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

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Running head: Effects of posture on regional V/Q ratio
ABSTRACT (250 Words)

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 (V̇A/Q̇) ratio. Using a novel functional lung magnetic resonance imaging technique to measure regional V̇A/Q̇ ratio, the gravitational gradients in proton density, ventilation, perfusion and V̇A/Q̇ ratio were measured in prone and supine posture. Data were acquired in 7 healthy subjects in a single sagittal slice of the right lung at functional residual capacity. Regional specific ventilation quantified using Specific Ventilation Imaging (SVI) was combined with proton density obtained using a fast gradient-echo sequence to calculate regional alveolar ventilation. Perfusion was measured using arterial spin labeling. Ventilation (ml/min/ml) and perfusion (ml/min/ml) images were registered, smoothed, and divided on a voxel-by-voxel basis to obtain regional V̇A/Q̇ 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/ml)/cm supine, -0.040±0.03 prone, P=0.02) as was the slope of the perfusion-height relationship (-0.14±0.05 (ml/min/ml)/cm supine, -0.08±0.09 prone, P=0.02). There was a significant gravitational gradient in V̇A/Q̇ ratio in both postures (P<0.05) that was less in prone (0.09±0.08 cm⁻¹ supine, 0.04±0.03 prone, P=0.04). The gravitational gradients in ventilation, perfusion, and regional V̇A/Q̇ ratio were greater supine than prone suggesting an interplay between thoracic cavity configuration, airway and vascular tree anatomy, and the effects of gravity on V̇A/Q̇ matching.

KEY WORDS
magnetic resonance imaging, arterial spin labeling, specific ventilation imaging, ventilation-perfusion ratio, gravity
INTRODUCTION

While the lung has a number of functions, it is primarily a gas exchange organ. Ventilation-perfusion ($V_{A}/Q$) matching, such that regions of the lung that receive fresh gas also receive deoxygenated capillary blood, is the most important mechanism determining gas exchange efficiency (53). Although several mechanisms are thought to accomplish $V_{A}/Q$ matching in the healthy lung (see (18) for review), it is thought that passive mechanisms dominate under normal conditions. Such 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 to supine (48). This predicts that the gravitational distribution of ventilation and perhaps $V_{A}/Q$ matching is also expected to be more uniform. This is consistent with animal studies where prone posture was associated with a reduction in regional ventilation-perfusion heterogeneity compared to supine posture, largely because of a reduction in the gravitational gradient in ventilation (35, 50). However, results in human studies have shown inconsistent results, with some studies reporting that the gravitational gradient in 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 is not measured, but rather is inferred from measures of specific ventilation (local tidal volume/functional residual capacity 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 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 manuscript we report a new technique for measuring regional $V_{A}/Q$ 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 functional residual capacity (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 alveolar ventilation ($V_A$) can be calculated. This, when combined with regional measures of perfusion, provides a new method to measure the regional distribution of $V_A/Q$. Using this new technique we tested the hypothesis that in humans, consistent with animal studies, the spatial distribution of ventilation and regional $V_A/Q$ 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 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 non-smokers, 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 Quadtrodes) 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 Tesla Signa HDx TwinSpeed MRI system (General Electric Medical Systems, Milwaukee, WI, USA). 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 were collected using the torso coil. Proton density images were collected using both the torso coil and the body coil built into the scanner (for reasons described in Image Processing).

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 mid-clavicular 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, repositioned, and then imaging was repeated in the other posture. The order of postures was balanced between subjects such that 4 completed the supine and 3 the prone posture first. The duration of imaging in each posture was ~45 minutes 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 in a single 9-second breath-hold. Six images (even images: 2, 4, 6, 8, 10, 12) were acquired with an echo time of 1.1 msec and six images (odd images: 1, 3, 5, 7, 9, 11) were acquired at an echo time of 1.8 msec. Imaging sequence parameters were TR = 10 msec, flip angle = 10 deg, slice thickness = 15 mm, field of view = 40 cm, receiver bandwidth = 125 kHz, and a full acquisition matrix of 64 x 64. A proton density image was
determined by fitting a single exponential to the last eight images for the two different echo times 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-SVI sequence**

Measurements of regional pulmonary blood flow and specific ventilation (described below) were merged into a single imaging sequence in order to facilitate imaging of ventilation and blood flow in parallel. Subjects performed 5 cycles alternating between 20 breaths of room air and 20 breaths of 100% oxygen as part of specific ventilation imaging. In each block of 20 breaths, 18 inversion recovery images were acquired (for specific ventilation imaging) and a pair of 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, prior to data acquisition, to ensure adequate breath-holds. Acquisition took place during ~1-2 second breath-holds with 4-5 seconds 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 minutes to complete.

**Measuring pulmonary blood flow using ASL**

Regional pulmonary blood flow was assessed using 2D arterial spin labeling (ASL) with a flow-sensitive alternating inversion recovery with an extra radiofrequency pulse (FAIRER) 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.
Arterial spin labeling exploits the capability of MRI to invert the magnetization of protons (primarily in water molecules) in a spatially selective way using a combination of radiofrequency pulses and spatial magnetic field gradient pulses (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 non-selective inversion). Both images are subsequently acquired after a delay chosen to be approximately 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 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: TI = 600-800 msec (based on subject’s heart rate), TE = 21.3 msec, field of view = 40 cm, slice thickness = 15mm. The collected image matrix size was 256x128 (reconstructed by scanner to 256x256) giving voxels of 0.156 x 0.156 x 1.5 cm, or ~0.037 cm³. The HASTE imaging sequence had an inter-echo time of 4.5 msec and 72 lines of phase encoding, resulting in a data acquisition time of 324 msec.
Specific ventilation imaging

Regional specific ventilation was measured as follows: oxygen delivered to and dissolved into lung tissues shortens the longitudinal relaxation time ($T_1$) (8, 10), increasing the local MRI signal intensity in a $T_1$-weighted image. Specific ventilation imaging (SVI) takes advantage of this to measure the wash-in/wash-out time constant, on a voxel-by-voxel basis, following a sudden change in inspired oxygen concentration (fractional inspired oxygen, or $F_{102}$). 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 $T_1$-weighted images at FRC while the subject was breathing air, followed by breathing $100\%$ oxygen, in alternating 20 breath cycles; five air-oxygen cycles were acquired for robustness. An inversion recovery sequence was used with the following imaging sequence parameters: $TI = 1,100$ msec (parameter set to optimize the contrast between air and oxygen breaths (8)), followed by the same HASTE image acquisition used for the ASL measurements.

Image Processing

Quantification of regional lung density in g/ml. 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 (water) density in units of g H$_2$O per ml lung. This proton density, which reflects protons in both tissue and blood, is subsequently referred to in this manuscript as density (49). This technique for quantifying regional lung density has been validated, showing a high correlation between measured MRI water content and gravimetric water content with $R^2=0.95, p<0.0001$ (23).
Quantification of regional blood delivered in ml/min/ml. In order to quantify all blood delivered (comprising both that in large conduit vessels and also that representing perfusion in the capillary bed) to the imaging slice the signal intensity was referenced to the mean signal in the calibration phantom ($T_1$ 620 msec, $T_2$ of 160 msec) and the $T_1$ and $T_2$ of the phantom relative to assumed values for human pulmonary arterial blood (47). This allowed blood delivered in units of ml/min/ml (averaged over one cardiac cycle) to be calculated (21) for each ASL image. This technique has been validated in a lung phantom model (26).

To maximize the signal-to-noise ratio in the ASL images of blood delivered, a torso coil was used, which has substantially higher sensitivity than the body coil built into the scanner. Unlike the body coil, which is quite homogeneous over the lung, the torso coil exhibits a degree of inhomogeneity in signal strength that varies in all three spatial dimensions. To correct for this inhomogeneity, the ASL image obtained from the torso coil was corrected for each subject individually. In order to map the spatial inhomogeneity of the coil sensitivity, the same fast gradient echo sequence used to measure proton density was used twice, once using the torso coil and once using the body coil. The resulting two average torso and body coil short echo time original magnitude images were spatially smoothed by applying a 2D Gaussian low-pass filter in frequency space, equivalent to convolving with a 2D Gaussian in image space with standard deviation of 3.4 voxels (2.1 cm) and full width at half maximum of 8 voxels (5 cm). The resultant smoothed images were divided (torso/body) to define the individual coil sensitivity map. Finally, the ASL images obtained using the torso coil were divided by the coil sensitivity function on a voxel-by-voxel basis in order to obtain a quantitative map of perfusion, independent of the spatial variations in coil sensitivity.

Quantification of regional perfusion in ml/min/ml by removal of large vessels. The arterial spin labeling technique measures blood delivered from outside the tagging band, into the imaging slice, in one RR-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 specific ventilation imaging 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 cut-off value (35% of maximum blood delivered in ml/min/ml, 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 mL/min/ml) or 2) “perfusion” comprising smaller vessels and lung tissue (blood delivered < 35% maximum in mL/min/ml). The 35% cutoff value was chosen based on previously 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 ventilation-perfusion images; however, they were not excluded from density images since these voxels contribute to the regional lung density.

Quantification of ventilation in ml/min/ml. 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 non-air 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, alveolar ventilation in ml/min/ml was calculated on a voxel-by-voxel basis as the product of specific ventilation, the volume fraction of air (1 – lung density), 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 3 voxels (0.47 cm) and full width at half maximum of 7 voxels
(1.1 cm), effectively giving the smoothed lung density, ventilation, perfusion, and $V_a/Q$ ratio
images a resolution of 1.1 x 1.1 x 1.5 cm, or ~1.8 cm$^3$. 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 $V_a/Q$ matching are minimized.

**Quantification of $V_a/Q$ ratio.** Regional $V_a/Q$ ratio was defined as the ratio of the
smoothed ventilation (calculated from the specific ventilation and density images) and
smoothed perfusion (ml/min/ml) 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/ml), perfusion (ml/min/ml), and $V_a/Q$ 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 alveolar ventilation and perfusion.

To evaluate the effects of gravity on the vertical distributions of density, ventilation, perfusion, and $V_a/Q$ 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 ($R^2$) obtained. Note that this approach explicitly excludes variability across an isogravitational plane.

Also since distributions of ventilation, perfusion and $V_a/Q$ 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 $V_a/Q$ ratio were calculated for each region (25, 44).

The relative dispersion (standard deviation / 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 ($\log SDV_a$) and perfusion ($\log SDQ$) versus $V_a/Q$ ratio distributions, which are both measures of the extent of $V_a/Q$ heterogeneity and analogous to those derived from the multiple inert gas elimination technique (51), were also calculated as follows: histograms of ventilation and perfusion versus $V_a/Q$ ratio were generated assuming 50 compartments, with compartment 1 for $V_a/Q$ ratio = 0 (shunt), compartments 2 to 49 equally spaced on a logarithmic scale from $V_a/Q$ ratios of 0.005 to 100, and compartment 50 for $V_a/Q$ ratio = infinity (dead space). From these histograms, the first moments $V_{A1}$ and $Q_1$ were calculated as:

$$\ln(V_{A1}) = \sum \frac{V_A \cdot \ln \left( \frac{V_A}{Q} \right)}{\sum V_A}$$

$$\ln(Q_1) = \sum \frac{Q \cdot \ln \left( \frac{V_A}{Q} \right)}{\sum Q}$$
for alveolar ventilation ($V_A$) and perfusion ($Q$) values for each of the compartments. The second moments $V_{A2}$ and $Q_2$ were calculated as:

\[
V_{A2} = \frac{\sum \left( V_A \cdot \left( \ln(V_A) - \ln\left( \frac{V_A}{Q} \right) \right)^2 \right)}{\sum V_A}
\]

\[
Q_2 = \frac{\sum \left( Q \cdot \left( \ln(Q) - \ln\left( \frac{V_A}{Q} \right) \right)^2 \right)}{\sum Q}
\]

Log SDV and Log SDQ were then calculated as the square root of $V_{A2}$ and $Q_2$.

**Statistical Analysis**

Overall mean data and slopes of the gravitational relationships for density, ventilation, perfusion and $V_A/Q$ 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 $V_A/Q$ 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 7 subjects in supine posture and 6 subjects in prone. Metabolic data obtained during imaging in each posture is 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 expired ventilation 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 image multiplied by the voxel size, was
significantly larger in prone posture (Table 3). Example images of density, alveolar
ventilation, perfusion, and $\dot{V}/Q$ ratio for a subject in the supine and prone posture are
shown in Figure 1.

Density

Density data are given in Tables 3, 4, and 5 and Figure 2B. 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 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/cm supine, -0.010±0.004 g/ml/cm prone, $P$
= 0.95). Heterogeneity of density as measured by the relative dispersion (standard
deviation/mean density) also did not differ between postures (Table 5, 0.21±0.06 supine,
0.21±0.08 prone, $P=0.76$).

Alveolar Ventilation

Specific ventilation data are given in Figure 2C. Data for calculated alveolar
ventilation are given in Tables 3, 4, and 5 and Figure 2D. Total alveolar ventilation to the
slice was not different between postures. However, mean alveolar ventilation was
significantly greater in supine posture than prone (Table 3, 2.79±0.48 ml/min/ml supine,
2.24±0.19 prone ml/min/ml, $P=0.047$). There was a highly significant gravitational
gradient in alveolar ventilation 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 alveolar
ventilation was less in prone posture than supine. In supine posture the slope of alveolar
ventilation (Table 4) was -0.17±0.10 (ml/min/ml)/cm height compared to -0.04±0.03
(ml/min/ml)/cm height in prone posture (P=0.02). The heterogeneity of alveolar ventilation 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, 4, and 5 and Figure 2E. 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/ml supine, 2.02±0.70 prone ml/min/ml, 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/ml)/cm height in supine and -0.08±0.09 (ml/min/ml)/cm 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 RD 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.

\( \dot{V}_l/\dot{Q} \) ratio

Regional \( \dot{V}_l/\dot{Q} \) ratio data are given in Tables 3, 4, and 5 and Figure 2F. Mean \( \dot{V}_l/\dot{Q} \) 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 \( \dot{V}_l/\dot{Q} \) (P<0.05) in both postures and there was a significant posture by lung region interaction (P<0.005). In supine posture, \( \dot{V}_l/\dot{Q} \) 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 \( \dot{V}_l/\dot{Q} \) 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 $\dot{V}/Q$ 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), LogSDV (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 calculated regional alveolar ventilation. This combined with regional blood flow measurements enables the quantification of regional $\dot{V}/Q$ ratio at a high resolution of 1.8 cm³ 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 to 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 $\dot{V}/Q$ ratio is also less in prone posture. In addition, mean alveolar ventilation 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 $\dot{V}/Q$ ratio of the imaged slice in prone posture. Despite these changes with respect to gravity, the relative dispersion of ventilation, perfusion and $\dot{V}/Q$ ratio were not significantly different between postures, nor were the LogSDQ and LogSDV.

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 to 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 to prone (48), affecting local transpulmonary pressure gradients and alveolar size (discussed below). In previous work, we 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 is likely 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 alveolar ventilation, averaged over the image slice, decreased in prone posture compared to supine, although overall expired ventilation ($\dot{V}_E$) 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 alveolar ventilation 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 the weight of the lung below it, and thus the local alveolar expanding pressure (transpulmonary pressure) at each plane is the force/area of the plane or weight of slices below the plane/area. Using the measured proton density and number of voxels in each 1 cm isogravitational (horizontal) plane, we calculated the weight and area of each plane. The local transpulmonary pressure at each plane was then calculated as the ratio of the summed weight of all the planes that were dependent to the plane of interest divided by the area of the plane of interest. Since the most anterior and posterior planes have a very small numbers of voxels (<1%), which might not be an adequate sample size to be representative of the lung, these were excluded from the analysis. The results are given in Figure 3 and Table 4. The mean gradient in transpulmonary pressure was -0.46 cmH2O/cm in supine posture and -0.22 cmH2O/cm in prone posture, a result remarkably consistent with modeling studies (-0.55 cmH2O/cm supine, -0.28 prone (48)) and experimentally derived data in dogs (-0.46 cmH2O/cm supine, -0.23 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 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 4 of their 6 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 alveolar ventilation 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.

**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 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 that 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 (36, 38)) these gradients reflect not only blood flow gradients but also those that are a result of gravitationally based tissue deformation. In this manuscript 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 manuscript was on ventilation-perfusion 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**_/Q** matching.** In the healthy resting lung **V**_/Q 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**_/Q 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**_/Q differs between prone and supine posture. In the present study there was a more gravitationally uniform distribution of both 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 alveolar ventilation 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**_/Q ratio of the image slice was reduced and there was a reduction of regions of high **V**_/Q ratio particularly in the nondependent lung. This resulted in an almost uniform distribution of **V**_/Q ratio with respect to gravity, that was centered around a **V**_/Q ratio of ~ 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 \( V_{A}/Q \) matching.** Despite these gravitationally based changes in the distribution of ventilation, perfusion and \( V_{A}/Q \) ratio the overall indices 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 \( V_{A}/Q \) ratio was not different between postures, nor were the LogSD\( Q \) or LogSD\( V \). 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 ventilation-perfusion 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 \( V_{A}/Q \) 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 \( V_{A}/Q \). 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 LogSD\( Q \) and LogSD\( V \) 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 LogSD\( Q \) and LogSD\( V \) were calculated from the second moments (on a log scale) of the perfusion and ventilation versus \( V_{A}/Q \) ratio distributions generated from the ventilation, perfusion, and regional \( V_{A}/Q \) ratio images that
were smoothed to ~1.8 cm³ resolution. The data were binned using the same 50-
 compartment model developed for the multiple inert gas elimination technique in order to
allow for a direct comparison with previously published results.

Technical aspects

**Measurement of alveolar ventilation.** In order to quantify alveolar ventilation, we
used specific ventilation imaging, 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 in order to quantify alveolar ventilation. We obtain
this from the lung proton density images. In our calculations we have assumed that the
lung is comprised 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/extra-cellular water, and a small non-water
component due to all other material that does not show up in the magnetic resonance
signal. This MR-invisible non-water fraction is less than 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. In order to give a better estimate of true perfusion, we applied a cut-off value (35% of maximum blood delivered in mL/min/ml) 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 V_A/Q matching. In order to minimize effects of misregistration in the calculation of V_A/Q, 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 V_A/Q, 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 ventilation-perfusion inequality such as log SDV and log SDQ.

The density images were collected with the torso coil and body coil in order to correct for inhomogeneities associated with the torso coil used for collection of the ASL images to quantify perfusion. When quantifying alveolar ventilation 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 specific ventilation imaging 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 V_A/Q ratio map was the ratio of the registered alveolar ventilation (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 V_A/Q 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 $\dot{V}/\dot{Q}$. 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 eighteen minutes for a single slice of lung. The lung region of interest in the images for this study were $\sim 150$ mL, thus we imaged $\sim 6\%$ of the lung. However, we have no reason to think that in this young healthy population of subjects with normal lung function that the imaged region of the lung differs from the lung as a whole.

Measurement of specific ventilation and alveolar ventilation. One of the advantages of specific ventilation imaging is that it does not depend on the magnitude of the signal change produced as the partial pressure of oxygen ($pO_2$) changes. Nevertheless the assumptions of the model are 1) that $pO_2$ is uniform within a voxel, and this is supported by numerical simulation (9, 11, 39) and 2) the equilibration of $pO_2$ between alveoli and lung water is rapid compared to the time scale of one breath ($\sim 5$s), which is supported by simulation studies (39) and by the fact it takes $\sim 0.25$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 $\sim 40 \text{mm}^3$ (1.56 x 1.56 x 15mm, FOV=40cm). 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 $\sim 187+/ - 79 \text{ mm}^3$ (19), $\sim 4x$ the voxel volume. However since the through-plane resolution is 15 mm, and a acinus may cross the boundaries between voxels, a single voxel may thus contain blended information from more than one acinus, and thus $PO_2$ 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 3 different resolutions (acquisition matrix of 256x256, 128x128, and 64x64) in a normal subject using the SVI protocol. This corresponds to reconstructed voxel volumes of ~40mm³, ~150mm³ and ~600mm³, respectively. In order to test for the presence of intra-voxel heterogeneity, we implemented the approach described in (52) by evaluating the signal characteristics from each acquisition for the presence of multi-exponential 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 mono-exponential decay, while the second model assumed a double exponential, accounting for the presence of 2 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 ~40mm³ and 150mm³, but not 600mm³, most voxels (>99%) within the lung slice were best described by a mono-exponential, supporting the validity of this assumption.

**Measurement of dead space and shunt.** Currently we are unable to quantify either dead space or shunt – the extremes of Vₐ/Q matching. This is because of the current limitation of specific ventilation imaging. Since specific ventilation imaging measures the rate of change in the MRI signal intensity following a change in the FIO₂ (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 Vₐ/Q 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. Specific ventilation imaging 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 to normoxia when normal subjects were given 30% oxygen to breathe. Since this level of hyperoxia is sufficient to raise the local PO2 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 to 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/A 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 NASA NCC 9-58, NIH K99/R00 HL093064, and NIH R01 HL104118, and a grant from UCSD Academic Senate.
**FIGURE LEGENDS**

**Figure 1.** Example images of density (A), alveolar ventilation (B), perfusion (C), and \( V_A/Q \) ratio (D) in a sagittal slice of the right lung in a normal subject in the supine posture. Images are also shown for the prone posture (E-H respectively). Voxels with larger conduit blood vessels are removed for the calculation of regional perfusion and \( V_A/Q \) ratio since they do not represent perfusion and incorrectly map as regions of shunt.

**Figure 2.** The effect of gravity on lung density, ventilation, perfusion, and \( V_A/Q \) ratio (means and standard deviations) in prone (n = 6) and supine posture (n = 7). Voxel-by-voxel data are binned for each centimeter of vertical distance from the most dependent portion of the lung for a sagittal lung slice in each posture. Note that the gravitational distribution of ventilation, perfusion, and \( V_A/Q \) ratio is more uniform in prone posture compared to supine.

**Figure 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 to supine (p<0.005).


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<table>
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<tbody>
<tr>
<td><strong>Table 1. Subject Descriptive Data (means ± SD)</strong></td>
<td></td>
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<tr>
<td>Age (years)</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>
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<tr>
<td>FVC (l)</td>
<td>4.52±0.99</td>
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<tr>
<td>% predicted</td>
<td>97±12</td>
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<tr>
<td>FEV₁ (l)</td>
<td>3.61±0.70</td>
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<tr>
<td>% predicted</td>
<td>94±9</td>
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<tr>
<td>FEV₁/FVC Ratio</td>
<td>0.80±0.06</td>
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<tr>
<td>% predicted</td>
<td>98±4</td>
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FVC = forced vital capacity, FEV₁ = forced expiratory volume in one second
Table 2. Metabolic Data

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Prone</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td>61±11</td>
<td>63±13</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>SaO₂ (%)</strong></td>
<td>98.7±0.8</td>
<td>98.8±0.8</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>(\dot{V}O₂) (l/min)</strong></td>
<td>0.23±0.04</td>
<td>0.24±0.05</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>(\dot{V}CO₂) (l/min)</strong></td>
<td>0.21±0.03</td>
<td>0.23±0.05</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Tidal Volume (l)</strong></td>
<td>0.62±0.15</td>
<td>0.67±0.16</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>(\dot{V}E) (l)</strong></td>
<td>6.3±1.5</td>
<td>6.9±1.6</td>
<td>0.08</td>
</tr>
</tbody>
</table>

SaO₂ = arterial blood oxygen saturation measured by pulse oximeter, \(\dot{V}O₂\) = oxygen consumption, \(\dot{V}CO₂\) = carbon dioxide production. \(\dot{V}E\) = Expired Ventilation
Table 3. Mean density, alveolar ventilation, perfusion and V̅/Q̅ data for the entire lung slice and by gravitational regions in supine and prone posture (means ±SD, n = 7 supine, n = 6 prone)

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Prone</th>
<th>P values</th>
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</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±05</td>
<td>0.26±04</td>
<td>P Posture = 0.76</td>
</tr>
<tr>
<td>Nondependent</td>
<td>0.23±05</td>
<td>0.23±05</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.25±04</td>
<td>0.28±05</td>
<td>P Region &lt;0.0001*</td>
</tr>
<tr>
<td>Dependent</td>
<td>0.28±04</td>
<td>0.32±06</td>
<td>P posture x region = 0.17</td>
</tr>
<tr>
<td>Total V. (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 V̅ (ml/min/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>2.79±048</td>
<td>2.24±019</td>
<td>P Posture = 0.047*</td>
</tr>
<tr>
<td>Nondependent</td>
<td>2.51±072</td>
<td>2.24±021</td>
<td>P Region &lt;0.0001*</td>
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<tr>
<td>Intermediate</td>
<td>2.88±056</td>
<td>2.40±025</td>
<td></td>
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<tr>
<td>Dependent</td>
<td>3.70±074</td>
<td>2.69±025</td>
<td>0.007 *</td>
</tr>
<tr>
<td>Total Q̅ (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 Q̅ (ml/min/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>1.94±080</td>
<td>2.02±070</td>
<td>P Posture = 0.68</td>
</tr>
<tr>
<td>Nondependent</td>
<td>1.61±077</td>
<td>2.21±061</td>
<td>P Region &lt;0.001*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.69±103</td>
<td>3.14±136</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>3.05±112</td>
<td>3.05±144</td>
<td>0.02*</td>
</tr>
<tr>
<td>Mean V̅/Q̅ ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole slice</td>
<td>1.83±062</td>
<td>1.31±032</td>
<td>P Posture = 0.047*</td>
</tr>
<tr>
<td>Nondependent</td>
<td>2.21±084</td>
<td>1.25±026</td>
<td>P Region &lt;0.005*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.32±045</td>
<td>0.95±032</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>1.45±049</td>
<td>1.05±042</td>
<td>&lt;0.005*</td>
</tr>
</tbody>
</table>
Table 4. Linear relationships between the average value for voxels lying within the same gravitational plane of 1 cm height in supine and prone posture (means ±SD, n = 7 supine, n = 6 prone)

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Prone</th>
<th>P values</th>
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<tbody>
<tr>
<td><strong>Density (g/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope (g/ml/cm)</td>
<td>0.010 ± 0.002</td>
<td>0.010 ± 0.004</td>
<td>0.95</td>
</tr>
<tr>
<td>R²</td>
<td>0.79 ± 0.08</td>
<td>0.66 ± 0.21</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Local Transpulmonary Pressure (cmH₂O/cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.46 ± 0.12</td>
<td>-0.22 ± 0.068</td>
<td>0.005*</td>
</tr>
<tr>
<td>R²</td>
<td>0.84 ± 0.07</td>
<td>0.89 ± 0.06</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Alveolar Ventilation (ml/min/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.17 ± 0.10</td>
<td>-0.04 ± 0.03</td>
<td>0.02*</td>
</tr>
<tr>
<td>R²</td>
<td>0.70 ± 0.35</td>
<td>0.28 ± 0.19</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Perfusion (ml/min/ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.14 ± 0.05</td>
<td>-0.08 ± 0.09</td>
<td>0.02*</td>
</tr>
<tr>
<td>R²</td>
<td>0.84 ± 0.15</td>
<td>0.47 ± 0.20</td>
<td>0.005*</td>
</tr>
<tr>
<td><strong>V̇A/Q</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.09 ± 0.08</td>
<td>0.04 ± 0.03</td>
<td>0.04*</td>
</tr>
<tr>
<td>R²</td>
<td>0.37 ± 0.22</td>
<td>0.23 ± 0.23</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Table 5. Measures of heterogeneity in supine and prone posture
(means ±SD, n = 7 supine, n = 6 prone)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Supine</th>
<th>Prone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density</td>
<td>RD</td>
<td>0.21±0.06</td>
<td>0.21±0.08</td>
</tr>
<tr>
<td>Alveolar ventilation</td>
<td>RD</td>
<td>0.27±0.06</td>
<td>0.19±0.06</td>
</tr>
<tr>
<td>Perfusion</td>
<td>RD</td>
<td>0.35±0.12</td>
<td>0.26±0.06</td>
</tr>
</tbody>
</table>
| V̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̍