Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans

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Departments of 1Anesthesia and Critical Care, 2Radiology (Division of Nuclear Medicine), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; 3Departments of Anesthesia and Critical Care, Medicine (Pulmonary and Critical Care Unit), and Radiology (Division of Nuclear Medicine), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; 4Massachusetts Institute of Technology, Boston, Massachusetts 02139; and 5Clinical of Anesthesiology and Intensive Care Medicine, University Clinic Carl Gustav Carus, Dresden University of Technology, Dresden 01307, Germany

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Musch, Guido, J. Dominick H. Layfield, R. Scott Harris, Marcos F. Vidal Melo, Tilo Winkler, Ronald J. Callahan, Alan J. Fischman, and Jose G. Venegas. Topographical distribution of pulmonary perfusion and ventilation, assessed by PET in supine and prone humans. J Appl Physiol 93: 1841–1851, 2002; 10.1152/japplphysiol.00223.2002.—Using positron emission tomography (PET) and intravenously injected 13N2, we assessed the topographical distribution of pulmonary perfusion (Q) and ventilation (V) in six healthy, spontaneously breathing subjects in the supine and prone position. In this technique, the intrapulmonary distribution of 13N2, measured during a short apnea, is proportional to regional Q. After resumption of breathing, regional specific alveolar V (sV A, ventilation per unit of alveolar gas volume) can be calculated from the tracer washout rate. The PET scanner imaged 15 contiguous, 6-mm-thick, slices of lung. Vertical gradients of Q and sV A were computed by linear regression, and spatial heterogeneity was assessed from the squared coefficient of variation (CV2). Both CV2 Q and CV2 sV A were corrected for the estimated contribution of random imaging noise. We found that 1) both Q and V had vertical gradients favoring dependent lung regions, 2) vertical gradients were similar in the supine and prone position and explained, on average, 24% of Q heterogeneity and 8% of V heterogeneity, 3) CV2 Q was similar in the supine and prone position, and 4) CV2 sV A was lower in the prone position. We conclude that, in recumbent, spontaneously breathing humans, 1) vertical gradients favoring dependent lung regions explain a significant fraction of heterogeneity, especially of Q, and 2) although Q does not seem to be systematically more homogeneous in the prone position, differences in individual behaviors may make the prone position advantageous, in terms of V-to-Q matching, in selected subjects.

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measuring the concentration of $^{13}$N$_2$ during apnea and the ensuing period of $^{13}$N$_2$ washout, the topographical distributions of Q and V can be assessed separately. The potential advantages of this method include its ability to assess both Q and V with a single administration of tracer, its minimal invasiveness, and the low radiation exposure to the subject. These characteristics might make this method suitable for future clinical applications in a variety of lung diseases.

In the present study, we used the $^{13}$N$_2$ bolus infusion technique and PET to pursue two aims: 1) to assess the topographical distribution of Q and V in healthy, spontaneously breathing humans in the supine and prone position and 2) to quantify the amount of spatial heterogeneity of Q and V explained by a vertical gradient, after accounting for the estimated contribution of random imaging noise to the measured heterogeneity of Q and V.

**METHODS**

*Experimental Subjects*

We studied six healthy adults (3 men, 3 women; ages 19–32 yr). All subjects were nonsmokers and nonobese and had normal pulmonary function tests. Informed consent was obtained from each subject before the study.

$^{13}$N$_2$-Saline Bolus Infusion Technique

To assess regional lung function, we used the $^{13}$N$_2$-saline bolus infusion technique (9, 14, 29, 32). Simultaneously with the start of a $^{13}$N$_2$-saline bolus infusion, the collection of a PET scan of the thorax was initiated. Each PET scan consisted of a series of consecutive PET images, acquired during an apnea (40 s) and the ensuing period of tracer washout. As the injected tracer reached the lung, its concentration rose until it reached a plateau for the remainder of the apnea (~30 s). When the subject resumed breathing, the tracer concentration decreased as $^{13}$N$_2$ was eliminated by ventilation (washout). From the tracer kinetics (Fig. 1), regional lung function was assessed for each volume element of lung in the tomogram (i.e., voxel) as follows.

**Assessment of Q.** The theoretical basis for the measurement of Q $^{13}$N$_2$ concentration during apnea was provided in detail by Mijailovich et al. (14). Because of the low solubility of $^{13}$N$_2$ in blood and tissues (partition coefficient $k_{water/air} = 0.015$ at 37°C), on arrival into the pulmonary capillaries, virtually all the tracer diffuses into the alveolar air space at first pass (23, 24, 30), and regional tracer content during apnea is proportional to regional Q (14, 32). Mean-normalized regional Q could thus be expressed as the ratio between tracer concentration in each voxel and mean tracer concentration of all voxels in the imaged lung field, measured during the plateau phase of the apnea. This approach to the calculation of Q is justified by the fact that $^{13}$N$_2$ reabsorption into pulmonary venous blood during the apnea is negligible in a normally aerated and perfused lung (see APPENDIX and Fig. 1).

**Assessment of V.** As the subject resumed spontaneous breathing, $^{13}$N$_2$ was eliminated from the lung almost exclusively by ventilation (30). Specific alveolar ventilation (VA, alveolar ventilation (VA) per unit of alveolar gas volume) was calculated as the reciprocal of the time constant ($\tau$) of the tracer washout curve (see APPENDIX). For a monoexponential washout, $\tau$ corresponds to the mean residence time (MRT) of the tracer (31) defined as

$$MRT = \int_0^\infty \frac{c(t)}{C_w} \, dt$$

where $c(t)$ is the concentration of $^{13}$N$_2$ at time $t$ and $C_w$ is the concentration of $^{13}$N$_2$ at the beginning of the washout [i.e., $c(0) = C_w$]. Because the amount of tracer remaining in the lung at the end of the washout was negligible (0.2–2.1% of the initial concentration), the integral in $\text{Eq. 1}$ was approximated by the integral of the tracer concentration over the finite washout imaging time. For each voxel, $sV/A$ was calculated as the reciprocal of the MRT.

**PET Transmission Scan**

A 10-min transmission scan was recorded for each subject in both body positions by using a uniform rotating pin-source of $^{68}$Ge (Fig. 2). The transmission scan was used to correct the emission scan for energy attenuation caused by body tissues and supporting structures, to demarcate the lung field, and to calculate fractional gas content (F$_{gas}$), as previously described (4, 9, 30). F$_{gas}$ represents the fraction of the volume of a voxel occupied by gas.

**Experimental Setup**

We used a PC-4096 PET scanner (Scanditronix) that imaged 15 contiguous, 6-mm-thick slices of thorax with an in-plane spatial resolution of 6 mm full width half maximum (FWHM).
Impedance plethysmography (Respirtrace, Non-Invasive Monitoring Systems, Miami Beach, FL) was used to monitor tidal volume and respiratory rate and to ensure that the subject held his or her breath at mean lung volume for the duration of the apnea. 

$^{13}$N$_2$ gas was dissolved into sterile saline solution. The specific activity of the injectate was $0.38 \pm 0.05$ (means $\pm$ SD) $\mu$Ci/ml and a dose of $8.9 \pm 2.3$ $\mu$Ci per scan was injected at a rate of 5 ml/s in a peripheral vein. This corresponded to a radiation exposure of $17.8 \pm 4.6$ mrem per scan.

**Experimental Protocol**

The study protocol was approved by the Human Research Committee of our Institutional Review Board. Subjects were randomized to start in the supine or prone position (subjects 1, 2, and 5 started supine, and subjects 3, 4, and 6 started prone). After placement of an intravenous catheter in one antecubital vein, subjects lay recumbent on the PET scanner table with arms abducted and thorax in the PET scanner field up to the level of the axilla. A 10-min transmission scan was then collected, after which the subject was instructed to take two large breaths to total lung capacity and then to resume normal breathing for five additional breaths. During the expiratory phase of the fifth breath, when mean lung volume was reached, as assessed by the Respirtrace, the subject was instructed to stop exhalation and remain apneic for 40 s. The lung volume signal from the Respirtrace was monitored continuously to ensure the absence of ventilation during the apnea. At the end of this period, spontaneous ventilation was resumed and the subject was encouraged to maintain a regular breathing pattern despite the increased respiratory drive that followed the apnea. The apnea was performed at mean lung volume to ensure that the lung volume during the apnea was the same as the mean lung volume during the washout. This should limit the effect of image registration artifacts on the measurement of $sV_A$.

Simultaneously with the beginning of the apnea, a bolus of $^{13}$N$_2$-saline was injected intravenously and a PET scan lasting 3 min and 40 s (40 s of apnea followed by 3 min of washout) was started. Each PET scan consisted of a series of sequential PET images. At the end of the scan, the subject turned to the opposite body position, and the imaging protocol was repeated. Care was taken to image the same cross section of thorax in both body positions by aligning the laser pointer of the PET scanner with skin marks on the chest of the subject.

Four subjects had an additional emission scan in the last of the two body positions (subjects 2 and 5 had two prone scans and 3 and 4 had two supine scans). This third scan, taken ~30 min after the second scan, was used to assess reproducibility of the measurements.

**Image Processing and Analysis**

The projection data were corrected for nonuniformity of detector response, dead time, random coincidences, attenuation, and scattered radiation. The PET scanner was cross-calibrated with a well scintillation counter by comparing the scanner response from a fluoride-18 solution in a 20-cm cylindrical phantom with the response of the well counter to an aliquot of the same solution. All emission scans were reconstructed by using a conventional filtered back-projection algorithm to an in-plane resolution of 7 mm FWHM.

**Selection of voxels for analysis.** Lung “masks” were defined by thresholding the transmission scan (4, 24). These masks were then refined to exclude regions corresponding to the main bronchi and large pulmonary vessels. In subject 1 in the supine position, small dependent areas of tracer retention were identified on the last PET image of the washout and were excluded from the lung mask that was used to obtain the V and $Q/V$ measurements.

Because $sV_A$ is effectively calculated as the ratio of two variables (i.e., the tracer concentration at the beginning of the washout and the integral of the washout curve; see Eq. 1), the frequency distribution of $sV_A$ is particularly prone to have outliers. These outliers would profoundly affect the estimate of $V$ heterogeneity, although they probably reflect the uncertainty of our method in estimating $sV_A$ in regions of very low $Q/V$ rather than true extreme values of $sV_A$. Outliers, defined as voxels with $sV_A < (Q_1 - 2(Q_3 - Q_1))$ or $sV_A > (Q_3 + 2(Q_3 - Q_1))$, where $Q_1$ and $Q_3$ are the 25th and 75th percentile of the $sV_A$ distribution (26), were excluded from the analysis of $V$.

**PET scans.** Emission scans, corrected for tracer radioactive decay (half-life of $^{13}$N$_2$: 9.96 min), were low-pass filtered to a length scale of 12 mm and corrected for edge effects (32). After scans were filtered, the size of the effective resolution element corresponded to $12 \times 12 \times 6$ mm. For each voxel within the lung mask, $Q$, $sV_A$, and $Q/sV_A$ were calculated from the tracer kinetics of the PET scan and displayed on a color-coded scale to yield functional images (Fig. 2).

**Assessment of vertical (“gravitational”) gradients.** For each voxel, $Q$, $sV_A$, and $Q/sV_A$ and $F_{gas}$ were regressed vs. the vertical distance from the most dependent point of the imaged lung field. Gradients, measured from the slope of the corresponding regression line, were expressed in percent per centimeter, relative to the mean (Fig. 3). Negative gradients indicate a decrease of $Q$, $sV_A$, $Q/sV_A$, or $F_{gas}$ from the dependent to the nondependent regions (i.e., higher values of $Q$, $sV_A$, $Q/sV_A$, or $F_{gas}$ in dependent than in nondependent regions, Fig. 3).

**Assessment of spatial heterogeneity.** Spatial heterogeneity of $Q$, $sV_A$, and $Q/sV_A$ was assessed from the squared coefficient of variation ($CV^2 = (SD/mean)^2$) of the respective functional images (29, 32).

$Q$. To correct the measured $Q$ heterogeneity for the contribution of random imaging noise caused by finite count statistics, an approach similar to the one reported by Venegas et al. (33) was used. The assumption behind this approach is that, during the plateau phase of the apnea, regional tracer concentration remains constant. Thus differences in the tracer concentration measured in a given voxel on the PET images collected during the plateau of the apnea are due to random imaging noise. This assumption is valid if tracer reabsorption into pulmonary venous blood is negligible, a condition that is met in the normal human lung (see Appendix and Fig. 1). For each injection of tracer, a number of sequential PET images corresponding to the plateau phase of the apnea were identified by inspection. In the analysis of the data, these images were averaged in different combinations by calculating a voxel-by-voxel duration-weighted mean of the tracer activities of the images included in each combination. For example, if $a_{i,j}$ denotes the tracer activity of the $i$th voxel ($i = 1, \ldots, N$, where $N$ is the number of voxels in the lung mask) in the $j$th image ($j = 1, \ldots, M$, where $M$ is the number of images corresponding to the plateau of the apnea) and $t_j$ is the duration of the $j$th image, then the tracer activity of the $i$th voxel in the combination image made of, for instance, the first, second and $M$th image is

$$a_i = \frac{\sum_{j=1}^M t_j \cdot a_{i,j}}{\sum_{j=1}^M t_j} \quad (2)$$
In particular, if $j$ in the summations in Eq. 2 ranges from 1 to $M$, then $a_i$ represents the average activity of the $i$th voxel during the entire plateau phase of the apnea and the corresponding combination image is the Q image (Fig. 2). The CV$^2$ of each combination image (i.e., the CV$^2$ of $\{a_{i,j}\}_{j=1, \ldots, N}$) was then calculated and regressed vs. the reciprocal of the duration-weighted sum of the mean voxel activity of the images included in each combination. For the same example as above, in which we considered the combination image made of the first, second and $M$th image, the duration-weighted sum of the mean voxel activities is

$$S_{1,2,M} = \sum_{j=1,2,M} t_j \cdot \left( \frac{1}{N} \sum_{i=1}^{N} a_{i,j} \right)$$

This sum, which represents the mean activity-time integral of the combination image, is proportional to the number of counts recorded by the PET scanner over the acquisition time of the combination image. The intercept of the regression line (Fig. 4) represents the estimated heterogeneity of Q, had a Q image with an infinite number of counts been acquired. The intercept is therefore a measure of Q heterogeneity, corrected for the contribution of random imaging noise (33). We will denote the value of the intercept as CV$^2_{Q, im}$ and the CV$^2$ of the Q image (i.e., the CV$^2$ of $\{a_{i,j}\}_{j=1, \ldots, N}$ when $j = 1, \ldots, M$ in Eq. 2) as CV$^2_{Q, im}$.

The importance of the linear relationship between CV$^2$ and the reciprocal of the mean activity-time integral of a PET image (the “CV$^2$ vs. activity” line, Fig. 4) is that it allows estimation of the CV$^2$ due to random noise for a PET image with arbitrary mean activity and arbitrary duration. Indeed, if the mean activity and the acquisition time of any PET image from a subject are known, the CV$^2$ due to random noise can be estimated by multiplying the reciprocal of the activity-time integral of the image by the slope of the line obtained from that subject. The CV$^2$ vs. activity line was calculated for each subject in each body position and was used to correct the corresponding heterogeneity measurement.

CV$^2$ was subdivided in the amount explained by the vertical gradient (CV$^2_{Q, \text{vert}}$) and the residual heterogeneity (CV$^2_{Q, \text{res}} = CV^2_{Q} - CV^2_{Q, \text{vert}}$). CV$^2_{Q, \text{vert}}$ was calculated, by linear regression, from the Q image. The ratio $R^2_{Q} = (CV^2_{Q, \text{vert}})(CV^2_{Q})$ thus represents the fraction of Q heterogeneity explained by the vertical gradient.

**Q/V** and **V**. For each PET scan, the duration-weighted sum of the mean activity of the PET images taken during tracer washout was calculated as

$$S = \sum_{k=1}^{L} t_k \cdot \left( \frac{1}{N} \sum_{i=1}^{N} a_{i,k} \right)$$

where $k = 1, \ldots, L$ indexes the washout images. This sum is proportional to the number of counts recorded by the PET
scanner during the washout phase [note that this sum is conceptually equivalent to the duration-weighted sum of the mean activity of the apnea images (Eq. 3) that was used to estimate the CV² vs. activity regression line]. The reciprocal of this sum was then multiplied by the slope of the CV² vs. activity regression line obtained from the apnea images of the same scan (Fig. 4). This yielded an estimate of the CV² caused by random imaging noise for the PET image corresponding to the duration-weighted sum of the washout images, i.e., the Q/sVA image. The CV² due to random imaging noise was then subtracted from the CV² of the Q/sVA image (CV²_{Q/sVA,im}) to obtain a measure of Q/sVA heterogeneity (CV²_{Q/sVA}). As for CV²_A, CV²_{Q/sVA} was subdivided in the amount explained by the vertical gradient (CV²_{Q/sVA,q}) and the residual heterogeneity (CV²_{Q/sVA,r}), and the ratio R^2_{Q/sVA} = (CV²_{Q/sVA,q})/(CV²_{Q/sVA,r}) was calculated.

To estimate the contribution of random noise to the measurement of sVA, we used a Monte Carlo approach. Because sVA was computed as the ratio of the Q image and the Q/sVA image, a ratio that corresponds to the reciprocal of the MRT (see Eq. 1), the parameters describing the distribution of noise in the Q image and in the Q/sVA image were used for the Monte Carlo simulation as follows. A normally distributed random variable (r.v.), with mean equal to the mean activity of the Q image and CV² equal to the product of the reciprocal of the activity-time integral of the Q image (Eq. 3 for j = 1, . . . , M) by the slope of the CV² vs. activity regression line, was generated. The distribution of this r.v. characterizes the distribution of random noise in the Q image, under the assumption that such noise can be modeled as a normally distributed stochastic process. Similarly, a second normally distributed r.v., with mean equal to the mean activity of the Q/sVA image and CV² equal to the product of the reciprocal of the activity-time integral of the Q/sVA image (Eq. 4) by the slope of the CV² vs. activity regression line, was generated. The distribution of this second r.v. represents the distribution of random noise in a PET image with the same mean activity as the Q/sVA image. Because sVA was computed as the ratio of Q and Q/sVA, a third r.v. was generated as the ratio of the first and the second r.v. The distribution of this third r.v. represents the effect that random noise in the Q and Q/sVA images has on the distribution of sVA. One hundred thousand empiric realizations of this r.v. were generated by computer simulation (Matlab, The MathWorks, Natick, MA), and their CV² was calculated. This CV² represents an estimate of the sVA heterogeneity that could be attributed to random imaging noise. This was subtracted from the CV² of the sVA image (CV²_{sVA,im}) to obtain a measure of sVA heterogeneity (CV²_{sVA}). As with the previous variables, CV²_{sVA} was subdivided in CV²_{sVA,q} and CV²_{sVA,r} and the ratio R^2_{sVA} = (CV²_{sVA,q})/(CV²_{sVA,r}) was calculated.

Statistical Analysis

Least squares linear regression was used to estimate all regression relationships. When calculating the regression of the supine-to-prone difference in the Fgas gradient vs. the supine-to-prone difference in the Q gradient (see below), the constraint of a zero intercept was imposed. This constraint reflected the assumption that, if the Q gradients were equal in the supine and prone position, then the Fgas gradients would also be equal. This assumption was justified by the consideration that, if the lung behaved as a passive structure under the influence of hydrostatic forces, then the gradients of Q and lung density (and therefore of Fgas) would not differ between the two body positions.

Two-tailed Student’s t-test was used to assess any significant difference from zero and to compare the results in the supine and prone position (t-test for paired data). Statistical significance was set at P < 0.05. To control the “experiment-wise” type I error and limit the number of statistical comparisons, the following approach was used. It was decided a priori that the primary comparisons of interest were those involving the gradients and the total heterogeneity. Only if these were statistically significant, then comparisons involving the different components of the total heterogeneity were performed as secondary endpoints. Values are presented as means ± SD.

RESULTS

Vertical Gradients

The Q gradient was different from zero in both body positions, without a significant difference between supine and prone (Table 1). There was, however, large intersubject variability in the Q gradients, ranging from +0.5%/cm to −10.6%/cm (Fig. 5). Only in one subject (subject 6 in prone position) there was a slightly positive Q gradient; otherwise, Q was consistently greater in dependent than in nondependent lung regions (i.e., Q had a negative gradient).

The Fgas gradient was positive in both body positions (Table 1). The difference in Fgas gradient between the supine and prone positions (Δgrad Fgas) was negatively correlated (r = −0.778) with the difference in Q gradient (Δgrad Q), as shown in Fig. 6. The slope of the regression line was −0.162 (95% confidence interval: −0.313 to −0.012).

There was a significant, negative sVA gradient in both supine and prone positions (Table 1), and all subjects had greater sVA in dependent regions (Fig. 5).

The average Q/sVA gradient was not significantly different from zero in either body position (Table 1). However, two subjects in both body positions (2 and 6) and one subject in the supine position (3) had positive Q/sVA gradients, consistent with the finding that, in these cases, the Q gradient was less pronounced than the sVA gradient (Fig. 5). Consequently, in these cases, the Q/sVA was higher in nondependent than in dependent regions. In contrast, negative Q/sVA gradients (subjects 1, 3 in prone position, 4, and 5) corresponded to cases in which the magnitude of the Q gradient was greater than the magnitude of the sVA gradient.

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<th>Table 1. Vertical gradients</th>
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<tr>
<td>Q</td>
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<tr>
<td>sVA</td>
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<tr>
<td>Q/sVA</td>
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<tr>
<td>Fgas</td>
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</table>

Values are means ± SD. Vertical gradients of perfusion (Q), specific alveolar ventilation (sVA), perfusion-to-ventilation ratio (Q/sVA), and fractional gas content (Fgas). All gradients are expressed in %/cm, relative to the mean. Negative gradients indicate a decrease from the dependent to the nondependent regions (i.e., higher values in dependent regions, Fig. 3). *Different from 0 (P < 0.05); †different from 0 (P < 0.01).
implies that, in these cases, the fraction of $\dot{Q}$ going to dependent lung regions was greater than the fraction of $\dot{sV_A}$ in these regions (Fig. 5).

The difference in vertical gradients between the first and second scan obtained in the same body position $(n = 4)$ was $0.4 \pm 1.1\%/cm$ for $\dot{Q}$, $0.9 \pm 1.2\%/cm$ for $\dot{sV_A}$, and $-0.5 \pm 2.3\%/cm$ for $\dot{Q}/\dot{sV_A}$.

**Heterogeneity**

There was no statistically significant difference in $\dot{Q}$ heterogeneity, $CV_{\dot{Q}}^2$, between the supine and prone positions (Table 2). The fraction of $\dot{Q}$ heterogeneity explained by the vertical gradient, $R_{\dot{Q}}^2$, was significantly different from zero and averaged 0.22 and 0.26 in, respectively, the supine and prone position (Table 2). Despite this variability, there was internal consistency between the heterogeneity and the gradient data. Subjects with pronounced vertical $\dot{Q}$ gradients (subject 4 and subject 3 in prone position) had higher values of $CV_{\dot{Q},v}$ and $R_{\dot{Q}}^2$ than subjects with small gradients (Fig. 5, Fig. 7). The residual $\dot{Q}$ heterogeneity, $CV_{\dot{Q},r}$, was significantly different from zero (Table 2, Fig. 7).

$\dot{V}$ heterogeneity, $CV_{\dot{V},v}$, was on average higher in the supine than in the prone position (Table 2). The fraction of $\dot{V}$ heterogeneity explained by the vertical gradient, $R_{\dot{V},v}$, was different from zero in both body positions, but significant residual $\dot{V}$ heterogeneity persisted after subtraction of the component due to the vertical gradient (Table 2, Fig. 7).

There was no difference in $\dot{Q}/\dot{sV_A}$ heterogeneity, $CV_{\dot{Q}/\dot{sV_A}}^2$, between the supine and prone positions (Table 2). Because we did not find significant $\dot{Q}/\dot{sV_A}$ gradients, we did not test the components of $CV_{\dot{Q}/\dot{sV_A}}^2$.

**DISCUSSION**

**Comparison to Other Methods and Critique of the Technique**

Several methods have been employed to assess regional $\dot{Q}$ in animals and humans (5, 7, 8, 10, 15, 17–19, 27). Because $^{13}$N$_2$ has a first-pass retention of virtually 100% in aerated lung regions (23, 30), the $^{13}$N$_2$-saline bolus infusion technique is conceptually similar to methods that utilize tracers that are retained in the pulmonary microvasculature, such as microspheres or macroaggregated albumin. The advantage of using $^{13}$N$_2$, though, is that N$_2$, like O$_2$ and CO$_2$, is a low-molecular-weight gas that is dissolved in the blood. Its distribution through the pulmonary capillary network should therefore resemble that of the respiratory gases more closely than the bulkier (10–100 $\mu$m in diameter) microspheres or albumin macroaggregates. Furthermore, compared with the macroaggregated albumin method, the $^{13}$N$_2$ infusion technique reduces radiation exposure for the subject because $^{13}$N$_2$ has a shorter half-life and is eliminated more rapidly than $^{99m}$Tc.

For the $^{13}$N$_2$ content during apnea to accurately reflect regional $\dot{Q}$, two basic conditions need to be met. First, the apnea itself needs not to influence the
of the infusion, the effect of the apnea should be negligible. Because tracer distribution into the lung is virtually complete within the first 10 s since the start of the infusion, the effect of the apnea should be minimal. To further limit the potential effect of the apnea on regional Q, the subjects took two inspirations to total lung capacity five breaths before the beginning of the apnea. This maneuver should prevent the development of alveolar atelectasis and reduce the level of hypercapnia reached during the apnea. Because of the low solubility of 13N2 in blood, tracer reabsorption into pulmonary venous blood during the apnea is minimal. In normally aerated and perfused lungs, tracer reabsorption can be expected to result in a <2% drop in tracer concentration during the apnea (see APPENDIX).

The MRT of a gas tracer has been previously used to characterize the regional distribution of V (31). We assessed V from the reciprocal of the MRT during the washout. This approach has the following implications. First, because 13N2 is removed from the lung also by the pulmonary venous blood, the MRT is shorter than if 13N2 had been eliminated exclusively by ventilation. However, in a normally aerated and perfused lung, this should lead to an overestimation of specific ventilation (i.e., ventilation per unit of compartment volume) by only 1.5% (see APPENDIX). Therefore, the reciprocal of the MRT appears to be a reasonable estimate of specific ventilation. Second, the reciprocal of the MRT represents the rate at which the concentration of 13N2 within the voxel decreases. If the voxel behaves as a well-mixed single compartment, the rate of decrease of the concentration of 13N2 within the voxel equals the rate of decrease of the alveolar concentration of 13N2 (although the alveolar and the voxel concentration of 13N2 may differ because λwater/air = 0.015 for 13N2). Therefore, the reciprocal of the MRT effectively repre-

### Table 2. Spatial heterogeneity

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<thead>
<tr>
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<th>Supine</th>
<th>Prone</th>
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<tr>
<td>CV2,im</td>
<td>0.26 ± 0.15</td>
<td>0.21 ± 0.09</td>
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<tr>
<td>CV2</td>
<td>0.15 ± 0.11*</td>
<td>0.12 ± 0.06†</td>
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<tr>
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<td>0.07 ± 0.02†</td>
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<td>0.07 ± 0.03†</td>
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Values are means ± SD. CV2,im, CV2,Va,im, and CV2,Q/Va,im represent the heterogeneity of, respectively, the Q, sVa, and Q/sVa image (Fig. 2). CV2,Q, CV2,Va, and CV2,Q/Va represent the heterogeneity of Q, sVa, and Q/sVa, obtained by subtracting the contribution of random noise from the heterogeneity of the corresponding image. CV2,Q, and CV2,Va represent the residual heterogeneity of Q and sVa, obtained by subtracting the contribution of the vertical gradient from, respectively, CV2,Q and CV2,Va. R2,Q and R2,Va represent the fraction of, respectively, CV2,Q and CV2,Va, that is explained by the vertical gradient. Statistical tests were not performed on CV2,Q, CV2,Va, and CV2,Q/Va, which are shown only for comparison with the corresponding noise-corrected values. *Different from 0 (P < 0.05); † different from 0 (P < 0.01); ‡ different between supine and prone (P < 0.05).
Gradients and Heterogeneity

\( Q \). In this study, we found vertical \( Q \) gradients favoring dependent lung regions in both supine and prone positions. These gradients are similar to those reported previously in spontaneously breathing humans with magnetic resonance imaging (28) and single-photon-emission computed tomography (19) and corroborate the results of earlier studies that employed low-resolution planar imaging techniques (11, 12). Whereas it is generally accepted that \( Q \) is highest in dependent lung regions in the supine position, the vertical dependence of \( Q \) in the prone position is more controversial. Animal data, mostly from quadrupeds, indicate that there may be structural factors (3) or biochemical modulators (20) of the pulmonary vasculature that favor perfusion in dorsal lung regions. This is consistent with the results of Treppo et al. (29), who found a marked vertical gradient in supine (where both structural/biochemical factors and gravity would tend to increase \( Q \) in dependent, dorsal, regions) but not in prone dogs. These factors, by contrasting the action of gravity in the prone position, would serve the purpose of rendering the distribution of \( Q \) more homogeneous in quadrupeds. Recent studies, employing single-photon-emission computed tomography, suggested that also in humans the vertical \( Q \) gradient is either less or nil in the prone position (17, 18). Our data do not corroborate these findings, and caution on the extent to which results of studies that showed greater dorsal \( Q \) in prone quadrupeds (7) can be extended to biped humans. Our results are in line with those of Amis et al. (2) and Jones et al. (10), which also showed higher \( Q \) in dependent (ventral) than in nondependent (dorsal) regions in prone humans. Our results do, however, show a wide variability in individual behaviors that may partly explain the discrepant findings in the literature. The fact that vertical gradients were reproducible on repeated measurements in the same body position argues against the possibility that this variability was a measurement artifact. The fact that the change in gradient between the supine and prone positions was not dictated by the order of randomization (i.e., gradients were not systematically higher, or lower, in the first than in the second position, Fig. 5) virtually excludes the possibility that the intersubject variability in the change in gradient was merely the result of a systematic difference between the gradients in the first and the second body position. Whereas supine gradients were very similar in five of the six subjects, prone gradients were more disperse (Fig. 5). This suggests that, on turning prone, \( Q \) redistributed toward ventral, dependent lung regions in all subjects, but the extent to which this occurred was much greater in some subjects (e.g., subject 6) than in others (e.g., subject 4). Future studies will be needed to address whether a lesser degree of \( Q \) redistribution toward dependent, ventral regions is associated with a favorable response to prone positioning in patients with ARDS, in whom lung densities have been shown to shift to ventral regions in the prone position (13).

Interestingly, the supine-to-prone difference in the \( \Delta_{F_{\text{gas}}} \) gradient (\( \Delta_{F_{\text{gas}}} \)) was negatively correlated with the supine-to-prone difference in \( Q \) gradient (\( \Delta_{Q} \)), but the 95% confidence interval of the slope of the regression line did not include \(-1\). If perfusion per unit of lung tissue, and therefore perfusion per alveolus, were constant and the redistribution of \( Q \) between the supine and prone positions were merely a consequence of redistribution of lung tissue, then the change in the mean-normalized \( Q \) gradient would equal the change in the mean-normalized lung density gradient. As a result, \( \Delta_{Q} \) would be equal in magnitude but opposite in sign to \( \Delta_{F_{\text{gas}}} \), and the slope of the regression line in Fig. 6 would be \(-1\). Our finding instead suggests that redistribution of lung tissue cannot be the only explanation for the redistribution of \( Q \) that is associated with body position changes and that perfusion per unit of lung tissue, and therefore perfusion per alveolus, increases when a nondependent region of lung becomes dependent as a result of the position change. This is consistent with a decreased vascular resistance of dependent lung regions compared with nondependent regions.

Over the past decade, animal data obtained with the intravenous injection of microspheres have suggested that vertical gradients explain only a minor fraction (i.e., \(-5\%\)) of \( Q \) heterogeneity in the supine or prone position (7). To avoid an underestimation of the relative importance of vertical gradients, because of an overestimation of the total heterogeneity, we applied a method that allows estimation of the heterogeneity due to finite count statistics, which can then be used to correct the total measured heterogeneity (33). It is important to acknowledge, though, that this method does not correct for systematic sources of imaging noise such as reconstruction and registration artifacts. On average, the vertical gradient explained \(-24\%\) of \( Q \) heterogeneity in both positions. Both the total heterogeneity and the residual heterogeneity were similar in the supine and prone position (Table 2), suggesting that, in humans, \( Q \) is not systematically more uniform in the prone position. There were marked differences, though, in individual behaviors, and in four subjects \( Q \) heterogeneity was lower in the prone position (Fig. 7).

For subject 4, vertical gradients explained the majority of \( Q \) heterogeneity (57% in both positions), whereas for subject 6 the contribution of the vertical gradient to \( Q \) heterogeneity in the prone position was insignificant. These differences may reflect a variable contribution of structural factors and active regulation of the pulmonary vasculature to the topographical distribution of \( Q \).

\( V \). In both the supine and prone positions, we found vertical \( sVA \) gradients that favored dependent lung regions (Table 1, Fig. 5). These results are consistent with early reports (11, 22) and with more recent PET studies.
(4) but differ from the observations of other authors that reported \( V \) to be uniform (1) or even greater in nondependent (dorsal) than in dependent (ventral) regions in the prone position (17, 19, 21). This discrepancy of results in the literature is not surprising in view of the different factors that can affect the topographical distribution of \( V \) in awake, spontaneously breathing humans. These include the pleural pressure gradient and the pattern of contraction of the respiratory muscles. The vertical gradient of pleural pressure has been suggested to be less in the prone position (34). This would favor a more uniform distribution of \( V \) when prone. Although the difference was not statistically significant, we did find, on average, lower \( sVA \) gradients in prone subjects (Table 1), and \( sVA \) heterogeneity was significantly smaller in the prone than in the supine position (Table 2, Fig. 7). These findings are consistent with a more uniform distribution of \( V \) in the prone position.

In awake, spontaneously breathing humans, the pattern of respiratory muscle contraction, which may differ among subjects, can also influence regional \( V \) (25) and explain part of the discrepancies in the literature. This is consistent with our results, which show that only a small fraction of \( V \) heterogeneity is explained by the vertical gradient and that residual, "nongravitational," heterogeneity is significant.

Finally, our findings show that estimates of the regional distribution of \( V \) are profoundly affected by the occurrence of gas trapping. Dependent, crescent-shaped areas of very low \( V/Q \) were reported, in healthy humans, by Rhodes et al. (24) and attributed to low \( V \). We detected areas of tracer retention during the washout (i.e., areas of gas trapping) in the dependent lung regions of subject 1 in the supine position. This finding suggests that airway closure may occur in dependent lung regions during tidal breathing. Despite the fact that these areas represented only 9% of the imaged lung field, the \( sVA \) gradient decreased from 0.9 to \(-1.5\%\)/cm and the \( sVA \) heterogeneity decreased from 0.26 to 0.16 after these areas were removed from the lung mask of this subject. In contrast to methods like ours that use the intravenous infusion of inert insoluble gases, methods that image \( V \) by inhalation of tracer will not reveal areas of gas trapping, because inhaled tracer cannot reach the airspace distal to closed airways. These implications of different methods may represent a further explanation for the discordant data on the regional distribution of \( V \) reported in the literature.

\( Q/V \). We did not find significant \( Q/sVA \) gradients in either body position (Table 1), and the spatial heterogeneity of \( Q/sVA \) was similar in the supine and prone position (Table 2). This is consistent with the rest of our results and suggests that, on average, the vertical gradient of \( Q \) match the gradient of \( V \). These findings contrast with the results of animal studies that have shown both the vertical gradient and the heterogeneity of the \( V/Q \) ratio to be substantially reduced in the prone position (15, 29). Interspecies differences and the fact that animals were studied during anesthesia and mechanical ventilation may account for this discrepancy.

In conclusion, we have shown that regional \( Q \) and \( V \) can be assessed noninvasively, in humans, with the \( ^{13}\text{N}_2 \) saline bolus infusion technique and PET. Our results suggest that both \( Q \) and \( V \) are distributed preferentially to dependent lung regions in the supine as well as in the prone position and that, in awake spontaneously breathing humans, the prone position does not offer any systematic advantage, in terms of \( V\text{-to}-Q \) matching, compared with the supine position. However, individual differences, especially in the distribution of \( Q \), may explain why the prone position is effective in improving gas exchange in some subjects. The next step is to identify patterns of distribution of \( Q \) and \( V \) that may be predictive of a favorable response to prone positioning.

**APPENDIX**

The purpose of this appendix is to present a one-compartment model for a voxel of lung to elucidate the rationale of the measurements of \( sVA \) and \( Q/sVA \) obtained with the \( ^{13}\text{N}_2 \)-saline bolus infusion method, and 2) quantify the effect of \( ^{13}\text{N}_2 \) reabsorption into pulmonary venous blood on \( Q \), \( sVA \), and \( Q/sVA \) measurements.

**Glossary**

- \( VA \): Alveolar gas volume
- \( V_A \): Alveolar ventilation
- \( sVA \): Specific alveolar ventilation (\( sVA = VA/V_A \))
- \( Q \): Pulmonary perfusion
- \( C_o \): Alveolar concentration (activity) of \( ^{13}\text{N}_2 \) immediately after arrival of the bolus of tracer (proportional to \( Q \); Ref. 14)
- \( c(t) \): Alveolar concentration (activity) of \( ^{13}\text{N}_2 \) at time \( t \)
- \( C_w \): Alveolar concentration (activity) of \( ^{13}\text{N}_2 \) at the beginning of the washout
- \( \lambda_{water/air} \): partition coefficient for \( ^{13}\text{N}_2 \) (\( \lambda = 0.015 \) at 37°C)

The rate of change of \( c(t) \) is given by the following first-order differential equation (14)

\[
\frac{dc(t)}{dt} = -c(t) \frac{V_A}{VA} + c(t) \lambda \frac{Q}{VA} \tag{A1}
\]

The solution is

\[
c(t) = C_o e^{-\left(\frac{V_A}{VA} + \lambda \frac{Q}{VA}\right)t} \tag{A2}
\]

Integrating \( c(t) \) from the beginning of the washout \( [c(0) = C_w] \) to infinity yields

\[
\int_0^\infty C_w e^{-\left(\frac{V_A}{VA} + \lambda \frac{Q}{VA}\right)t} dt = \frac{C_w Q}{sVA + \lambda \frac{Q}{VA}} \tag{A3}
\]

To quantify the effect of \( ^{13}\text{N}_2 \) reabsorption on the measurements of \( Q \), \( sVA \), and \( Q/sVA \), we will use global values of \( sVA \) and \( Q/sVA \) of normal human lungs in which \( Q = VA = 5 \) l/min and \( VA = 2.5 \) liters. This yields \( sVA = Q/sVA = 0.033/s \).

During the apnea, \( sVA = 0 \). According to Eq. 2, the tracer concentration is expected to decrease by 1.5%
over the 30 s of apnea that follow the arrival of the bolus of tracer. This warrants the assumption that c(t) is virtually constant during the plateau phase of the apnea and that Cc \( \approx C_v \). Because Cc \( \approx Q \) (Eq. A1) and Cc \( \approx C_v \), then Cc \( \approx Q \) (Eq. A3).

During the washout, ventilation is resumed. Equation A2 shows that the reciprocal of the time constant of the tracer washout curve is related to s\( V_A \). Equation A3 shows that the integral of the tracer washout curve is related to \( Q/sV_A \).

The error in the estimation of s\( V_A \) and \( Q/sV_A \) due to the fact that we neglect tracer reabsorption by the pulmonary venous blood and estimate s\( V_A \) from [s\( V_A + \lambda (Q/V_A) \)] is

\[
\varepsilon = \frac{Q}{V_A} \frac{sV_A + \lambda (Q/V_A) - sV_A}{sV_A} = \lambda = 1.5\%
\]

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