Vertical distribution of specific ventilation in normal supine humans measured by oxygen-enhanced proton MRI


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Vertical distribution of specific ventilation in normal supine humans measured by oxygen-enhanced proton MRI. *J Appl Physiol* 109: 1950–1959, 2010. First published October 7, 2010; doi:10.1152/japplphysiol.00220.2010.—Specific ventilation (SV) is the ratio of the volume of fresh gas entering a lung region divided by its end-expiratory volume. To quantify the vertical (gravitationally dependent) gradient of SV in eight healthy supine subjects, we implemented a novel proton magnetic resonance imaging (MRI) method. Oxygen is used as a contrast agent, which in solution changes the longitudinal relaxation time (T1) in lung tissue. Thus alterations in the MR signal resulting from the regional rise in O2 concentration determine the local change in T1 (16). Thus measurement of the regional rate of change of the MRI signal allows the quantification of SV: after a change in inspired FIO2 reflect SV—lung units with higher SV reach a new equilibrium faster than those with lower SV. We acquired T1-weighted inversion recovery images of a sagittal slice of the supine right lung with a 1.5-T MRI system. Images were voluntarily respiratory gated at functional residual capacity; 20 images were acquired with the subject breathing air and 20 breathing 100% O2, and this cycle was repeated five times. Expired tidal volume was measured simultaneously. The SV maps presented an average spatial fractal dimension of 1.13 ± 0.03. There was a vertical gradient in SV of 0.029 ± 0.012 cm−1, with SV being highest in the dependent lung. Dividing the lung vertically into thirds showed a statistically significant difference in SV, with SV of 0.42 ± 0.14 (mean ± SD), 0.29 ± 0.10, and 0.24 ± 0.08 in the dependent, intermediate, and nondependent regions, respectively (all differences, P < 0.05). This vertical gradient in SV is consistent with the known gravitationally induced deformation of the lung resulting in greater lung expansion in the dependent lung with inspiration. This SV imaging technique can be used to quantify regional SV in the lung with proton MRI.

Specific ventilation (SV) is the ratio of the volume of fresh gas (ΔV) moving into a region of the lung to the end-expiratory volume (V0) of that region, SV = ΔV/V0. SV is thus a dimensionless quantity that provides a measure of how efficiently a given lung region is ventilated. Regional SV is an important metric from a physiological standpoint (14, 16, 23). Three approaches have been used in the past to quantify the distribution of SV in humans. 1) Inhalation of radioactive 133Xe gas (or other tracers) yields information on the spatial distribution of ventilation; however, the radiation dose limits the applicability of this method in repeated-measurement studies (14, 22). 2) Using multiple-breath nitrogen washouts, Lewis et al. (16) described a method to estimate the distribution of SV; however, this method does not yield spatial information. 3) More recently, magnetic resonance imaging (MRI) using hyperpolarized gases (129Xe and, more commonly, 3He) has been used to quantify ventilation (1, 17, 21). MRI measurements of hyperpolarized gas provide good spatial resolution and do not require ionizing radiation, but they have several disadvantages: 3He is a rare gas; 129Xe, although more readily available, is soluble in blood and has anesthetic properties; and hyperpolarization requires dedicated hardware and a specific 3He (or 129Xe)-dedicated MR imaging coil, different from those used for standard proton (1H) MRI. All of these factors limit its generalization to routine use.

With proton MRI, it has been shown that inhaled oxygen (O2) can be used as a contrast agent to verify the presence or absence of ventilation (5). Oxygen is weakly paramagnetic, and when in solution in lung tissues it produces a measurable decrease in the longitudinal relaxation time (T1) of tissues, increasing the signal intensity of an appropriately timed inversion recovery proton MR image. A small body of work has been published on oxygen-enhanced ventilation, mainly focusing on optimizing MRI acquisition and postprocessing of image data (3, 18–20, 27) and on detecting ventilatory defects (25, 28, 29) (reviewed recently in Ref. 26). These publications demonstrate the use of O2 as a contrast agent in the lung and have shown the ability to detect ventilation defects. However, O2-enhanced MRI signal contains more information than just the presence or absence of ventilation. The change in O2 concentration in lung tissues (determining the local change in T1) depends on the rate of change of the alveolar O2 concentration, which is a function of the regional SV (16). Thus measurement of the regional rate of change of the MRI signal allows the quantification of SV: after a change in inspired fractional O2 content (F1O2), units that have higher SV reach the new equilibrium faster than units that have a lower SV. Thus the rapidity of the change in the MRI signal in a particular voxel or region following a change in F1O2 is a quantitative measure of the SV of that portion of the lung.

Previous studies (14, 23) have shown a vertical gradient in SV, i.e., SV is gravity dependent, with the dependent lung being better ventilated (higher SV) than the nondependent lung. We hypothesized that we could measure SV with proton MRI by using O2 as a contrast agent. With this approach we have mapped the distribution of SV in the lung and, as a test case, its gravitationally dependent gradient.

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METHODS

Quantification of Specific Ventilation: Basis of Measurement

After a sudden change in inspired fraction of O₂ (FIO₂), the rate of change of the alveolar O₂ concentration is a function of the local SV: lung units with higher SV reach a new equilibrium faster than units with a lower SV. Therefore, the time it takes to reach a new equilibrium is a measure of the local SV. This time is reflected in the MR images. For a series of inversion recovery images acquired with appropriate scanning parameters, the signal intensity change observed after a change in inspired gas is determined by the change in T₁, a change driven by the local amount of O₂ in solution, which is a function of the local O₂ partial pressure. Therefore, the time course of the regional MR signal intensity resulting from a change in FIO₂ reflects local SV. More specifically, the rise time of the MRI signal intensity following the onset of O₂ inhalation—the time required for the signal to change to a new equilibrium level—is directly related to SV (Fig. 1).

As an empirical measure of the rise time, we used the time delay that maximizes the cross-correlation of the measured signal time course from an image voxel with a square wave representing the onset of increased inspired O₂ (dashed lines, Fig. 2A), and we refer to this as the correlation delay time. This approach is illustrated in Fig. 2A. Mathematically, the cross-correlation is maximized when the response is shifted by about half the rise time, so that different rise times effectively translate to different delays in the cross-correlation analysis, allowing us to use the correlation delay time as an empirical index of the rise time. This calculation is done for the entire time series corresponding to each image voxel. (Note that dead space in the plumbing leading from the gas containers to the subject introduces a true global delay, but this delay is calculated from the geometry and flow rate of the delivery system and eliminated before the cross-correlation analysis.) To relate the correlation delay time to SV, we modeled the experiment with a simple lung unit and simulated the signal changes during the series of consecutive breaths following a sudden change in FIO₂. The simulated data for units with different SVs were then analyzed with the identical cross-correlation method used for the experimental data to derive a calibration curve of SV versus correlation delay time. This calibration curve was used to convert the measured correlation delay times into a quantitative estimate of SV for each image voxel (Fig. 2B). The details of these steps are described below.

Model and Simulated Data

To translate the MRI signal rise time into a quantification of SV, we constructed a model of a lung unit corresponding to the voxel size measured during the MRI imaging (see below). The only variable of interest in the model is the rate of equilibration—the rise time—and not the equilibrium values. Therefore, dead space, water vapor, and end-tidal PCO₂, factors that change the steady-state equilibrium alveolar O₂ partial pressure (PAO₂) but remain largely constant during the experiment, are ignored in the following description. The model describes solely the temporal behavior of the O₂ concentration from the air-breathing equilibrium value to the new 100% O₂ steady state.

Different ventilation-perfusion ratios (V˙/Q˙) result in different steady-state O₂ concentrations, for both inspired air (range 50–140 mmHg, for V˙/Q˙ between 0.001 and 10) and 100% inspired O₂ (550–600 mmHg, for the same range of V˙/Q˙) (37). These steady-state equilibrium conditions provide adequate (and essentially similar) contrast for all reasonable V˙/Q˙. Furthermore, our model is independent of the equilibrium or steady-state conditions—it depends solely on the rate of equilibration. Two lung units presenting identical V˙/Q˙ and different SVs are still distinguishable from each other by the
different rates of equilibration, with the unit presenting a higher SV having a faster turnover, and thus equilibrating faster.

The two assumptions in this model are that 1) voxel dimension (1.6 mm in the imaging plane, for a 15-mm-thick slice, volume 40 mm³) is small enough such that concentrations inside the unit at end expiration can be considered uniform, and therefore each voxel can be treated as a single ventilatory unit and 2) the time interval between two consecutive acquired images (>5 s) is long enough so that equilibrium between oxygen in the gas phase and in solution in blood and tissues is attained by end expiration. The first of these assumptions is supported by simulation work by Paiva (30), Davidson (4), and Engel (7). Using either continuous (trumpet model) or discrete (asymmetric branch point) models of the acinus, these approaches have shown that at the scale of our resolution O₂ concentration would be expected to be constant within a single respiratory pathway. Simulations in asymmetric branch point models suggest that differences in O₂ concentration can persist among parallel respiratory units, yet within each unit the O₂ concentration gradient is essentially abolished, matching our assumption.

Subjects self-gate their breathing to the 5-s interval between consecutive image acquisitions. Oxygen dissolves in tissues very rapidly compared with this 5-s interval between images. For instance, for a normal, room air inspired breath, it takes ~0.25 s for oxygen to diffuse through a 0.5-μm-thick capillary wall and reach its equilibrium with hemoglobin in the pulmonary capillary (36), a process that includes dissolving in tissue as well as other processes. The process of simple dissolution in tissue thus is assumed to be complete within this same time frame, as in our second assumption.

Each voxel is simulated as a single ventilatory unit, with end-expiratory volume $V_e$, to which inspiration transiently adds $\Delta V$ during
each breath (Fig. 1). The initial concentration in the unit at end
expiration is denoted $C_0$, and $C_n (n = 1, 2, 3, \ldots)$ denotes the
concentration in the unit at end expiration after $n$ breaths.
Let $C_{\text{insp}}^n$ denote the concentration of oxygen in the inspired gas for
breath $n$; the subjects are breathing air ($FIO_2 = 0.21$) during the first
20 breaths and are then changed to a gas mixture enriched in oxygen
(in our experiment, $FIO_2 = 1.0$).
At the end of the first breath following the switch in $FIO_2$, the
concentration in the unit is:
$$C_1 = \frac{V_0 \cdot C_0 + \Delta V \cdot C_{\text{insp}}}{V_0 + \Delta V} \quad (1)$$
The same reasoning can be used to establish a recursive formula for
concentration after $n$ breaths:
$$C_n = \frac{V_0 \cdot C_{n-1} + \Delta V \cdot C_{\text{insp}}}{V_0 + \Delta V} \quad (2)$$
which in turn can be rewritten as a function of the unit’s SV, with $SV = \Delta V/V_0$, as:
$$C_n = \frac{1}{1 + SV} C_{n-1} + \frac{SV}{1 + SV} C_{\text{insp}} \quad (3)$$
This equation is used to model oxygen concentration. A simulated
response for an individual voxel is obtained, for a given set of $FIO_2$
breaths (dotted line in Fig. 1). Figure 1 presents the time series of
two units, one with low SV ($SV = 0.2$) and a second with high SV
($SV = 0.8$).
A linear relationship between $R_1 = 1/T_1$ and $FIO_2$ has been
consistently reported (13, 33). The slope and zero-crossing values
reported for the $R_1$-$FIO_2$ function (13) result in a near linear
relationship between $T_1$ and $FIO_2$ in the range used in the present
experiment ($FIO_2 = 0.21$ or 1.0).
On the basis of numerical simulations, for the inversion time of our
experiment ($T_1 = 1,000$ ms) and the variation of $T_1$ with inspired
oxygen concentration reported by Jakob et al. (13), the error involved
in assuming that the MR signal varies linearly with oxygen concentra-
tion is <3% for these studies. Our calibration curve is based on
this assumption.

**Time-Shifted Cross-Correlation Between Driving Function and Simulated Units**

To determine the correlation delay time we computed the cross-
correlation between each simulated ventilatory unit response (contin-
uous and dashed lines, Fig. 1, bottom) and $FIO_2$ (dotted line, Fig. 1, bottom). The $FIO_2$ curve was shifted breath by breath, and the time
shift that maximizes the time-shifted cross-correlation is a measure of
how fast the unit equilibrates—correlation delay time (computed
similarly to Ref. 32). This is illustrated, for two simulated units ($SV = 0.12$ and $SV = 0.72$), in Fig. 2, top: the continuous line depicts the
unit response, and the dashed line depicts the time-shifted $FIO_2$ curve
that maximizes cross-correlation.

We simulated units with SV ranging from 0.05 to 1 in steps of 0.05,
and the simulated signal was analyzed by using the time-shifted
cross-correlation. The outcome of these simulations is shown in Fig.
2B. This figure is a conversion tool, allowing the translation of
correlation delay time measured by using the proton-MRI acquired
time series into quantitative values of ventilation, on a voxel-per-
voxel basis. Figure 2B also shows that when $SV$ is above 0.5 this
analysis is incapable of determining differences in $SV$ and lumps all
ventilations above that threshold. This is because equilibration for
these high-$SV$ units happens sufficiently fast that the correlation delay
time is less than 1 breath, and thus not resolvable. However, on the
basis of previous studies, relatively few lung units have $SV$ higher
than 0.5 (16), and the presence of lung disease is typically associated
with the development of regions of reduced $SV$ (11), as opposed to
increased $SV$, making this limitation of relatively minor significance.

Figure 2B also shows that, as expected, for a given measured
correlation delay time ($y$-axis) the corresponding $SV$ depends not only
on the $SV$ but also on an extrinsic delay resulting from plumbing
volume in the inspiratory line (see Specific ventilation imaging pro-
tocol below). In essence, any volume that exists within the experi-
mental configuration between the subject’s mouth and the valve used
to change between gases of different $FIO_2$, introduces a delay that will
appear to artificially reduce $SV$ unless properly accounted for. This
emphasizes the need to determine this delay by measuring respiratory
flow and inspiratory plumbing volume.

**Magnetic Resonance Imaging Data Collection**

**Subjects.** We studied eight healthy subjects (3 female, 5 male
subjects) in the supine posture. Table 1 presents subject characteristics
(sex, age, height, and weight) and pulmonary function data [forced
expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and
FEV1/FVC]. The Human Subjects Research Protection Program of the
University of California, San Diego, approved this study, and subjects
participated after giving written informed consent.

**MRI Data.** Data were collected with a 1.5-T Sigma HDx TwinSpeed MRI
system (General Electric Medical Systems, Milwaukee, WI). A single
sagittal slice was selected in the right lung, in order to avoid physi-
ological noise arising from cardiac movements. Slice selection was
aimed at selecting the slice within the lung presenting the largest
anterior-posterior dimension, while avoiding major hilar vessels.

**Specific ventilation imaging protocol.** Two-dimensional T1-weighted
images were acquired with an inversion recovery ($T_1 = 1,000$ ms)
single-shot fast spin echo (SSFSE) sequence, with images being acquired
with a half-Fourier acquisition [half-Fourier acquisition single-shot
turbo spin echo (HASTE)], with a $40 \times 40$-cm field of view, echo
time of $\sim30$ ms, and a 15-mm image slice thickness. A MRI

| Subject | Sex | Age, yr | Height, m | Weight, kg | FEV1, liters (% predicted) | FVC, liters (% predicted) | FEV1/FVC (% predicted) | $-1/slope$, cm$^{-1}$ | Spatial Fractal Dimension |
|---------|-----|---------|-----------|------------|--------------------------|--------------------------|------------------------|----------------------------|
| S1      | M   | 33      | 1.81      | 81         | 3.99 (88)                | 5.17 (93)                | 0.77 (95)              | 0.020                      | 1.15                      |
| S2      | M   | 26      | 1.85      | 93         | 4.57 (92)                | 5.28 (87)                | 0.87 (105)             | 0.015                      | 1.15                      |
| S3      | F   | 26      | 1.73      | 68         | 4.13 (115)               | 5.04 (118)               | 0.82 (96)              | 0.031                      | 1.15                      |
| S4      | F   | 39      | 1.62      | 66         | 3.03 (101)               | 3.65 (99)                | 0.83 (101)             | 0.038                      | 1.09                      |
| S5      | F   | 24      | 1.76      | 92         | 3.08 (102)               | 3.65 (99)                | 0.84 (102)             | 0.043                      | 1.11                      |
| S6      | M   | 52      | 1.86      | 113        | 4.50 (105)               | 5.36 (96)                | 0.84 (109)             | 0.046                      | 1.10                      |
| S7      | M   | 34      | 1.78      | 83         | 3.84 (89)                | 4.98 (93)                | 0.77 (95)              | 0.070                      | 1.16                      |
| S8      | M   | 28      | 1.70      | 60         | 4.43 (107)               | 5.16 (103)               | 0.86 (104)             | 0.019                      | 1.13                      |

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity. *Group average significantly different from zero, $P = 0.0002$.  

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homodyne reconstruction algorithm rescaled the data to a $256 \times 256$ matrix, with each voxel thus corresponding to $1.6 \times 1.6 \times 15$ mm ($\approx 40$ mm$^3$). A $T_1$ of 1,000 ms, approximating $T_1$ of lung tissue, ensured maximal sensitivity to changes in $O_2$ concentration (3). The long repetition time used in this SSFSE sequence (5 s, compared with the $T_1$ of blood, 1.4 s) renders the $O_2$-induced contrast independent of lung density; however, lung density does alter the local signal-to-noise ratio. HASTE acquisition was utilized to keep the echo time short to minimize signal loss due to the very short transverse relaxation time ($T_2^*$) observed in the lung (9, 34). Images were voluntarily respiratory gated. Subjects were instructed to take a normal breath in following the noise made by the MR image acquisition, and relax back to functional residual capacity (FRC), at a comfortable expiratory flow rate. All our subjects were comfortable with the default 5-s interbreath intervals (12 breaths/min). Images were acquired during a short (approximately hundreds of milliseconds), postexpiratory breath hold at FRC, resulting in a relatively natural respiratory maneuver only constrained by a constant breathing rate.

The addition of $O_2$ as a contrast agent followed a block-design functional MRI (fMRI) approach, typically utilized for neuroimaging studies. A lung image was acquired every 5 s, with 20 images acquired with the subject inspiring air (21% oxygen), and 20 images with the subject inspiring 100% $O_2$. This cycle was repeated five times, and an additional 20 breaths of 100% oxygen were added at the end of the last cycle, making a total of 220 images (total imaging time was 18 min 20 s). Blocks of 20 breaths of air and 100% oxygen were chosen to ensure an approach to full equilibration, for the ranges of SV and V/Q observed in normal healthy subjects (16, 35), in accordance with what has been observed in prior multiple-breath washout studies (31). Five cycles of air-oxygen provided an acceptable signal-to-noise ratio and were implemented as a compromise between keeping the total acquisition time below 20 min and an improved signal-to-noise ratio that would result from a longer sequence.

A face mask (Hans Rudolph; dead space 73–113 ml, depending on mask size) equipped with a nonrebreathing T valve (dead space 27.9 ml) was fitted to the subject. One end of the T valve was connected to the inlet, where a remote-controlled three-way pneumatic sliding valve (Hans Rudolph model 8500) allowed rapid switching between room air and $O_2$ contained in a 170-liter Douglas bag (Hans Rudolph type 6170). The inspiratory path resistances on the room air and $O_2$ circuits were matched to eliminate changes in FRC following changes in inspiratory path. The outlet of the T valve was connected to a $\sim 6$-m-long large-bore low-resistance expiratory line, leading out of the scanner room, where expired tidal volume was simultaneously measured with a ParvoMedics Metabolic Measurement System (ParvoMedics, Sandy, UT).

The experimental configuration for controlling the inspired gas (room air, 100% oxygen) introduced an extrinsic plumbing delay in the inspired signal that is determined by the volume of tubing that connects the remote control valve to the subject. This volume was made as small as possible (0.6 l) under constraints imposed by working in an MRI environment. This delay can be computed from each subject’s tidal volume and the tubing volume, by dividing the tubing volume by the tidal volume. In practice, this extrinsic delay was taken into account by computing individual inspired fractional oxygen concentration (FIO$_2$) time series on a breath-by-breath basis ($\Delta$Eq, in Eq. 3), taking the tubing volume as a delay chamber of fixed volume through which the inspired gas must pass. Once this extrinsic plumbing delay is corrected for, what is left corresponds to the signal intensity change over time, allowing the computation of SV as described in Specific ventilation imaging data analysis.

Specific ventilation imaging data analysis. A time series of the 220 images corresponding to the specific ventilation imaging (SVI) sequence was constructed. Quality control of the acquired image was performed at this stage, and images where the subject was not at FRC based on diaphragm position compared with adjacent images were removed from the series and replaced by an interpolated image constructed from the preceding and following images. A region of interest was manually drawn, and the subsequent analyses were restricted to the voxels inside the lung. The region of interest encompassed the entire lung, yet avoided partial volume effects from regions close to the chest wall and the diaphragm. Data analysis was performed on a voxel-by-voxel basis; the time course of each voxel—MRI signal intensity versus time—was used to compute the regional correlation delay time. All data analysis was performed with Matlab (Mathworks, Natick, MA).

**Fig. 3. Time series of signal intensity for a single voxel.** When the subject changed from breathing air to oxygen, signal intensity increased. FIO$_2$ is represented by the dashed line. Once the extrinsic plumbing delay has been accounted for, the correlation delay time (expressed in number of breaths) between the FIO$_2$ driving function and each voxel’s time series is a quantitative measure of ventilation. Units with higher SV equilibrate faster; thus signal intensity increases faster, and correlation delay time is shorter, than for units with lower SV. With application of the modeling and signal-processing algorithm described in METHODS, different correlation delay times were converted into a physiologically meaningful measure of SV. The correlation delay time for this voxel was 2 breaths, corresponding to a SV of 0.35 ($P < 0.0001$).
We computed the correlation delay time, using a shifted cross-correlation between the F\textsubscript{IO2} and the acquired signal intensity time series. The time-shifted cross-correlation is a fast and simple approach to implement, fitting only one parameter, the correlation delay time, and is independent of the asymptotic signal intensity. By removing this extra degree of freedom, the model can remain simple while capturing only the time course of the transition, leaving out the physiological dead space, water vapor, CO\textsubscript{2} concentration, and any effect of varying V/Q factors that alter the steady-state concentration but not the time course of the transition. Moreover, the shifted correlation delay approach acts as a smoothing low-pass filter, eliminating some of the high-frequency noise present in our data that did not allow a direct fit of the model (Eq. 3). In practice, the F\textsubscript{IO2} (driving function) is correlated with the time course of each voxel, and this process is repeated for delayed versions of the driving function (delayed by an integer number of breaths). The integer delay that maximizes the cross-correlation between the time-shifted driving function and the actual voxel response is the correlation delay time. The correlation delay time computed in this way will only retain voxels whose correlation with the optimal shifted F\textsubscript{IO2} was significant (P < 0.05) and the null hypothesis of no correlation rejected in these cases. In voxels in which the null hypothesis was accepted, the corresponding lung voxel was attributed no specific ventilation value and treated hereafter as missing data.

Figure 3 (filled circles, continuous lines) shows the time course of signal intensity for one such voxel. The arbitrarily chosen voxel plotted was located in the dependent portion of the lung. The corresponding driving function representing F\textsubscript{IO2} is also shown (Fig. 3, dotted line). The delay between the driving function and the measured signal intensity is a measure of the correlation delay time for that voxel.

Statistics

Each series of 220 breaths was considered as a single measure of SV, computed as described above, creating for each subject one map of SV. All the voxels presenting a statistically significant (P < 0.05) correlation with the optimally shifted drive function were included in the analysis. The remaining voxels were treated as missing data. Two different analyses were implemented: a comparison of SV by lung thirds and a finer analysis, on a centimeter-per-centimeter basis moving up the supine lung.

For the lung thirds analysis, SV was partitioned into three gravitational regions, corresponding to thirds of the lung based on equal vertical extent: the dependent portion, the intermediate region, and the nondependent region. The data were reduced to a subject-by-subject average SV per lung gravitational region. One-way repeated-measures ANOVA was used to compare the gravitational gradient in SV across the lung regions (3 levels: dependent, intermediate, nondependent). Where overall significance was present, post hoc testing was conducted with Student’s t-test, to determine where this significance occurred.

In a second analysis, linear regression was used to evaluate the linear relationship between the vertical height of the lung and SV, by dividing the data into isogravitational slices of 1-cm thickness (~6 vertical voxels). As subjects were studied in the supine position, the vertical height of the lung (isogravitational level) was measured along the anterior-posterior axis, with zero height corresponding to the most dependent isogravitational voxels. The linear relationships were evaluated independently for each subject. The intersubject averaged SV versus lung height values correspond to averages over vertical 1-cm regions for the eight subjects. Different subjects have different anterior-posterior lung dimensions; therefore, results are reported only for lung heights that included data from all eight subjects. The slope of the individual relationships between height and SV were compared with a zero slope by a one-group t-test.

All data are presented as means ± SD. When data for the eight subjects were averaged, SD corresponds to the intersubject variability. When relative dispersion is calculated, spatial SD refers to the intervoxel variability within a SV map. Spatial fractal dimension, a scale-independent index of spatial heterogeneity, was also computed for each SV map (8). The null hypothesis (no effect) was rejected when P < 0.05, two tailed, except where otherwise indicated. All statistical analyses were performed with Prism (GraphPad, San Diego, CA).

RESULTS

General Data

Subject descriptive data and pulmonary function measurements are presented in Table 1. The subjects studied had normal spirometry, as indicated by an average FEV\textsubscript{1} = 100 ± 10% predicted, FVC = 99 ± 9% predicted, and FEV\textsubscript{1}/FVC =

Fig. 4. A: correlation delay time map (in number of breaths) in a sagittal slice of the right lung of a typical subject. B: corresponding SV map, using the “translation” shown in Fig. 2B. In this plane, the head is located on right and the diaphragm on left. The vector g indicates the direction of gravity. The subject was supine. Note the shorter correlation delay time in the dependent regions (A), which indicates a greater SV in these regions than in the nondependent lung (B).
lated units had converged to their best estimation. As expected, analysis was restricted to the first 40 breaths 51.6% of simulating to 1, 2, 3, and 4 cycles, respectively). These estimations of air-oxygen cycles (first 40, 80, 120, 160 breaths, corresponding to 1.8% for oxygen. To test the robustness of the algorithm we have run the model with similar levels of noise (consistent with the experimental data). The data processing algorithm estimated SV by using an increasing number of cycles. The number of units presenting a significant correlation with the driving function increased as the analysis was extended to an increasing number of cycles.

From each individual voxel response, a map of the correlation delay time for all voxels within the lung was computed and is presented for a representative subject in Fig. 4A. The arrow indicates the direction of gravity; the head is located to the right of the image, and the diaphragm to the left. In Fig. 4A, warmer colors represent portions of the lung with a longer correlation delay time. The extrinsic delay resulting from the inspiratory plumbing was accounted for before the analysis. With the results presented in Fig. 2B, this correlation delay time was then translated into a quantitative measure of SV (Fig. 4B). In Fig. 4B, warmer colors represent regions of the lung with higher SV. Average SV in a slice of the right lung, averaged over all subjects, was 0.33 ± 0.11. Overall SV heterogeneity, as measured by the relative dispersion, averaged 0.63 ± 0.11 (individual range 0.50–0.79), comparable to that previously reported for perfusion (12). The average spatial fractal dimension of the SV maps was 1.13 ± 0.03 (individual range 1.09–1.16; Table 1), similar to that derived for perfusion maps (15).

On average (over all subjects), 3.7% of the lung failed to pass the null hypothesis test in the shifted correlation (individual range 0.1–17.8%; only a single subject had >5% of voxels), showing no statistically significant changes with changes in $F_{O_2}$. These voxels were excluded from the subsequent analysis.

In Fig. 4B a clear vertical (gravitational) gradient of SV is present. Units in the dependent portions of the lung have higher SV than those in the nondependent portions of the lung. This relationship is quantified in Fig. 5, where results for the regional dependence of SV over the eight subjects bring out such a relationship: a statistically significant difference in SV was observed, with the most dependent third of the lung having a SV of 0.42 ± 0.14, the intermediate third 0.29 ± 0.10, and the nondependent third 0.24 ± 0.08 (all differences, $P < 0.05$).

An approximately linear decrease in SV with height was observed, as evidenced in Fig. 6, where SV is plotted against height for one subject (Fig. 6A) and for the eight individual subjects (Fig. 6B). The average over all subjects is presented in

![Fig. 5. SV per third of the lung, grouped by the vertical distance from the most dependent portion. ANOVA for repeated measures comparing all 3 regions showed a highly significant difference (F = 26.8, $P < 0.0001$). Post hoc testing (paired t-test) $P$ values are shown (7 degrees of freedom, $t$ values of 5.5, 2.4, and 5.8 for the dependent-intermediate, intermediate-nondependent, and dependent-nondependent region paired comparisons, respectively).](http://jap.physiology.org/)

**Specific Ventilation Imaging**

Figure 3 presents the time series of a voxel (continuous line) together with the inspired $F_{O_2}$ (dotted line) for a voxel in the dependent lung region. Five repetitions of a block of 20 air breaths and 20 100% oxygen breaths were performed. Signal intensity increased when the inspired line was changed from air to 100% oxygen and decreased for the opposite change, from oxygen back to room air. After the five cycles of air-100% oxygen, 20 additional breaths on 100% oxygen were added. Noise, expressed as the CV of the steady-state signal (first 20 breaths on air and last 20 breaths inspiring $O_2$) averaged over the entire lung of the eight subjects studied, was 22.8 ± 1.5% for air and 18.4 ± 1.8% for oxygen. To test the robustness of the algorithm we have run the model with similar levels of random noise. The average SV estimation error introduced by 20% noise levels is extremely small (average error in estimating SV ~0.003); the maximal SV estimation error was −0.013 and was observed for very low-SV units (SV < 0.02), below the normal healthy range (16).

The convergence of the data processing algorithm to a solution was tested by using simulated data with 25% added noise (consistent with the experimental data). The data processing algorithm estimated SV by using an increasing number of air-oxygen cycles (first 40, 80, 120, 160 breaths, corresponding to 1, 2, 3, and 4 cycles, respectively). These estimations were compared with the best estimation of SV, obtained by using the entire 220-breath simulated time series. When the analysis was restricted to the first 40 breaths 51.6% of simulated units had converged to their best estimation. As expected, as the number of cycles increased, so did the number of units having converged: 90.9% for 2 cycles, 97.7% for 3 cycles, and 98.8% when the first 160 breaths were used for the analysis (4 cycles). The number of units presenting a significant correlation with the driving function increased as the analysis was extended to an increasing number of cycles.

101 ± 5% predicted (Table 1). Subjects maintained a relatively constant expired tidal volume throughout the experiment, averaging 0.87 ± 0.18 liters. Heart rate during SVI data acquisition averaged 65 ± 9 beats/min (no difference between inspiration and 100% oxygen), and arterial oxygen saturation ($S_{O_2}$) measured by pulse oximetry was 97.4 ± 1.7% during breathing of room air and increased to 97.8 ± 1.5% during inspiration of 100% oxygen. The selected breathing rate was followed by all subjects, and tidal volume was relatively stable throughout the 220 breaths [the average coefficient of variation (CV) for the 8 subjects was 16%]. Tidal volume did not change when comparing breaths taken while inspiring air and oxygen (average over 8 subjects: 0.86 ± 0.15 vs. 0.87 ± 0.17 l; 2-tailed $t$-test paired comparison, $P = 0.82$).

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The inverse of the slope of this line is a measure of the decrease in SV per centimeter. SV was found to decrease 0.029 ± 0.012 cm⁻¹ (average slope over the 8 individual subjects). Subject-by-subject fitted slopes, reported in Table 1, showed a decrease in SV with increasing height ranging from 0.015 to 0.046 cm⁻¹. The slope of the height-SV relationship was significantly different from a zero slope (P = 0.0002). An exception to the linearity is present in the most dependent portions of the lung (height < 1.0 cm). This most dependent portion of the lung had, on average, lower SV than the layers immediately above them; however, this difference failed to reach statistical significance.

Two independent SV maps of subject S1 were obtained, 20 days apart. A Bland-Altman analysis on the centimeter-per-centimeter SV data was performed; the average difference between the two runs was found to be 3.0%, with a 95% confidence interval of ±9.5%.

**DISCUSSION**

This study shows that with O₂-enhanced proton MRI regional quantification of SV is possible, extracting more information from the method than the mere absence or presence of ventilation. From a physiological standpoint, SVI shows a clear gravitational gradient, with higher values seen in dependent lung as expected. The springlike self-deformation of the lung (23), the Slinky effect (12, 23), is likely the main determinant of the gravitational gradient observed in SV. However, in the most dependent third of the supine lung there are deviations from this overall behavior, suggesting important influences of other factors such as the nonlinearity of the pressure-volume curve of the lung, the large vessels in the lung, and dependent airways closure.

**Vertical Gradient in Specific Ventilation**

The measurements show a clear, and for the most part, linear vertical gradient in SV (Figs. 4 and 6). As expected, the dependent portions of the lung have a higher SV than the nondependent portions (Fig. 5). Because the dependent portion of the lung partially supports the weight of the upper portions, it is more “compressed,” and therefore its V₀ is smaller. Furthermore, it is subject to a higher (less negative) pleural pressure than an equivalent nondependent region, therefore placing it on a steeper portion of the pressure-volume curve. Therefore, a given change in pleural pressure resulting from an inspiratory effort will result in a greater increase in volume. Both the lower initial (end-expiratory) volume and the increased change in volume would be expected to contribute to the higher SV observed in the dependent regions of the lung compared with the nondependent region (36).

**Comparison with Published Specific Ventilation Distributions**

Kaneko et al. (14), using a 133Xe technique, reported a vertical gradient of SV for three supine subjects (normal healthy subjects of similar age to the group studied here) of 0.020, 0.022, and 0.026 cm⁻¹, in close accordance with the 0.029 cm⁻¹ measured with our SVI technique. Using two different krypton isotopes, Amis et al. (2) reported a vertical gradient of SV in three supine subjects and found a ~45% decrease from the most dependent part of the lung to the most nondependent portion, in close accordance with the ~53% decrease found in our data. Using PET, Musch et al. (24) reported a SV gradient relative to the mean, in the supine posture, of ~4.5 ± 2.5%, slightly lower than the ~8.4 ± 1.9% (range 5.3–10.2%) we observed in our group.
The breathing pattern used for image acquisition in this particular study is not directly comparable to that presented here, for it starts with a 40-s breath hold, followed by \(\sim 160\) s of free breathing.

Prisk et al. (31) reported an average SV of 0.364 \pm 0.028, in a population of four supine subjects somewhat older than those studied here (average age 43 yr compared with 33 yr in this study) and with tidal volume constrained to \(\sim 650\) ml. This compares with an average of 0.33 \pm 0.11 in our subject group (individual range 0.19–0.47) and suggests a close agreement between the techniques. Comparison with upright subjects is inappropriate since there are large changes in FRC with posture (6), which serves to alter SV.

Possible Effects of Airways Closure

The approximately linear increase in SV with decreasing lung height is not always seen in the most dependent portion of the lung (Fig. 6C). Airway closure occurs when small airways, thought to be respiratory bronchioles, collapse, resulting in trapped gas in the alveoli distal to that point. Trapped gas means higher initial volumes and also lower volumes of inspired air, both effects contributing to a decrease in SV (36). We observed SV patterns consistent with airway closure in four of the eight subjects imaged (subjects S3, S4, S7, and, to a lesser extent, S5). For these subjects, SV in the most dependent part of the lung (height \(< 1\) cm) was lower than in the subsequent 1- to 2-cm-height slice.

Assumptions and Limitations

The technique is currently limited to a single lung imaging slice. For each subject, we selected a midlung sagittal slice in the right lung that presented a low percentage of large vessels. Large pulmonary veins transport to the imaging plane changes in \(\text{O}_2\) concentration that occur in distant regions of the lung. In different lung slices or imaging planes, this can be a confounding effect, addressable by masking of large vessels based on voxel intensity (10).

The present voxel size corresponds to rodlike shaped structures, with 1.6 \(\times\) 1.6 mm in the plane surface but 15 mm in the perpendicular direction. An individual voxel may contain multiple adjacent acini, and as such the method measures the average response. The true resolution obtained in SVI is somewhat lower than the nominal resolution, because of small registration errors that inevitably occur from image to image, resulting in some averaging of responses of neighboring in-plane voxels.

In our present implementation, we have assumed that the subject reaches a constant and reproducible FRC for each acquired image and that each breath is identical (a tidal breath). Based on the measured tidal volume data this was true in this subject population; however, this might prove not to be the case for studies in some patient populations. Patients might not be able to comply with the 220-breath sequence and might be less proficient in attaining a reproducible FRC. In such circumstances, subject training, respiratory MR image acquisition triggering, image registration, or an individualized approach to translating correlation delay time to SV in the face of changing total ventilation might be required. Misregistration resulting from patient movement or failure to attain FRC at the time of imaging introduces an additional error in the measurement of SV. Image registration of deformable structures such as the lung is not an easy task, yet it will likely be required for the extension of the proposed method to patients suffering from severe pulmonary disorders. We anticipate that the signal-to-noise ratio associated with our measurement will be worse in patients with lung disease such as chronic obstructive pulmonary disease (COPD). Low signal-to-noise ratio might only impact specific regions of the lung, namely regions with lower SV than that observed in normal healthy subjects; low-SV regions are known to be present in patient populations (16). To capture regions of lower SV, longer blocks of air-oxygen would be required; longer blocks improve contrast, especially in low-SV units, as they allow more time for equilibration. Depending on the specific signal-to-noise conditions of the population and their ability to cope with longer periods in the scanner, this can be achieved either by reducing the number of cycles or by extending the total acquisition time.

Breathing 100% \(\text{O}_2\) will result in a small increase of hemoglobin-bound \(\text{O}_2\) (by \(\sim 1\%\) in this study). The main effect of hemoglobin-bound \(\text{O}_2\) is a T2* change and a much smaller effect on the T1 (5). Adapting the data reported by Silvennoinen et al. for a 1.5-T field (33), a 1% \(\text{SaO}_2\) increase would be expected to result in a <0.5% change in the T1 of blood, a negligible effect compared with the observed 12.5% change in T1 between breathing 21% \(\text{O}_2\) and 100% \(\text{O}_2\) (3, 13). Thus the measurement is dominated by the increase in the amount of oxygen in solution in blood and tissues and not by the increase in hemoglobin-bound oxygen.

Conclusion

Quantification of SV in the human lung is practical with proton MRI SVI, which uses \(\text{O}_2\) as a contrast agent. As expected, there was a clearly defined vertical gradient in SV in the supine human lung, and this was most likely a result of the self-deformation of the lung (the Slinky effect). However, in the most dependent third of the lung, other factors such as dependent airways closure, the nonlinear nature of the lung pressure-volume curve, and the large pulmonary vessels likely play important roles in determining regional SV over and above Slinky behavior.

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DISCLOSURES

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

REFERENCES

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