial spin labeling (ASL) (3, 6, 20, 24). Recently, we developed a MRI technique to measure regional specific ventilation (i.e., the local volume of delivered fresh gas divided by local gas volume at FRC) (46) using inhalation of 100% oxygen (4, 10) as a contrast agent. By combining the measurement of specific ventilation with a measure of regional proton density (23, 49), the regional VA can be calculated. This, when combined with regional measures of perfusion, provides a new method to measure the regional distribution of VA/Q. Using this new technique, we tested the hypothesis that in humans, consistent with animal studies, the spatial distribution of ventilation and regional VA/Q ratio is more uniform in prone posture than supine.

METHODS

Subjects

The Human Subjects Research Protection Program of the University of California, San Diego, approved this study. Seven healthy

1This article is the topic of an Invited Editorial by H. Thomas Robertson (44a).

Address for reprint requests and other correspondence: A. C. Henderson, Dept. of Medicine, Univ. of California, San Diego, 9500 Gilman Dr., 0623A, La Jolla, CA 92093-0623 (e-mail: achenderson@ucsd.edu).
volunteers (4 male, 3 female) participated in this study after giving informed consent. Each subject was screened using an MRI safety questionnaire and a medical history was taken. All subjects were lifelong nonsmokers, with no history of pulmonary or cardiovascular disease. Spirometry was performed in the standing position using an EasyOne spirometer (NDD Medical Technologies, Zurich, Switzerland) to characterize pulmonary function. Subject characteristics are given in Table 1.

Protocol Overview

Subjects were positioned in the scanner in either a supine or prone posture, and MRI-compatible ECG electrodes (Invivo ECG Quadrrodes) were placed on the left chest. Subjects wore a facemask (7600 series Oro-nasal Mask, Hans-Rudolph) equipped with a non-rebreathing valve (2600 series, Hans Rudolph). The expired side of the non-rebreathing valve was connected via MRI-compatible respiratory tubing to a metabolic cart in the console room (Parvomedics, Truemax 2400, Sandy, UT) to allow for measurements of metabolic and ventilatory data.

All images were collected using a 1.5-T Signa HDx TwinSpeed MRI system (General Electric Medical Systems, Milwaukee, WI). A silicone phantom was placed on the subject’s chest or back within the field of view for absolute quantification of perfusion and lung density (see below). A torso coil was then placed around the subject’s chest for image acquisition. Pulmonary blood flow and specific ventilation images for a single 15-mm sagittal slice were acquired during breath holds at FRC with the subject voluntarily respiratory gating (described below). The right lung was chosen to eliminate motion artifacts from the aorta and heart in the left hemithorax. The image slice was positioned in the midclavicular line to capture the maximum anterior-posterior diameter of the lung, and the image slice position was referenced to the spinal cord so that it could be duplicated in the other posture. After data were collected in one posture, the subject was removed from the scanner and repositioned, and then imaging was repeated in the other posture. The order of postures was balanced between subjects such that four completed the supine and three the prone posture first. The duration of imaging in each posture was ~45 min for each subject. In the prone posture, the subject’s head and neck were supported for comfort using a “U” shaped pillow to allow the facemask to be positioned over the nasopharynx, and a pillow was placed under the subjects hips. The subject’s chest and abdomen were otherwise unsupported.

Proton Density Imaging

Regional proton density was measured using a fast gradient echo sequence described in detail elsewhere (49). The sequence collects 12 images alternating between two echo times (TE) in a single 9-s breath hold. Six images (even images: 2, 4, 6, 8, 10, 12) were acquired with a TE of 1.1 ms, and six images (odd images: 1, 3, 5, 7, 9, 11) were acquired at a TE of 1.8 ms. Imaging sequence parameters were repetition time = 10 ms, flip angle = 10°, slice thickness = 15 mm, field of view = 40 cm, receiver bandwidth = 125 kHz, and a full acquisition matrix of 64 × 64. A proton density image was determined by fitting a single exponential to the last eight images for the two different TE values and back-extrapolating to determine the magnetization at time zero on a voxel-by-voxel basis (49). Subjects were trained to breath hold at the end of a normal expiration (FRC), beginning just before the images were acquired and until the imaging sequence finished.

Combined ASL-Specific Ventilation Imaging Sequence

Measurements of regional pulmonary blood flow using ASL and specific ventilation using specific ventilation imaging (SVI) (described below) were merged into a single imaging sequence to facilitate imaging of ventilation and blood flow in parallel. Subjects performed five cycles alternating between 20 breaths of room air and 20 breaths of 100% oxygen as part of specific ventilation imaging (SVI). In each block of 20 breaths, 18 inversion recovery images were acquired (for SVI), and a pair of ASL images was acquired after breaths 17 and 18 for measurement of pulmonary blood flow. For respiratory gating, subjects synchronized their breathing with the scanner and were trained to breath hold at FRC when image acquisition occurred. Because the scans generate a loud sound for each image preparation and acquisition, subjects had audible cues to guide their breathing. Subjects were given brief trials in which to practice, before data acquisition, to ensure adequate breath holds. Acquisition took place during ~1–2 s breath holds with 4–5 s in between, during which time the subject took a normal breath in and then relaxed to FRC before the next image was collected. The entire combined measurement took ~18 min to complete.

Measuring Pulmonary Blood Flow Using ASL

Regional pulmonary blood flow was assessed using two-dimenional (2D) ASL with a flow-sensitive alternating inversion recovery with an extra radio-frequency pulse imaging sequence and a half-Fourier acquisition single-shot turbo spin-echo (HASTE) data collection scheme (5, 32). This has been described in detail (5, 25) and used in a number of studies by our group (20, 25) and is only briefly described here.

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 radio-frequency pulses and spatial magnetic field gradient pulses (5, 32, 33). By inverting the magnetization of arterial blood, these “tagged” protons in blood act as an endogenous tracer. During each measurement, two images of a lung slice are acquired during consecutive breath holds 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) during diastole, leaving the arterial blood outside the imaged section undisturbed. When tipped over to create an image, the longitudinal magnetization of the arterial blood will generate a strong magnetic resonance signal. 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 nonselective inversion). Both images are subsequently acquired after a delay chosen to be ~80% of one R-R interval. During this delay, blood flows into 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 delay, or inversion time (TI) interval, weighted by a decay

Table 1. Subject descriptive data

<table>
<thead>
<tr>
<th>Description</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>29.4 ± 7.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 10</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.6 ± 11.1</td>
</tr>
<tr>
<td>FVC</td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>4.52 ± 0.99</td>
</tr>
<tr>
<td>%Predicted</td>
<td>97 ± 12</td>
</tr>
<tr>
<td>FEV1</td>
<td></td>
</tr>
<tr>
<td>Liters</td>
<td>3.61 ± 0.70</td>
</tr>
<tr>
<td>%Predicted</td>
<td>94 ± 9</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td></td>
</tr>
<tr>
<td>Ratio</td>
<td>0.80 ± 0.06</td>
</tr>
<tr>
<td>%Predicted</td>
<td>98 ± 4</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s.
factor due to the relaxation of the blood magnetization during that interval (21).

To prevent any potential confounding effect on perfusion from the hyperoxia used in the ventilation part of the combined sequence, only the images acquired during the normoxic portion of the combined sequence were used for quantification of perfusion. Imaging sequence parameters were as follows: $T1 = 550–950$ ms (based on subject’s heart rate), $TE = 21.3$ ms, field of view $= 40$ cm, slice thickness $= 15$ mm. The collected image matrix size was $256 \times 128$ (reconstructed by scanner to $256 \times 256$), giving voxels of $0.156 \times 0.156 \times 1.5$ cm$^3$, or $\sim 0.037$ cm$^3$. The HASTE imaging sequence had an inter-TE of 4.5 ms and 72 lines of phase encoding, resulting in a data acquisition time of 324 ms.

SVI

Regional specific ventilation was measured as follows: oxygen delivered to and dissolved into lung tissues shortsens the longitudinal relaxation time ($T1$) (8, 10), increasing the local MRI signal intensity in a $T1$-weighted image. SVI takes advantage of this to measure the washin/washout time constant, on a voxel-by-voxel basis, following a sudden change in inspired oxygen concentration. The amount of locally dissolved oxygen depends on local availability, which, in turn, is determined by specific ventilation: the ratio of fresh gas entering a lung region divided by its end-expiratory volume. Following a switch from air to 100% $O_2$, regions with high specific ventilation reach the new equilibrium faster. The time delay between the change in inspired gas concentration and the response of a particular voxel is uniquely determined by specific ventilation. We have used this technique to measure the gravitational gradient of specific ventilation present in the supine lung (46).

Regional specific ventilation was measured by acquiring $T1$-weighted images at FRC while the subject was breathing air, followed by a sudden change in inspired oxygen concentration. The amount of locally dissolved oxygen depends on local availability, which, in turn, is determined by specific ventilation: the ratio of fresh gas entering a lung region divided by its end-expiratory volume. Following a switch from air to 100% $O_2$, regions with high specific ventilation reach the new equilibrium faster. The time delay between the change in inspired gas concentration and the response of a particular voxel is uniquely determined by specific ventilation. We have used this technique to measure the gravitational gradient of specific ventilation present in the supine lung (46).

### Image Processing

#### Quantification of regional lung density in grams per milliliter.

The proton density image collected using the body coil (which has relatively homogeneous sensitivity across the lung, therefore no coil inhomogeneity correction was needed) was normalized to the signal derived from the silicone phantom to obtain regional lung proton density in grams of $H_2O$ per milliliter lung. This proton density, which reflects protons in both tissue and blood, is determined by specific ventilation: the ratio of fresh gas entering a lung region divided by its end-expiratory volume. Following a switch from air to 100% $O_2$, regions with high specific ventilation reach the new equilibrium faster. The time delay between the change in inspired gas concentration and the response of a particular voxel is uniquely determined by specific ventilation. We have used this technique to measure the gravitational gradient of specific ventilation present in the supine lung (46).

Regional specific ventilation was measured by acquiring $T1$-weighted images at FRC while the subject was breathing air, followed by a sudden change in inspired oxygen concentration. The amount of locally dissolved oxygen depends on local availability, which, in turn, is determined by specific ventilation: the ratio of fresh gas entering a lung region divided by its end-expiratory volume. Following a switch from air to 100% $O_2$, regions with high specific ventilation reach the new equilibrium faster. The time delay between the change in inspired gas concentration and the response of a particular voxel is uniquely determined by specific ventilation. We have used this technique to measure the gravitational gradient of specific ventilation present in the supine lung (46).

#### Quantification of ventilation in milliliters per minute per milliliter by removal of large vessels.

The ASL technique measures blood delivered from outside the tagging band, into the imaging slice, in one R-R interval. This differs from capillary perfusion, since it includes blood flow in large conduit vessels that may be destined for distal capillary beds. In addition, voxels contained within these large vessels will not demonstrate enhancement with SVI because they are completely full of blood and not ventilated, with the result that they would be incorrectly mapped as shunt (regions of the lung that are perfused but not ventilated). For these reasons, we applied a cutoff value (35% of maximum blood delivered in milliliters per minute per milliliter, which was calculated from the mean value of the top 1% of voxels with highest values of blood delivered) and assigned voxels in images of blood delivered to one of two data sets: 1) larger conduit vessels (blood delivered > 35% maximum in milliliters per minute per milliliter) or 2) “perfusion” comprising smaller vessels and lung tissue (blood delivered < 35% maximum in milliliters per minute per milliliter). The 35% cutoff value was chosen based on previous published modeling studies of our technique (7). A binary mask of the lung region of interest with voxels containing larger conduit vessels excluded was generated and applied to the ventilation and perfusion images. Voxels containing larger conduit blood vessels were also excluded from calculated $V_{A}$/Q images; however, they were not excluded from density images, since these voxels contribute to the regional lung density.

#### Quantification of perfusion in milliliters per minute per milliliter.

Specific ventilation image analysis was performed as previously described (46). Since specific ventilation is the ratio of the delivery of fresh air to resident air in a voxel, we considered a voxel as a binary compartment of air elements and nonair elements and made the assumption that the proton density measurements accurately captured the elements of the compartment that were not air, so that a lung voxel with no air would have a density of 1. Thus the measured proton density in a voxel was assumed to provide a measure of the resident air in a voxel at FRC. Following registration of the specific ventilation and lung density images, $V_a$ in milliliters per minute per milliliter was calculated on a voxel-by-voxel basis as the product of specific ventilation, the volume fraction of air ($1 - V_d$), and the frequency of breathing. Since SVI depends on the rate of change of the magnetic resonance signal as opposed to absolute signal and the lung density image was collected using the body coil, no coil inhomogeneity correction was required in the quantification of ventilation.

#### Image registration and smoothing

Specific ventilation, volume fraction of air, and perfusion images were registered using normalized cross-correlation in MATLAB. Our registration algorithm works well for correcting small $x$-$y$ displacements, but if the displacement is larger (e.g., due to failure to return to FRC at the time of the acquisition), we discard the image. To further protect the calculation of regional $V_{A}$/Q ratio against misregistration errors, we smoothed the images by convolving them with a 2D Gaussian with standard deviation of three voxels (0.47 cm) and full width at half maximum of seven voxels (1.1 cm), effectively giving the smoothed lung density, ventilation, perfusion, and $V_{A}$/Q ratio.
images a resolution of 1.1 × 1.1 × 1.5 cm, or ~1.8 cm³. The smoothing algorithm uses a lung mask, excluding voxels outside the lung and voxels identified as large conduit vessels. The Gaussian weights for averaging the lung voxels are adjusted to account for removal of the masked voxels, essentially treating them as missing data. In doing so, small displacements that might otherwise lead to errors in assessment of regional VA/Q matching are minimized.

**Quantification of VA/Q ratio.** Regional VA/Q ratio was defined as the ratio of the ventilation (calculated from the smoothed specific ventilation and smoothed density images) and smoothed perfusion (mL·min⁻¹·mL⁻¹) images on a voxel-by-voxel basis. A binary mask was applied to identify the lung region of interest, and any voxels that did not fall within lung regions of interest for all three images used in the calculation (specific ventilation, density, and perfusion) were excluded.

**Data Analysis**

The mean and standard deviation of smoothed regional density (g/ml), ventilation (mL·min⁻¹·mL⁻¹), perfusion (mL·min⁻¹·mL⁻¹), and VA/Q ratio (dimensionless) were calculated for a region of interest encompassing the lung in the sagittal image in the prone and supine position. The total ventilation and perfusion to the imaged slice was calculated as the sum of the individual voxel values for VA and perfusion multiplied by the voxel volume.

To evaluate the effects of gravity on the vertical distributions of density, ventilation, perfusion, and VA/Q ratio, data were plotted in 1-cm increments of the distance above the most dependent portion of the lung for each subject in each position. The relationship between these variables for voxels lying within the same gravitational plane and vertical height were characterized using least squares linear regression, and the slope and strength of the association (R²) was obtained. Note that this approach explicitly excludes variability across an isogravitational plane.

Also, since distributions of ventilation, perfusion, and VA/Q ratio across vertical distances may not necessarily be best expressed as linear relationships, the sagittal slice image was also divided into three gravitationally based regions of interest: nondependent, intermediate, and dependent regions to allow for comparison between regions. The regions were defined to have equal vertical extent based on the maximum anterior-to-posterior dimension of the lung. Mean density, ventilation, perfusion, and VA/Q ratio were calculated for each region (25, 44).

The relative dispersion (SD/mean) was calculated for the sagittal lung image and used as an index of overall heterogeneity (15). This relative dispersion, also known as the coefficient of variation, is a variable that globally quantifies the overall magnitude of spatial heterogeneity, but reduces heterogeneity to a single number without regard to the spatial location. The second moments (on a log scale) of the ventilation (log SDV) and perfusion (log SDQ) vs. VA/Q ratio distributions, which are both measures of the extent of VA/Q heterogeneity and analogous to those derived from the multiple inert gas elimination technique (51), were also calculated as follows: histograms of ventilation and perfusion vs. VA/Q ratio were generated assuming 50 compartments, with compartment 1 for VA/Q ratio = 0 (shunt), compartments 2–49 equally spaced on a logarithmic scale from VA/Q ratios of 0.005–100, and compartment 50 for VA/Q ratio = infinity (dead space). From these histograms, the first moments VA₁ and Q₁ were calculated as:

\[
\ln(VA_1) = \sum \frac{\ln(VA)}{\sum V_A}
\]

for VA₁ and perfusion (Q) values for each of the compartments. The second moments VA₂ and Q₂ were calculated as:

\[
VA_2 = \frac{\sum VA \cdot [\ln(VA_1) - \ln(VA/Q)]^2}{\sum Q}
\]

\[
Q_2 = \frac{\sum Q \cdot [\ln(Q_1) - \ln(VA/Q)]^2}{\sum Q}
\]

log SDV and log SDQ were then calculated as the square root of VA₂ and Q₂.

**Statistical Analysis**

Overall mean data and slopes of the gravitational relationships for density, ventilation, perfusion, and VA/Q ratio were compared between postures using a paired t-test. ANOVA for repeated measures (Statview, 5.0.1 SAS Institute, Cary, NC) was used to statistically evaluate changes in the major dependent variables (density, ventilation, perfusion, and VA/Q ratio), over two repeated measures: 1) posture (2 levels: prone and supine), and 2) gravitational region (3 levels: nondependent, intermediate, dependent region). Where overall significance occurred, post hoc testing was conducted using Fisher’s protected least significant difference. All data are presented as means ± SD; the null-hypothesis (no effect) was rejected for P < 0.05, two-tailed.

**RESULTS**

All subjects (descriptive data in Table 1) tolerated the study well. In one subject, the specific ventilation data from prone posture was discarded for technical reasons. For this reason, we report data from seven subjects in supine posture and six subjects in prone. Metabolic data obtained during imaging in each posture are reported in Table 2. There were no significant differences between postures for arterial oxygen saturation as measured by pulse oximeter, heart rate, oxygen consumption, or carbon dioxide production. Although VE and tidal volume were slightly larger in prone posture, these were not statistically significant (P = 0.08 and P = 0.2, respectively). The volume of the lung imaged, calculated from the number of voxels in the lung region of interest multiplied by the voxel size, was significantly larger in prone posture (Table 3). Ext-

<table>
<thead>
<tr>
<th>Table 2. Metabolic data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Supine</strong></td>
</tr>
<tr>
<td><strong>Prone</strong></td>
</tr>
<tr>
<td><strong>P Value</strong></td>
</tr>
<tr>
<td><strong>Heart rate, beats/min</strong></td>
</tr>
<tr>
<td><strong>SpO₂, %</strong></td>
</tr>
<tr>
<td><strong>VO₂, l/min</strong></td>
</tr>
<tr>
<td><strong>VCO₂, l/min</strong></td>
</tr>
<tr>
<td><strong>Tidal volume, liters</strong></td>
</tr>
<tr>
<td><strong>VE, liters</strong></td>
</tr>
</tbody>
</table>

Values are means ± SD. SpO₂, arterial blood oxygen saturation measured by pulse oximeter; VO₂, oxygen consumption; VCO₂, carbon dioxide production; VE, expired ventilation.
Table 3. Mean density, alveolar ventilation, perfusion, and V˙A/Q˙ data for the entire lung slice and by gravitational regions in supine and prone posture

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Prone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume imaged, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>141 ± 51</td>
<td>165 ± 43</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean density, g/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>0.25 ± 0.05</td>
<td>0.26 ± 0.04</td>
<td>0.76 (posture)</td>
</tr>
<tr>
<td>Nondependent</td>
<td>0.23 ± 0.05</td>
<td>0.23 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.25 ± 0.04</td>
<td>0.28 ± 0.05</td>
<td>&lt;0.0001 (region)*</td>
</tr>
<tr>
<td>Dependent</td>
<td>0.28 ± 0.04</td>
<td>0.32 ± 0.06</td>
<td>0.17 (posture × region)</td>
</tr>
<tr>
<td>Total V˙A, ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>387 ± 85</td>
<td>327 ± 85</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean V˙A, ml·min⁻¹·ml⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>2.79 ± 0.48</td>
<td>2.24 ± 0.19</td>
<td>0.047 (posture)*</td>
</tr>
<tr>
<td>Nondependent</td>
<td>2.51 ± 0.72</td>
<td>2.24 ± 0.21</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.88 ± 0.56</td>
<td>2.40 ± 0.25</td>
<td>&lt;0.0001 (region)*</td>
</tr>
<tr>
<td>Dependent</td>
<td>3.70 ± 0.74</td>
<td>2.69 ± 0.25</td>
<td>0.007 (posture × region)*</td>
</tr>
<tr>
<td>Total Q˙, ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>259 ± 93</td>
<td>296 ± 142</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean Q˙, ml·min⁻¹·ml⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>1.94 ± 0.80</td>
<td>2.02 ± 0.70</td>
<td>0.68 (posture)</td>
</tr>
<tr>
<td>Nondependent</td>
<td>1.61 ± 0.77</td>
<td>2.21 ± 0.61</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.69 ± 1.03</td>
<td>3.14 ± 1.36</td>
<td>&lt;0.001 (region)*</td>
</tr>
<tr>
<td>Dependent</td>
<td>3.05 ± 1.12</td>
<td>3.05 ± 1.44</td>
<td>0.02 (posture × region)*</td>
</tr>
<tr>
<td>Mean V˙A/Q ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>1.83 ± 0.62</td>
<td>1.31 ± 0.32</td>
<td>0.047 (posture)*</td>
</tr>
<tr>
<td>Nondependent</td>
<td>2.21 ± 0.84</td>
<td>1.25 ± 0.26</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.32 ± 0.45</td>
<td>0.95 ± 0.32</td>
<td>&lt;0.005 (region)*</td>
</tr>
<tr>
<td>Dependent</td>
<td>1.45 ± 0.49</td>
<td>1.05 ± 0.42</td>
<td>&lt;0.005 (posture × region)*</td>
</tr>
</tbody>
</table>

Values are means ±SD; n = 7 supine, n = 6 prone. V˙A, alveolar ventilation; Q˙, perfusion. *Significant difference.

density in nondependent lung was lower than the intermediate lung and the dependent lung (P < 0.0001 for both postures). The slope of the relationship between height of the lung from most dependent lung and density was not different between postures (Table 4, −0.010 ± 0.002 g·ml⁻¹·cm⁻¹ supine, −0.010 ± 0.004 g·ml⁻¹·cm⁻¹ prone, P = 0.95). Heterogeneity of density as measured by the relative dispersion (SD/mean density) also did not differ between postures (Table 5, 0.21 ± 0.06 supine, 0.21 ± 0.08 prone, P = 0.76).

sample images of density, V˙A, perfusion, and V˙A/Q˙ ratio for a subject in the supine and prone posture are shown in Fig. 1.

Density

Density data are given in Tables 3–5, and Fig. 2, top right. There was no significant difference in mean density in the image slice between postures (Table 3, 0.25 ± 0.05 supine, 0.26 ± 0.04 prone, P = 0.76). There was a highly significant gravitational gradient in density in both postures such that
VA

Specific ventilation data are given in Fig. 2, middle left. Data for calculated VA are given in Tables 3–5 and Fig. 2, middle right. Total VA to the slice was not different between postures. However, mean VA was significantly greater in supine posture than prone (Table 3, 2.79 ± 0.48 ml·min⁻¹·ml⁻¹ supine, 2.24 ± 0.19 prone ml·min⁻¹·ml⁻¹, P = 0.047). There was a highly significant gravitational gradient in VA in both postures such that the dependent lung was better ventilated than the intermediate lung and nondependent lung (P < 0.0001 for both postures). There also was a significant posture by lung region interaction (P = 0.007), reflecting that the slope of the relationship between height of the lung and VA was less in prone posture than supine. In supine posture, the slope of VA (Table 4) was -0.17 ± 0.10 ml·min⁻¹·cm⁻¹·cm⁻¹ height compared with -0.04 ± 0.03 ml·min⁻¹·cm⁻¹·cm⁻¹ height in prone posture (P = 0.02). The heterogeneity of VA across the entire image as measured by the relative dispersion was somewhat lower in prone posture than supine, but this was of borderline statistical significance (Table 5, 0.27 ± 0.06 supine, 0.19 ± 0.06 prone, P = 0.09).

Perfusion

Perfusion data are given in Tables 3–5 and Fig. 2, bottom left. Total perfusion to the imaged slice was not different between postures, and mean perfusion was also not significantly different between postures (Table 3, 1.94 ± 0.80 ml·min⁻¹·ml⁻¹ supine, 2.02 ± 0.70 prone ml·min⁻¹·ml⁻¹, P = 0.68). There was a significant gravitational gradient in perfusion in both postures (P < 0.001), and there was a significant posture by lung region interaction (P = 0.02). In both supine and prone posture, perfusion was less in the nondependent lung than the middle or dependent lung (all P < 0.05). The slope of the relationship between height of the lung and perfusion was less in prone posture than supine and was -0.14 ± 0.05 ml·min⁻¹·ml⁻¹·cm⁻¹·cm⁻¹ height in supine and -0.08 ± 0.09 ml·min⁻¹·ml⁻¹·cm⁻¹·cm⁻¹ height in prone (P = 0.02) posture (Table 4). The heterogeneity of perfusion, as measured by the relative dispersion, although lower in prone posture than supine, was not statistically different (Table 5, 0.35 ± 0.12 supine, 0.26 ± 0.06 prone, P = 0.13). Note that this value for relative dispersion is numerically lower than previously reported for young healthy subjects (3, 25, 31) because of the removal of large conduit vessel signal and spatial smoothing to ~1.8 cm³ voxel size.

VA/Q Ratio

Regional VA/Q ratio data are given in Tables 3–5 and Fig. 2, bottom right. Mean VA/Q ratio was significantly greater in supine posture than prone (Table 3, 1.83 ± 0.62 supine, 1.31 ± 0.32 prone, P = 0.047). There was a significant gravitational gradient in VA/Q (P < 0.05) in both postures, and there was a significant posture by lung region interaction (P < 0.005). In supine posture, VA/Q ratio was greater in the nondependent lung than the middle or dependent lung (all P < 0.05). However, in prone posture, this was not seen, and the slope of the relationship between height of the lung and VA/Q was significantly less in prone posture than supine (Table 4, 0.09 ± 0.08 supine, 0.04 ± 0.03 prone, P = 0.04). Despite these gravitational differences, there was no significant difference in regional VA/Q heterogeneity assessed over the entire lung image, as measured by the relative dispersion (Table 5, 0.44 ± 0.16 supine, 0.35 ± 0.14 prone, P = 0.27), log SDV (0.36 ± 0.10 supine, 0.33 ± 0.10 prone, P = 0.60), or log SDQ (0.34 ± 0.09 supine, 0.34 ± 0.12 prone, P = 0.96).

DISCUSSION

We have used functional lung imaging with proton MRI to measure lung density and specific ventilation and from this

| Density, g/ml | Slope, g·ml⁻¹·cm⁻¹ | R² | Slope, cmH₂O/cm | R² | VA, ml·min⁻¹·ml⁻¹ | Slope, ml·min⁻¹·cm⁻¹·cm⁻¹ | R² | Q, ml·min⁻¹·ml⁻¹ | Slope, ml·min⁻¹·cm⁻¹·cm⁻¹ | R² | VA/Q | Slope, 1/cm | R² | Slope, 1·ml H | R² | Value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>Prone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
calculated regional \( V_A \). This combined with regional blood flow measurements enables the quantification of regional \( V_A/Q \) ratio at a high resolution of 1.8 cm\(^3\) noninvasively without ionizing radiation, which is beneficial for studies such as this where measurements must be repeated. Using this new technique, we have shown that consistent with the prediction of modeling studies (48) and similar to work in animals (35, 50), the gravitational gradients of both ventilation and perfusion are less in prone compared with supine posture. This is evidenced by a reduction in the slope of the relationship of ventilation and perfusion with height from dependent lung. The net result of these changes with posture is that the gravitational gradient in regional \( V_A/Q \) ratio is also less in prone posture. In addition, mean \( V_A \) in the imaged slice was reduced in the prone posture, and, since mean perfusion in the slice was not different between postures, this resulted in a reduction of the overall \( V_A/Q \) ratio of the imaged slice in prone posture. Despite these changes with respect to gravity, the relative dispersion of ventilation, perfusion, and \( V_A/Q \) ratio were not significantly different between postures, nor were the log SDQ and log SDV.

Effects of Posture

Lung density. In the present study there was no significant difference in the lung density gradient with posture. The gravitational gradient in tissue density in prone posture in
Humans has been suggested to be reduced compared with supine (44, 48) and is generally considered to be an effect of the heart and mediastinal contents compressing dependent lung (44). However, the effect is present in modeling studies even when the heart and mediastinum are not included (48). For this reason, the differences in density gradient between postures have also been attributed to differences in lung shape, where there is a larger volume of dependent lung in supine posture compared with prone (48), affecting local transpulmonary pressure gradients and alveolar size (discussed below). In previous work, our laboratory showed that the changes in the gradient in density were greatest in the medial lung and much less pronounced in the remaining lung (44), and the lack of a significant difference between postures in the present work may be because of the relatively lateral position of the imaged slice used in this study. In addition, counterbalancing any potential changes in local tissue density as a result of differences in the distribution of alveolar size (air) between postures, there was an increase in pulmonary blood flow in nondependent lung in prone posture.

Ventilation and local transpulmonary pressure gradients. In our study, mean \( \dot{V}_A \), averaged over the image slice, decreased in prone posture compared with supine, although overall expired ventilation was unchanged. The reason for this finding is likely because of a larger lung volume in prone posture, which leads to a reduction in ventilation when expressed per unit lung volume. Prone posture is well known to increase lung volume (45), and, in the present study, the volume of lung imaged in the prone posture was \( \sim 17\% \) larger than supine. In keeping with this idea, the total \( \dot{V}_A \) to the image slice was not significantly different between postures.

We found that the gravitational gradient in ventilation in a single sagittal slice of lung was less in prone posture than supine, similar to animal studies using microspheres (35). As mentioned above, this gradient in ventilation has been suggested to arise from compression of tissue by the heart and mediastinal contents, such that the gradient in tissue density and thus intrapleural pressure gradient is greater in supine posture (1, 22, 44). However, modeling studies predict that the effect of prone posture on the transpulmonary pressure gradient is present even when the effect of the heart and changes in the chest wall are excluded (48). We used a simple model developed by Glazier et al. (14) to calculate local transpulmonary pressure in 1-cm horizontal planes, starting from the most gravitationally nondependent portion of the lung (posterior lung in prone posture, anterior lung in supine) on a subject-by-subject basis. This model considers each horizontal plane as supporting all of the weight of the lung below the plane, unlike the other plots, data are plotted in 1-cm horizontal bins using the most gravitationally nondependent portion of the lung (posterior lung in prone posture, anterior lung in supine) as a reference point. The mean calculated gradient in transpulmonary pressure is significantly less in prone posture compared with supine (\( P < 0.005 \)).

Although the calculated gradient in transpulmonary pressure was \(-0.46 \text{cmH}_2\text{O/cm} \) in supine posture and \(-0.22 \text{cmH}_2\text{O/cm} \) in prone posture, a result remarkably consistent with modeling studies \([-0.55 \text{cmH}_2\text{O/cm supine, } -0.28 \text{cmH}_2\text{O/cm prone (48)}]\) and experimentally derived data in dogs \([-0.46 \text{cmH}_2\text{O/cm supine, } -0.23 \text{cmH}_2\text{O/cm prone (54)}]\). The calculated gradient in transpulmonary pressure in the present study is significantly less (\( P < 0.005 \)) in prone posture than supine. This implies that, in prone posture, alveolar size was more uniform and thus so was the distribution of local lung compliances, resulting in more uniform ventilation.

In some human studies using positron emission tomography (PET) (36) and single-photon emission computed tomography (SPECT) (38, 42), the gravitational gradient in ventilation was not significantly different between postures, conflicting with the animal studies and the present work. However, there are important differences between those studies and our work. The spatial resolution of both SPECT and PET measurements of ventilation are less than the present study, which may affect conclusions. We measured a limited sample of the lung, whereas the PET and SPECT studies sample more of the lung, and thus the difference may reflect a sampling difference. In the case of the PET studies (36), the gradient in specific ventilation was less in prone posture in four of their six subjects; thus there may have been limited power to detect these differences. SPECT imaging measures the distribution of labeled particles into the airways that are delivered by the process of ventilation and remain in place after they contact the airway wall, and not \( \dot{V}_A \) per se, which is delivery of fresh gas to the alveolus. Also, as typically implemented in the case of SPECT (38, 42), the measures of ventilation are normalized to the mean and, therefore, are expressed relative to the overall ventilation. This means that redistribution of ventilation can be quantified, but changes related to overall changes in absolute ventilation are obscured and may affect the comparisons and interpretation of results across techniques.

Fig. 3. Local transpulmonary pressure calculated using the analysis of Glazier et al. (14) for all subjects in supine and prone postures with linear regression model fits to the aggregate data in each posture. Since this analysis considers each 1-cm plane as supporting all of the weight of the lung below the plane, unlike the other plots, data are plotted in 1-cm horizontal bins using the most gravitationally nondependent portion of the lung (posterior lung in prone posture, anterior lung in supine) as a reference point. The mean calculated gradient in transpulmonary pressure is significantly less in prone posture compared with supine (\( P < 0.005 \)).
Perfusion. In this study, overall mean pulmonary blood flow in the image slice was not significantly different between postures. This is not consistent with our laboratory’s previous work, which showed an increase in mean blood flow in prone posture (44). In that study, more of the lung was sampled, and the changes with posture tended to be greater in the more medial lung. The differences between this study and our prior work are likely because of the relatively lateral location of the imaged slice in this study.

Consistent with numerous other studies (27, 29, 36, 38, 44), we found a gravitational gradient in lung perfusion in both postures that was greater in supine posture than prone. However, there are inconsistent results in the literature. For example, studies have shown blood flow to have a more uniform (35, 37) distribution: no difference in blood flow gradients (27, 29) or greater gradients (2, 36) in prone than in supine posture. In imaging studies (such as Refs. 36, 38), these gradients reflect not only blood flow gradients, but also those that are a result of gravitationally based tissue deformation. In this paper, we report perfusion per imaged volume of lung and did not normalize for regional tissue density and thus alveolar size (25). This is because the primary focus of the paper was on \( V_{\Delta}A/Q_{\Delta} \) relationships, and the volume imaged cancels out when both ventilation and perfusion are normalized and divided. When perfusion is normalized to proton density (reflecting underlying tissue density) and compared between postures, supine posture has a significantly greater slope in density normalized perfusion as a function of height from dependent lung \( (P < 0.005) \), and thus the conclusions are unchanged. The reason for this difference in perfusion gradients between postures in the present study is unknown. It may reflect the unique characteristics of this particular group of subjects, or the particular region of the lung imaged in the present study. Alternately, it may reflect the effect of a more uniform transpulmonary pressure gradient in prone posture, such that alveoli in nondependent lung are less stretched, resulting in increased recruitment of blood vessels and increased flow (13).

\( V_{\Delta}A/Q_{\Delta} \) matching. In the healthy resting lung, \( V_{\Delta}A/Q_{\Delta} \) matching is thought to occur largely as a result of passive mechanisms, such as vascular branching structure and the effect of gravity (18). The effects of gravity are manifested as gradients in hydrostatic pressure (affecting blood flow), intrapleural pressure (affecting alveolar size and therefore ventilation) interacting to affect alveolar expansion, airway or blood vessel diameter, and local resistances, facilitating \( V_{\Delta}A/Q_{\Delta} \) matching. The results of the present study show that, similar to work in animals (35, 50) and modeling studies (48), the gravitational gradient of \( V_{\Delta}A/Q_{\Delta} \) differs between prone and supine posture. In the present study, there was a more gravitationally uniform distribution both of ventilation and of perfusion in prone posture, which we speculate is due to a more uniform distribution of transpulmonary pressures with respect to gravity (41). In addition, \( V_{A} \) was reduced in the imaged slice in prone posture, but mean perfusion was not significantly different between the two postures. Thus two things occurred in prone posture: the overall \( V_{\Delta}A/Q_{\Delta} \) ratio of the image slice was reduced, and there was a reduction of regions of high \( V_{\Delta}A/Q_{\Delta} \) ratio, particularly in the nondependent lung. This resulted in an almost uniform distribution of \( V_{\Delta}A/Q_{\Delta} \) ratio with respect to gravity that was centered around a \( V_{\Delta}A/Q_{\Delta} \) ratio of \( \sim 1 \) in prone posture. These changes suggest that the effects of posture on the lung may have effects on overall pulmonary gas exchange consistent with studies in patients with lung injury (30, 40).

Heterogeneity of ventilation, perfusion, and \( V_{\Delta}A/Q_{\Delta} \) matching. Despite these gravitationally based changes in the distribution of ventilation, perfusion, and \( V_{\Delta}A/Q_{\Delta} \) ratio, the overall indexes of heterogeneity of these measures were not significantly different between postures. Although there was a trend for relative dispersion of ventilation and perfusion to be lower in the prone posture, this did not reach statistical significance \( (P = 0.09 \) and 0.13, respectively). Relative dispersion of \( V_{\Delta}A/Q_{\Delta} \) ratio was not different between postures, nor were the log SDQ and log SDV. Our calculation of gravitational gradients explicitly excludes any heterogeneity within the 1-cm heights used for voxels averaged isogravitationally. However, the results are unchanged when the heterogeneity within an isogravitational plane is analyzed. The likely reason for this is that, in the healthy normal lung, such as in our subjects, overall \( V_{\Delta}A/Q_{\Delta} \) matching is already quite uniform. This is consistent with data obtained in zero gravity, which showed reductions in the heterogeneity of both ventilation and perfusion, but no change in the overall \( V_{\Delta}A/Q_{\Delta} \) heterogeneity (43).

The relative dispersion of perfusion reported in this study was less than previously reported by our group for two reasons (3, 6, 24, 25, 44). First, in this study, we removed voxels with high blood flow using a cutoff value determined based on modeling studies (7), since this signal primarily reflects signal from blood flow in large conduit vessels and does not reflect signal from perfusion. This reduces overall relative dispersion, because these voxels are of high signal intensity. Second, we smoothed the images to a resolution of 1.8 cm\(^3\) before calculating an image of \( V_{\Delta}A/Q_{\Delta} \). This lower resolution reduces the relative dispersion, which is dependent on the resolution of measurement. However, these issues would not affect the interpretation of the changes between postures, unless they were occurring on a smaller spatial scale than our measurement.

The log SDQ and log SDV values reported in this study are remarkably similar to the values reported for similar populations of young subjects measured using the multiple inert-gas elimination technique (51). In this study, log SDQ and log SDV were calculated from the second moments (on a log scale) of the perfusion and ventilation vs. \( V_{\Delta}A/Q_{\Delta} \) ratio distributions generated from the ventilation, perfusion, and regional \( V_{\Delta}A/Q_{\Delta} \) ratio images that were smoothed to \( \sim 1.8 \)-cm\(^3\) resolution. The data were binned using the same 50-compartment model developed for the multiple inert-gas elimination technique to allow for a direct comparison with previously published results.

Technical Aspects

Measurement of \( V_{A} \). To quantify \( V_{A} \), we used SVI, which was recently developed by our group (46). Specific ventilation measures the ratio of the delivery of fresh gas to resident gas, and thus a measure of the resident gas is required to quantify \( V_{A} \). We obtain this from the lung proton density images. In our calculations, we have assumed that the lung is composed of two compartments: one with water (protons), and one with air for the purpose of calculating the resident air. However, a voxel in the lung contains a mixture of air, water, including both blood and other intra-/extracellular water, and a small
nonwater component due to all other material that does not show up in the magnetic resonance signal. This magnetic resonance-invisible nonwater fraction is <10% of the water fraction (28), and by neglecting this component our approach will slightly overestimate the resident gas volume. Since the overall water fraction of the lung is small (mean 0.25 in the present study) relative to the air fraction, this effect is very small. For example, in the lowest density regions of the lung (~0.2 g/ml), the estimate of resident gas is overestimated by ~3%, whereas in the most dense region of the lung (~0.35 g/ml) this effect increases to ~5% overestimation.

Measurement of perfusion. The largest blood vessels present a problem for quantitative accuracy for two reasons. First, in an ASL experiment, they tend to appear bright because they are full of tagged blood. However, this signal intensity is more a reflection of blood volume than blood flow. Smaller vessels will not be filled with tagged blood, and so the signal will reflect the amount of blood that has been delivered during the experiment, i.e., perfusion. Second, a voxel entirely contained within a large vessel would map as a region of shunt, because it has a perfusion signal but no ventilation signal. In truth, this is not a gas exchange shunt, because the large conduit vessels are not part of the gas-exchanging portion of the lung. To give a better estimate of true perfusion, we applied a cutoff value (35% of maximum blood delivered in ml-min^-1-ml^-1) based on modeling studies (7) and assigned voxels in images of blood delivered to be larger conduit vessels or “perfusion” comprising smaller vessels and lung tissue. This approach ensures that the contribution of perfusion to the total ASL signal is at least 80% (7), and thus this problem of incorrect assignment of regions of shunt is minimized.

Quantification of V̇A/Q̇ matching. To minimize effects of misregistration in the calculation of V̇A/Q̇, we smoothed the images to a resolution of ~1.8 cm³. This resolution was chosen because it is comparable to the resolution of measurements from previous animal studies (16, 17). Smoothing too little could lead to errors in the calculation of V̇A/Q̇, since the ventilation and perfusion images may not correspond exactly for every voxel within the lung region of interest. However, smoothing too much reduces resolution and thus removes spatial information contained in the images. Over-smoothing would be expected to greatly reduce measures of heterogeneity in the individual images, such as relative dispersion, and measures of V̇A/Q̇ inequality, such as log SDV and log SDQ.

The density images were collected with the torso coil and body coil to correct for inhomogeneities associated with the torso coil used for collection of the ASL images to quantify perfusion. When quantifying V̇A using the density and specific ventilation images, however, no such correction is required. The body coil provides sufficient signal in the acquisition to accurately estimate the proton density (23), and since SVI utilizes the change in the magnetic resonance signal over time and not the absolute change in signal, it is uncorrupted by any torso coil inhomogeneity. Thus the V̇A/Q̇ ratio map was the ratio of the registered V̇A (no need for coil correction) and perfusion (coil corrected) images on a voxel-by-voxel basis. Therefore, the effect of coil heterogeneity in the quantification of V̇A/Q̇ ratio in this study is minimal.

Limitations

Single slice. We performed our imaging in the sagittal plane because we were interested in studying gravitational gradients of ventilation, perfusion, and V̇A/Q̇. We selected a sagittal slice with maximal anterior-posterior dimension in the right lung to maximize the amount of lung sampled and study the effects of posture independent of the effects of the heart and mediastinum on lung tissue. Nevertheless, this slice may not necessarily be representative of the entire lung, and this is a limitation of our study. This limited evaluation is because the current acquisition time for the specific ventilation measurement is 18 min for a single slice of lung. The lung region of interest in the images for this study were ~150 ml; thus we imaged ~6% of the lung. However, we have no reason to think that, in this young healthy population of subjects with normal lung function, the imaged region of the lung is not representative of the lung as a whole.

Measurement of specific ventilation and V̇A. One of the advantages of SVI is that it does not depend on the magnitude of the signal change produced as the partial pressure of oxygen (PO₂) changes. Nevertheless, the assumptions of the model are 1) that PO₂ is uniform within a voxel, and this is supported by numerical simulation (9, 11, 39); and 2) the equilibration of PO₂ between alveoli and lung water is rapid compared with the time scale of one breath (~5 s), which is supported by simulation studies (39) and by the fact that it takes ~0.25 s for oxygen to reach equilibrium with hemoglobin (53), a process that involves, but is not limited to, dissolution in tissue. In the SVI approach used in our paper, a typical voxel volume is ~40 mm³ (1.56 × 1.56 × 15 mm, field of view = 40 cm). The analysis of SVI is performed at this spatial scale, and smoothing is performed later during image processing. For comparison, the volume of a typical human acinus is ~187 ± 79 mm³ (19), approximately four times the voxel volume. However, since the through-plane resolution is 15 mm, and an acinus may cross the boundaries between voxels, a single voxel may thus contain blended information from more than one acinus, and thus PO₂ may not be uniform. Since our model assumes that each voxel can be represented by a single ventilatory unit with a unique specific ventilation, this may affect our measurement of regional specific ventilation.

We have tested the limits of this assumption, by acquiring SVI data at lower spatial resolutions than in the present study. Data from a single sagittal slice in the right lung, as in this study, were acquired at three different resolutions (acquisition matrix of 256 × 256, 128 × 128, and 64 × 64) in a normal subject using the SVI protocol. This corresponds to reconstructed voxel volumes of ~40, ~150, and ~600 mm³, respectively. To test for the presence of intravoxel heterogeneity, we implemented the approach described in Ref. 52 by evaluating the signal characteristics from each acquisition for the presence of multieponential behavior. In the presence of intravoxel heterogeneity, recovery of more than a single exponential decay is expected. We fit two models to the signal intensity decay on a voxel-by-voxel basis. The first model was a monoexponential decay, while the second model assumed a double exponential, accounting for the presence of two different compartments within the voxel. The Akaike information criterion was used to select the optimal model, taking into account the additional degrees of freedom. At voxel volumes
of ~40 and 150 mm$^3$, but not 600 mm$^3$, most voxels (>99\%) within the lung slice were best described by a monoeponential, supporting the validity of this assumption.

**Measurement of dead space and shunt.** Presently, we are unable to quantify either dead space or shunt, the extremes of V\(\dot{A}\)/Q\(\dot{O}\) matching. This is because of the current limitation of SVI. Since SVI measures the rate of change in the MRI signal intensity following a change in the fractional inspired oxygen (46), when the specific ventilation is >0.6, equilibration for these units occurs within a single breath and is, in the present analysis, not resolvable. Thus all specific ventilations above that threshold are lumped together. This limits our ability to resolve high V\(\dot{A}\)/Q\(\dot{O}\) regions. In addition, very rapidly equilibrating units showing perfect correspondence with the driving function are eliminated from the analysis. Thus voxels consistent with dead space are excluded. Similarly, voxels that show no correlation with the driving function are also eliminated. These voxels represent regions of poor signal intensity that correspond to either voxels entirely within large blood vessels, composed of noise, or unventilated regions. Since at this time we cannot distinguish between the latter two, this limits our resolution of shunt.

**Use of hyperoxia.** SVI uses oxygen as a contrast agent, and although the exposure to hyperoxia is brief, this could have an effect on the underlying physiology, although this is unlikely in the present study. Nonetheless, for this reason, perfusion was measured during the air-breathing segments only. The onset of hypoxic pulmonary vasoconstriction in humans occurs within minutes of exposure to hypoxia (34), but the duration of hyperoxia (20 breaths) is too short to have a large effect. In addition, limited experimental evidence suggests that hypoxic pulmonary vasoconstriction is not active under normal conditions. This includes the lack of change in pulmonary arterial pressure when inhaled nitric oxide is administered to normal subjects (12), and recent work by our group (3) showing no change in the spatial heterogeneity of pulmonary perfusion compared with normoxia when normal subjects were given 30\% oxygen to breathe. Since this level of hyperoxia is sufficient to raise the local PO$_2$ in all alveoli above the threshold for hypoxic pulmonary vasoconstriction, this argues against a significant effect.

**Conclusion**

Using a new proton MRI technique, we have found that compared with supine posture, the gravitational gradients of both ventilation and perfusion are more uniform in the prone posture with a reduction in the slope of the relationship of ventilation and perfusion with height from dependent lung. Calculated local transpulmonary pressure gradients were also significantly reduced in prone posture, suggesting that changes in local alveolar pressure-volume relationships may be responsible for the observed changes. The net result is a gravitational gradient in regional V\(\dot{A}\)/Q\(\dot{O}\) ratio that is more uniform in prone posture, consistent with the changes documented in animal studies.

**GRANTS**

This work was supported by the National Space Biomedical Research Institute through National Aeronautics and Space Administration Grant NCC 9-58, National Heart, Lung, and Blood Institute Grants K99/R00 HL-093064 and NIH R01 HL-104118, and a grant from the University of California San Diego Academic Senate.

**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


