Determination of regional ventilation and perfusion in the lung using xenon and computed tomography

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Krecek, Thomas C., Melissa A. Krueger, William A. Altemeier, Scott E. Sinclair, H. Thomas Robertson, Erin D. Shade, Jacob Hildebrandt, Wayne J. E. Lamm, David A. Frazer, Nayak L. Polissar, and Michael P. Hlastala. Determination of regional ventilation and perfusion in the lung using xenon and computed tomography. J Appl Physiol 91: 1741–1749, 2001.—We propose a model to measure both regional ventilation (V) and perfusion (Q) in which the regional radiodensity (RD) in the lung during xenon (Xe) washin is a function of regional V (increasing RD) and Q (decreasing RD). We studied five anesthetized, paralyzed, mechanically ventilated, supine sheep. Four 2.5-mm-thick computed tomography (CT) images were simultaneously acquired immediately cephalad to the diaphragm at end inspiration for each breath during 3 min of Xe breathing. Observed changes in RD during Xe washin were used to determine regional V and Q. For 16-mm³ regions, V displayed more variance than Q; the coefficient of variance of Q (CVQ) = 1.58 ± 0.23, the CV of V (CVV) = 0.46 ± 0.07, and the ratio of CVQ to CVV (2.4 ± 1.2) were smaller at 1,000-mm³ scale, but CVV (0.53 ± 0.09) was not. V/Q distributions also displayed scale dependence: log SD of V and log SD of Q were 0.79 ± 0.05 and 0.85 ± 0.10 for 16-mm³ and 0.69 ± 0.20 and 0.67 ± 0.10 for 1,000-mm³ regions of lung, respectively. V and Q measurements made with CT and Xe also demonstrate vertically oriented and isogravitational heterogeneity, which are described using other methodologies. Sequential images acquired by CT during Xe breathing can be used to determine both regional V and Q noninvasively with high spatial resolution.

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Efficient gas exchange in the lung requires close matching of regional ventilation (V) and perfusion (Q). It has been demonstrated that V and Q and V-to-Q ratio (V/Q) vary spatially throughout the lung (1, 2, 11, 12, 15, 36, 41) and that this spatial variation affects overall gas exchange in the lung (3, 23, 45). Therefore, measurement of regional movement of gas and blood in the lung is required to fully understand the factors governing gas exchange. Much has been learned about regional lung function in healthy and diseased lungs using a variety of techniques, such as aerosolized and injected microspheres, positron emission tomography, computed tomography (CT), and magnetic resonance imaging. Because V and Q both demonstrate scale-dependent spatial heterogeneity (2, 12, 17, 19, 41), obtaining measurements at higher resolution than previously reported will provide further insight into the mechanism of gas exchange in the lung.

Because of its ability to obtain high-resolution images of the lung in vivo, CT has been used to obtain V measurements using nonradioactive xenon (Xe; mol wt = 131), a gas with significant X-ray absorption (42). Early studies obtained rough estimates of V by digitally subtracting images of the lung obtained before and after inhalation of Xe (24). Subsequent measurement of changing regional Xe concentration (Xe), over multiple breaths, allowed estimation of regional V with high spatial resolution (20, 21, 31, 35, 37, 38). Although this was a promising advance in V measurement, regional Q remained unmeasured, limiting the technique’s ability to study gas exchange.

These previous studies used the simplifying assumption that Xe is insoluble in blood, and, therefore, the change of regional density during Xe washin or washout is dependent only on regional V. Although the solubility of Xe in blood is low, it is not insignificant; therefore, [Xe] in the lung is actually dependent on both regional V and Q. Two examples of loss of Xe into pulmonary blood flow are the application of Xe in cerebral blood flow studies and the anesthetic properties of Xe at high [Xe] in inhaled gas (8, 22, 44). In humans, the blood-to-air Ostwald partition coefficient (λblood/air) is ~0.13 at 37°C and is a function of Xe solubility in red blood cells (RBC) (λRBC/air = 0.21) and plasma (λplasma/air = 0.10) (28, 32, 40).

We propose an improved model of inert tracer-gas movement in the lung that takes into account the
solubility of the gas in tissue and blood. Using CT, we demonstrate that sequential images acquired at end inspiration during Xe washing can be used to simultaneously measure regional V and Q in the lung with a high degree of spatial resolution.

THEORY

An idealized volume element of the lung (voxel) is illustrated in Fig. 1. This representative voxel is displayed at end inspiration and contains air space [alveolar volume (VA)] and tissue and capillary blood [tissue volume (Vtissue)] compartments. Tracer gas is delivered or removed from the alveolar space via four routes: 1) delivery of gas through inhalation, 2) loss of gas through exhalation, 3) loss of gas into capillary blood, and 4) delivery of gas through mixed venous blood. Mass conservation of the tracer gas into the alveolar and tissue compartments within the voxel boundary is

$$\frac{dM_{gas}}{dt} = d(VA_C A + V_{tissue} C_{tissue})$$

$$= VC A - VC A(t) - QC_{capillary}(t) + QC A(t)$$  (1)

where $M_{gas}$ is the mass of tracer gas in a voxel; $C A$ is the concentration (mass/volume) of tracer gas delivered to the trachea; $C A$ is the tracer concentration in the alveolus; $C_{tissue}$ is the tissue concentration of tracer; $C_{capillary}$ is the tracer concentration in the end-capillary blood; $C v$ is the concentration of tracer gas in mixed venous blood; and $V_{voxel} = VA + V_{tissue}$.

This model includes the following simplifications: 1) tidal V can be adequately represented by unidirectional flow with a constant $V A$; 2) for each voxel, dead space [dead space volume (VD)] is a fixed fraction of $V A$ and contains only exhaled gas from the voxel in question (“personal” dead space); 3) $C A$, regional V, and regional Q do not change during the period of tracer gas washin; 4) tracer gas fully equilibrates among all alveolar gas, lung parenchyma ($C_{tissue} = \lambda_{tissue/air} C_A$, where $\lambda_{tissue/air}$ is the tissue-to-air Ostwald partition coefficient), and end-capillary blood ($C_{capillary} = \lambda_{blood/air} C_A$) within the voxel.

If

$$\frac{dC A}{dt} = \frac{C A - C A^{-1} t}{T},$$

where $i$ denotes breath number and $T$ represents the period of one breath, then Eq. 1 can be rearranged to define the $C A$ as

$$C A^i = \frac{(VA + \lambda_{tissue/air} V_{tissue} + VD)C A^{-1} + (VD - VD)C A + QC A^{-1}}{VA + \lambda_{tissue/air} V_{tissue} + V + \lambda_{blood/air} Q}$$  (2)

If the tracer is radiodense (absorbs X-rays), sequential CT scans can be used to track the regional tracer concentrations. $C A$, $C A(t)$, and $C v(t)$ are measured by observing radiodensity (RD) in large airways, lung parenchyma, and vena cava, respectively. Using CT, regional RD is measured by using the linear Hounsfield unit (HU) scale (RD of air, approximately $-1,000$ HU; RD of water, approximately zero HU; and RD of bone, approximately $+1,000$ HU). Assuming a linear relationship between CT and tracer concentration within a voxel (30, 31, 35, 38), the evolution of RD for a voxel containing air and tissue follows the same form as the evolution of $C A$, during Xe breathing (2)

$$\Delta HU_{voxel} = \frac{(VA + \lambda_{tissue/air} V_{tissue} + VD)H U_{AI}^{-1} + (VD - VD)H U_{AI} + QC A^{-1}}{V_{voxel}(VA + \lambda_{tissue/air} V_{tissue} + V + \lambda_{blood/air} Q)}$$  (3)

where $\Delta HU_{voxel}$ is change in RD of a voxel of lung referenced to baseline RD (in HU), $\Delta HU$, is change in RD of alveolar fraction of a voxel of lung referenced to baseline RD (in HU), $\Delta HU$ is the difference in RD between the room-air gas (HUair) and the gas mixture containing $\sim 65\%$ Xe, and $\Delta HU$ is the change in RD of the vena cava referenced to baseline RD (in HU).

METHODS

Animal Model

This study was approved by the University of Washington Institutional Animal Care and Use Committee, and the National Institutes of Health guidelines for animal use and care were followed throughout. Five adult sheep (27.5–36 kg) of either sex were studied and remained in the supine posture throughout the study. The sheep were anesthetized with an intravenous bolus of thiopental sodium (20 mg/kg) followed by a constant infusion titrated to suppress hemodynamic and motor responses to noxious stimuli. Tracheotomy was performed, and the animal was mechanically ventilated through a short no. 9 endotracheal tube. Additional instrumentation included catheterization of 1) the femoral artery for blood pressure and blood-gas monitoring, 2) the femoral vein for administration of fluid and anesthesia, and 3) the right external jugular vein for cardiac output and pulmonary ar-
terial and pulmonary capillary wedge pressure measurement via a Swan Ganz catheter. Hemodynamic and blood-gas measurements were made immediately before Xe breathing and immediately after washout of Xe. Before scanning, the sheep were paralyzed with a 2.5-mg iv injection of pancuronium bromide. The sheep were killed after completion of the study using a concentrated pentobarbital injection.

V was maintained throughout the study with a custom V circuit consisting of two Servo 900C ventilators (Siemens-Elema): one delivering an N2-O2 mixture and the other a Xe-O2 mixture, both with an inspired O2 fraction of ~0.35. Both devices were connected to the endotracheal tube via a three-port valve with switching between ventilators performed manually. Before the switch from N2-O2 to Xe-O2, the bellows of the Xe ventilator were purged to ensure consistent [Xe] during washin. V parameters for both devices were identical: pressure cycled V respiratory rate (RR) = 10 breaths/min, maximum airway pressure set to maintain PCO2 between 30 and 35 Torr, inspiratory time = 67% (combination of inspiratory and breath-hold time), and positive end-expiratory pressure = 0. A personal computer was used to synchronize the respiratory pattern of both ventilators, overriding the RR setting of each ventilator.

Scanning Protocol

Scans were performed using a LightSpeed CT scanner (GE Medical Systems, Milwaukee, WI). Scan settings included standard reconstruction, kVp = 80, mA = 400, scan time = 1 s, interscan delay = 5 s, slice thickness = 2.5 mm, peristalsis filter, field of view = 25 cm, axial mode, and four images per rotation. The washin protocol lasted 4.5 min and consisted of 15 breaths of 35% O2-balance N2 breathing (baseline) and 30 breaths of 35% O2-balance Xe breathing (Xe washin). Images were obtained during end-inspiratory breath hold for each breath of the washin protocol. The initial image was triggered manually with the remaining images occurring at 6-s intervals, matching exactly the respiratory period of the ventilators. The scanning area remained the same for each breath and was located immediately cephalad to the dome of the diaphragm, chosen to obtain the maximum amount of lung possible for analysis.

Data Analysis

Identification of lung parenchyma. Before V, Q, and VA were obtained from parameter matching, all structures that were not pulmonary parenchyma (chest wall, airways, blood vessels, and mediastinal structures) were eliminated from analysis by discarding all pixels with >95% or <10% air space. The RD of each pixel for each of the 15 baseline breaths was used to estimate VA and Vtissue (26)

\[
V_A = \frac{H_U - H_{U_{water}}}{H_{U_{air}} - H_{U_{water}}} V_{voxel}
\]

and Vtissue = Vvoxel - VA. HUwater was defined as the mean RD of a region of the heart for all 15 baseline images (before Xe inhalation). Similarly, HUair was defined as the mean RD of an airway for all 15 baseline images.

Next, with the use of a grid overlay, each 2.5-mm-thick axial slice was divided into voxels of 6 x 6 pixels (2.52 x 2.52 mm2) for a resultant voxel volume of 16 mm3. For the 1,000-mm3 voxel size, the four 2.5-mm-thick axial images were combined to form one 10-mm-thick image, with this resulting image divided into 25 x 25 pixel voxels.

The RD of each voxel was defined as the mean RD of all of its constituent pixels. Voxels were eliminated from analysis if the slope of RD of all 15 baseline scans was less than −2 or greater than 2 HU per breath, eliminating regions demonstrating significant registration artifact (changes in regional tissue density) during baseline scanning. Voxels were also eliminated if ≥80% of the possible pixels were discarded.

Parameter matching. With the use of the relationship described in Eq. 3, values for V, Q, and VA were determined that best fit the observed RD readings over a 30-breath Xe washin for each voxel in each series of lung images. The values of ΔHU1, ΔHU2(t), λblood/air, and λtissue/air are determined as described below. The value of VD is assumed to be similar throughout the lung image and is assigned a value of 0.25 Va for each voxel.

ΔHU1 and ΔHU2(t). ΔHU1 is the difference in RD between the room-air gas (HUair) and the gas mixture containing ~65% Xe. ΔHU1 was determined by subtracting the RD of the lumen of a large airway during room-air breathing from the RD of the same airway lumen during Xe breathing. To minimize the effect of noise on this measurement, the mean RD of 15 baseline breaths was subtracted from the mean RD of 30 Xe breaths.

ΔHU2(t) was obtained by measuring RD changes in the inferior vena cava (IVC). RD was measured in the IVC at each breath during baseline breathing and Xe washin, and changes in RD, linearly related to changes in [Xe], were fit to an exponential function, ΔHU2(t). Although the factors affecting the [Xe] in the IVC are complex, an exponential function appeared to adequately represent the observed changes in RD of the IVC and allowed for determination of the time delay between the start of Xe breathing and the start of recirculation. This parameter matching also described the rate of change of [Xe] in the venous blood, given the known quantities of Xe in the venous blood during baseline breathing (zero) and at full body equilibration (λblood/air * C2). Baseline RD for IVC was obtained by averaging the RD of the first 15 breaths (baseline V), and the amplitude of the exponential was given by λblood/air * ΔHU1, the maximum possible RD change in the IVC for a given [Xe] in the inhaled gas.

TRACER GAS SOLUBILITY. Xe solubility is similar in human, dog, and cow blood and depends on hematocrit (Hct). For a Hct of 27% (the mean Hct of our sheep), λblood/air = 0.13 for human (28, 32, 40), dog (6, 9, 32), and cow (32) based on published values of λplasma/air and λblood/air. Therefore, for our study, we assumed λblood/air = 0.13. For Xe solubility in tissue, we use the value reported for Xe solubility in plasma, which is also conserved across these species (λtissue/air = 0.10).

RESULTS

Xe inhalation did not alter hemodynamic or gas-exchange parameters (Table 1). RD measurements, during inspiratory hold, for a representative voxel of lung and the IVC are shown in Fig. 2; 15 room-air (baseline) breaths precede 30 breaths of Xe (65% inhaled gas). The baseline RD of the IVC curve is higher than that of the lung voxel because of aeration of the lung. The magnitude of the IVC curve is smaller than the voxel curve because of the limited solubility of Xe in blood; the maximum [Xe] in the IVC is 13% of that of the [Xe] in the inhaled gas. The onset of RD change in the IVC lags behind that of the voxel because of the time required for blood to traverse the systemic circulatory system and the large volume of distribution of

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Xe in the systemic circulation because of its significant lipid solubility.

Figure 3 shows how changes in $V\dot{\alpha},Q\dot{\alpha}$, and $V_{D}$ affect the time evolution of $RD$ for an idealized voxel during Xe washin, assuming no recirculation of tracer gas. Increasing regional $V\dot{\alpha}$ increases the rate and magnitude of $RD$ change; conversely, increasing either $V_{D}$ or $Q\dot{\alpha}$ results in a decrease in the rate and magnitude of $RD$ change. Because both $Q\dot{\alpha}$ and $V_{D}$ have similar effects, these variables cannot be distinguished from each other.

In this study, we have assumed $V_{D}$ to be a fixed fraction of $V_{A}$ (25%). For a representative voxel of lung from sheep 5, if $V_{D}$ is assumed to be 25% of $V_{A}$ ($V_{D}/V_{A}$), then $V\dot{\alpha}=1.55$ mm$^3$/s, $Q\dot{\alpha}=1.55$ mm$^3$/s, and $V\dot{\alpha}/Q\dot{\alpha}=1.0$. If this voxel were reanalyzed with an assumed $V_{D}/V_{A}$ of 30%, then $V\dot{\alpha}=1.69$ mm$^3$/s (a 9% increase), $Q\dot{\alpha}=1.61$ mm$^3$/s (a 4% increase), and $V\dot{\alpha}/Q\dot{\alpha}=1.05$. If we assume a lower dead space fraction, $V_{D}/V_{A}=20\%$, then $V\dot{\alpha}=1.41$ mm$^3$/s (a 9% decrease), $Q\dot{\alpha}=1.49$ mm$^3$/s (a 4% decrease), and $V\dot{\alpha}/Q\dot{\alpha}=0.95$.

Figure 4 demonstrates regional $V\dot{\alpha}$, $Q\dot{\alpha}$, and $V\dot{\alpha}/Q\dot{\alpha}$ at a 16-mm$^3$ scale for a 2.5-mm-thick transverse region of lung. These in vivo measurements can be correlated with lung anatomy by comparing $V\dot{\alpha}$, $Q\dot{\alpha}$, and $V\dot{\alpha}/Q\dot{\alpha}$ maps to CT images of the same portion of the lung. Because the CT-Xe method requires air space for sufficient detection of tracer gas, measurements of $V\dot{\alpha}$ or $Q\dot{\alpha}$ in atelectatic regions of lung are not possible, and these regions are not represented in the lung function maps.

Examination of Fig. 4 reveals vertically oriented and isogravitational heterogeneity for both $V\dot{\alpha}$ and $Q\dot{\alpha}$. Figure 5 shows that, in 16-mm$^3$ voxels, both vertically oriented and isogravitational heterogeneity are greater for $Q\dot{\alpha}$ than $V\dot{\alpha}$.

Table 2 lists the coefficients of variance (CV) for $V\dot{\alpha}$ ($CV_{V\dot{\alpha}}$) and $Q\dot{\alpha}$ ($CV_{Q\dot{\alpha}}$) at 16-mm$^3$ and 1,000-mm$^3$ scales of resolution. For 16 mm$^3$, $Q\dot{\alpha}$ displayed more variance than $V\dot{\alpha}$: $CV_{Q\dot{\alpha}}=1.58$, $CV_{V\dot{\alpha}}=0.46$, and $CV_{Q\dot{\alpha}}/CV_{V\dot{\alpha}}=3.5$. $CV_{Q\dot{\alpha}}$ (1.21) and $CV_{Q\dot{\alpha}}/CV_{V\dot{\alpha}}$ (2.4) were smaller at the 1,000-mm$^3$ scale of resolution, but $CV_{V\dot{\alpha}}$ was not (0.53).

$V\dot{\alpha}$- and $Q\dot{\alpha}$-weighted $V\dot{\alpha}/Q\dot{\alpha}$ distributions for a single transverse portion of lung, as measured by CT-Xe, demonstrate an approximate unimodal log normalized shape (Fig. 6) similar to findings from multiple inert-gas elimination technique (MIGET) and microsphere studies of normal whole lungs. The width of the $Q\dot{\alpha}$-weighted $V\dot{\alpha}/Q\dot{\alpha}$ distributions decreases with increasing voxel size. For sheep 5, log SD of $V\dot{\alpha}$ was 0.62 at a 16-mm$^3$ scale and 0.79 at a 1,000-mm$^3$ scale. Log SD of $Q\dot{\alpha}$ was 0.63 at a 16-mm$^3$ scale and 0.82 at a 1,000-mm$^3$ scale.

**DISCUSSION**

**Advantages of CT-Xe**

We describe an improved model of inhaled radiodense tracer gas kinetics, the soluble gas model, that...
allows for the simultaneous quantification of absolute regional $V$ and $Q$ in vivo using Xe and CT (Fig. 4). Although multiple methods have been employed to measure regional $V$ and $Q$, CT-Xe is nondestructive and permits simultaneous measurement with very high spatial resolution. High-resolution measurements are key to understanding gas exchange because the spatial variability of both $V$ and $Q$ increases as piece size decreases (2, 5, 17, 19, 41). Unlike previous studies using CT and Xe that only measured regional $V$, we have maximized the changes in regional RD and incorporated blood solubility of Xe, dead space ventilation, and recirculation of tracer gas into a model that allows for measurement of regional $V$ and $Q$.

**Maximizing Xe signal.** Because Xe is only 13% as soluble in blood as in air, the magnitude of effect of $Q$ on regional tracer gas concentration is expected to be smaller than that of $V$. To reliably assess regional $Q$, we have maximized the changes in regional RD and incorporated blood solubility of Xe, dead space ventilation, and recirculation of tracer gas into a model that allows for measurement of regional $V$ and $Q$.

**Fig. 3.** Changes in $V$ (A), $Q$ (B), and dead space fraction ($V_D$) affect rate regional RD increase during Xe washin. For all curves, recirculation is assumed negligible. A–C: a reference case, $V = 1$, $Q = 1$, ratio of $V$ to $Q$ ($V/Q$) = 1, $V_D = 0.25$, is indicated with a solid line. A: the rate and magnitude of RD change increases as $V$ increases. B: the rate and magnitude of RD change decreases as $Q$ increases. C: the rate and magnitude of RD change decreases as $V_D$ increases but to a smaller degree than for changes in $Q$.

**Fig. 4.** Single 2.5-mm-thick computed tomography (CT) image of sheep 5 obtained at end inspiration (A) and corresponding $V/Q$ (B), $V$ (C), and $Q$ (D) for 16-mm$^3$ regions of lung. The top scale refers to $V/Q$ plot (B). Bottom scale refers to both $V$ (C) and $Q$ (D) plots. Note the vertical gradient, isogravitational heterogeneity, and spatial clustering of $V$ and $Q$. At this scale of resolution, $Q$ demonstrates significantly more spatial heterogeneity than $V$. Significant regional variation also exists in regional $V/Q$ relationships.
we maximized the Xe RD signal by 1) inhaling ~65% Xe, 2) scanning at a low-beam energy (80 kVp) to increase X-ray absorption of Xe (31, 42), and 3) scanning at large lung volumes (end inhalation). As a result, we obtained a maximum change in RD in airways (HUI) of 165 HU, which exceeds the mean change in RD of 30–80 HU reported by others (31, 35, 37, 38).

The advantages of end-inspiratory imaging are significant and are primarily responsible for the dramatic increase in the Xe signal seen in our study. Because the majority of the tracer gas in a voxel exists in the alveolar space, maximizing the voxel fraction that is gas filled maximizes the amount of tracer in the voxel. The gas fraction in a voxel can be as much as two- to threefold greater at end inspiration than at end expiration in the dependent lung regions in the supine position (25). In addition, at end expiration, dependent lung regions have overall lower signal-to-noise ratios than nondependent areas; this variance is minimized by imaging at end inspiration (25, 27). Finally, scanning at end inspiration minimizes the effect of atelectasis (38) on our measurements.

**Dead space ventilation.** The effect of reinspired dead space has not been accounted for in previous models using CT, magnetic resonance imaging, microspheres, or single-photon-emission computed tomography (SPECT) to image regional V˙ (1, 29, 31, 36–38). This simplification can introduce error if the difference in gas concentration between breaths is significant. The effect of dead space ventilation is to slow the rate of rise of [Xe] in the air spaces (Fig. 3C). The content of the gas entering a region of lung with each breath is not exactly the same as the gas inspired at the mouth but is a mixture of fresh gas and a small portion of gas remaining in the airways after the previous exhalation. The magnitude of this error is correlated with both the blood solubility of the tracer gas and regional Q; loss of tracer into blood increases the discrepancy between tracer gas concentration at the mouth and in the previously exhaled alveolar gas.

We have included dead space in the soluble gas model. Because Q also serves to slow the rate of Xe accumulation in the lung (Fig. 3B), it is not possible to differentiate the effects of Q and V˙D in the present model. Therefore, for the purposes of this study, V˙D is assumed to be a fixed percentage of the VA for all voxels studied, namely, 25% of VA.

**Recirculation of tracer gas.** Our model predicts that Xe solubility in blood may affect regional alveolar [Xe] in two ways: loss of Xe into arterial blood and delivery of Xe via venous blood (Fig. 1). Using CT, we are able to measure the concentration of tracer gas in a region of lung as well as estimate the concentration of tracer gas returning to the lung via recirculation by measuring RD changes in the vena cava. For washin periods of 0.5–1 min, the effect of recirculated tracer gas on V˙ and Q˙ measurements is minimal. However, accurate analysis of low-V˙ regions requires an extended washin period, necessitating the inclusion of this recirculation effect.

**Comparison to Other Methods**

Direct comparison of regional V˙ and Q˙ measurements obtained by CT-Xe and ex vivo methods on a

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**Table 2. Coefficient of variance for V˙, Q˙, and V˙/Q˙ for 16- and 1,000-mm³ scales of resolution**

<table>
<thead>
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<th>Animal No.</th>
<th>Voxel Volume = 16 mm³</th>
<th>Voxel Volume = 1,000 mm³</th>
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<td>CVQ</td>
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<tr>
<td>Mean ± SD</td>
<td>0.46 ± 0.07</td>
<td>1.68 ± 0.23</td>
</tr>
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CVV, CVQ, CVQ/CVV: coefficient of variance of ventilation, perfusion, and ventilation-to-perfusion ratio, respectively.

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**Fig. 5. V˙ (A) and Q˙ (B) as a function of dorsal-to-ventral distance for sheep 5. Both V˙ and Q˙ demonstrate a vertical gradient and significant isogravitational variance.**
region-by-region basis may be difficult because of registration differences introduced by removing lungs from the chest wall. Comparison of gas-exchange data between CT-Xe and whole lung methods, such as MIGET, is difficult because CT-Xe is presently only able to measure V and Q in portions of the lung and MIGET does not allow for regional analysis. Because significant regional differences in V and Q exist, measurements from one region of the lung may not adequately represent global gas exchange. However, comparisons of spatial patterns, such as the vertical distributions of V and Q, V- and Q-weighted V/Q distributions, and the scale-dependence of V and Q heterogeneity, between data obtained by CT-Xe and that reported by other methods is possible.

Comparison to other measures of regional V and Q. Because there are no published measurements of regional V and Q at the scale of resolution reported here, direct comparison of spatial variance in V and Q measured by CT-Xe and other methods is not possible. However, because the scale-dependent properties of regional Q have been well established for larger scales of resolution (2, 17, 19, 41), and this fractal nature has been confirmed to continue well below the scale of the acinus in rats (12), we can compare the Q variance for the 16-mm$^3$ scale predicted by other methods to that measured by CT-Xe. The mean CV$_Q$ at a 16-mm$^3$ scale of resolution for all five sheep in this study was 1.58. This is similar to the CV$_Q$ of 1.53 predicted for a regional volume of 16 mm$^3$ using the fractal dimension (i.e., 1.14) for Q measured in sheep by Caruthers and Harris (5).

Interestingly, we observed a CV$_Q$ two to five times that of CV$_V$ at a 16-mm$^3$ scale of resolution. Studies using other techniques do not demonstrate a significant difference between CV$_V$ and CV$_Q$ or significant differences in fractal dimensions between V and Q at larger scales of resolution. Similarly, we observed less disparity between CV$_V$ and CV$_Q$ at a resolution of 1,000 mm$^3$. A possible explanation for the dramatic difference between CV$_V$ and CV$_Q$ at 16 mm$^3$ may be that this lung volume is below the functional unit of V, the volume of lung at which V is homogeneous. Whereas it has been shown using microspheres that Q variance does increase below the level of the acinus, there have been no comparable studies of V.

An alternative explanation for why CV$_Q$ appears more sensitive to voxel size than CV$_V$ may be that the measurement of Q is more sensitive to noise in this model. This may be the case because Xe is only 13% as soluble in blood as it is in air. If the Xe washin signal becomes significantly more noisy with smaller voxel volumes, this could result in increased variance of both V and Q, but Q measurements may be affected to a greater degree. Because there is no increase in CV$_V$ between the two voxel volumes measured, this explanation would have to assume that all variance due to noise is represented in the Q measurement. Further analysis of the sensitivity of V and Q to noise will be needed to evaluate the limitations of the CT-Xe method.

The caudal region of the lung was imaged to afford a wide range of V, Q, and V/Q for study. This section of lung has the largest possible vertical gradient as well as areas of atelectasis and low aeration, enabling us to examine regions with extremes of V, Q, and V/Q. The finding of vertical and isogravitational heterogeneity in both V and Q in this study (Fig. 5) is consistent with the findings of Q heterogeneity using microspheres (13, 14, 16). These prior studies have concluded that gravity is not the predominant factor determining regional Q, and our results appear to support this hypothesis.

Comparison to other measures of whole lung gas exchange. V- and Q-weighted V/Q distributions can be calculated using data obtained by CT-Xe (Fig. 6). For a transverse region of lung, the V- and Q-weighted V/Q distributions obtained by CT-Xe approximate a unimodal log-normalized shape in normal sheep. Unlike the MIGET method, CT-Xe assumed no particular shape for the V- and Q-weighted V/Q distributions and does not apply smoothing to V/Q distributions. It is interesting to note that the shape of the V/Q distributions is similar to that found for the entire lung using different methodologies, although data from each transverse region of lung need not mimic the findings for the entire lung.

Figure 6 reveals a significant portion of Q being delivered to regions of lung with V/Q < 1, whereas the lung as a whole is hyperventilated. Alveolar V/Q for the whole lung is estimated at 1.25 for the sheep in Fig. 6 and 1.34 ± 0.32 for all sheep studied; alveolar V/Q was calculated from values for tidal volume, RR, and car-
diotic output immediately before and after Xe inhalation, assuming Vd/tidal volume = 0.25. In addition, arterial PCO2 = 30.4 ± 2.7 Torr, which was likely due to a combination of both hyperventilation and decreased CO2 production secondary to general anesthesia and paralysis. The observation of low V/Q areas in the dorsal lung of these anesthetized, paralyzed supine sheep is consistent with previous studies (4, 14, 33, 39).

The V- and Q-weighted V/Q distributions, measured by CT-Xe, show scale dependence. Figure 6 demonstrates that the V- and Q-weighted V/Q distributions are wider at 16 mm3 than at 1,000 mm3. This scale-dependent variance may eventually be used to identify the size of the functional unit of gas exchange. The scale of resolution at which V/Q distributions obtained by CT-Xe best match those obtained using MIGET may represent the scale at which gas exchange occurs.

Potential Limitations

**Fixed personal dead space.** Whereas this study assumes a fixed Vd/VA, this is not likely the case in vivo. Just as regional V and Q vary regionally, so too may Vd/VA. In addition, Vd/VA may be scale dependent. If the assumed Vd/VA in this model does not represent the true Vd/VA in a region of lung, the calculated values of V and Q will be affected. For a representative voxel of lung with a V/Q = 1, a 20% increase (or decrease) in the dead space fraction above the 25% value assumed in the model results in a 9% change, increase (or decrease) in V, a 4% increase (or decrease) in Q, and a 5% increase (or decrease) in V/Q.

We assume that dead space is “personal,” i.e., each region of lung re-inspires only its own exhaled gas. Our assumption that dead space is personal, rather than “common,” may underestimate V and Q heterogeneity. If region A (high V/Q) shared common dead space with region B (low V/Q), the mixed dead space gas would have a lower [Xe] than the exhalate of region A and a higher [Xe] than the exhalate of region B. Region A would have less Xe delivered per breath, which would be interpreted by the model as a decreased V/Q; conversely, region B would have more Xe delivered per breath, resulting in a higher measured V/Q. This effect is likely small because V and Q are spatially clustered, limiting dramatic differences between adjacent lung regions. Additionally, it has been demonstrated that the effects of common dead space can be adequately approximated by assuming that dead space is personal in a multicompartment model of gas exchange (10).

**Image noise.** Image-related noise affects the calculation of V and Q. The most significant sources of image noise in our study are registration artifact and reconstruction artifact. Registration artifact occurs when movement of the lung between images causes changes in regional tissue density, resulting in changes in regional RD. These changes in tissue RD may overwhelm the changes in RD due to Xe inhalation because the difference between end-inspiratory and end-expiratory RD can be on the order of 300 HU, and the maximum Xe signal possible during our study is <175 HU. Scanning at identical lung volumes at each breath minimizes this effect.

The heart can introduce both registration and reconstruction artifacts. Movement of pericardiac lung regions may cause cyclic registration artifact, which can be compensated for by parameter matching. Changes in cardiac dimensions between scans can also affect regional RD measurements over time, even in nonpericardiac areas of the lung. This reconstruction artifact relates to changes in assigned RD of a region, as a result of actual changes in RD of other regions, and is due to the nature of CT image reconstruction from linear X-ray data. Similar effects on regional RD are possible if other structures change dimension or location with the cardiac cycle, such as the aorta or bones in unrestrained upper extremities, which can move slightly due to arterial pulsations. Including a larger number of breaths may mitigate the effect of cardiac noise on washin curves, but this correction increases the chance of recirculation effects. In the future, it may be possible to greatly reduce the effect of cardiac oscillations by obtaining end-inspiratory images gated to the cardiac cycle or by averaging two or more images obtained during each end-inspiratory breath hold.

**Gas density.** When bulk quantities of imaging agent are used, the properties of the tracer agent itself may affect the measurements being made. For example, the density of our Xe-O2 mixture is nearly four times that of room air, and the viscosity is 20% greater than air. The effect of increased gas density on pulmonary gas exchange is complex. Low-density gases (He) decrease the efficiency of O2 exchange but increase the efficiency of CO2 exchange. Conversely, more dense gases such as Ar and SF6 have been shown to produce the opposite effects on gas exchange (7, 43). Neither high- nor low-density gases affect the transport of carbon monoxide in the lung. Extrapolation of these findings to our study are difficult because the changes noted are significantly more pronounced during hypoxia and have not been studied during conditions similar to those in our study.

In conclusion, we report the first noninvasive method that simultaneously measures regional V and Q in vivo. These measurements are possible using an improved model of tracer-gas movement in the lungs that includes the effects of gas solubility in blood, tracer gas recirculation, and dead space V. Using Xe and CT, we can measure V and Q in regions of lung 20- to 100-fold smaller than reported using positron emission tomography or microspheres and correlate gas-exchange data with anatomic structure. Further evaluation of this method is required to determine spatial resolution limits, the range for which V and Q can be accurately assessed, and the effect of image noise on V and Q determination. Ultimately, CT-Xe may be used to study gas exchange in the human lung.
REFERENCES


