Effect of low-xenon and krypton supplementation on signal/noise of regional CT-based ventilation measurements

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Chon D, Beck KC, Simon BA, Shikata H, Saba OI, Hoffman EA. Effect of low-xenon and krypton supplementation on signal/noise of regional CT-based ventilation measurements. J Appl Physiol 102: 1535–1544, 2007. First published November 22, 2006; doi:10.1152/japplphysiol.01235.2005.—Xenon computed tomography (Xe-CT) is used to estimate regional ventilation by measuring regional attenuation changes over multiple breaths while rebreathing a constant Xe concentration ([Xe]). Xe-CT has potential human applications, although anesthetic properties limit [Xe] to \( \leq 35\% \). We investigate effects of lower [Xe], including a low [Xe]-krypton (Kr) combination, on time constant (TC) determination. Six anesthetized sheep were scanned prone and supine using multidetector row CT. Lungs were imaged by respiratory gating during washin of a 30%, 40%, 55% Xe, and a 30% Xe/30% Kr mixture. Using Kr avoids unwanted effects of Xe. Mean TCs, coefficients of variation (CV), and half confidence intervals (CI)/mean served as indexes of sensitivity to noise. Mean supine and prone TCs of three [Xe] values were not significantly different. Average CVs of TCs increased from 57% (55% Xe), 58% (40% Xe), and 73% (30% Xe) \( (P < 0.05); \) paired \( t \)-tests; 30% Xe vs. higher [Xe]). Monte Carlo simulation indicated a CV based on inherent image noise was 8% for 55% Xe and 17% for 30% Xe \( (P < 0.05) \). Adding 30% Kr to 30% Xe gave a washin signal equivalent to 40% Xe. Half CI/mean using the 30% Xe/30% Kr mixture was not significantly different from 55 and 40% Xe. Although average TCs were not affected by changes in [Xe], the higher CV and half CI/mean suggested reduced signal-to-noise ratio at the 30% [Xe]. The 30% Xe/30% Kr mixture was comparable to that of 40% Xe, providing an important agent for CT-based assessment of regional ventilation in humans.

Since xenon (Xe) gas was first introduced by Knipping and coworkers (21) as a contrast material applicable to the assessment of pulmonary function, it has been used extensively in scintigraphy (2, 3, 26), MRI (36), single-photon emission computed tomography (CT) (1), and X-ray CT (10, 25, 28). Stable (nonradioactive) Xe gas has a K-edge similar to that of iodine and is a potent X-ray attenuator, providing good contrast enhancement when used in conjunction with CT scanning (42). When imaged in a conventional CT scanner, lung attenuation varies linearly with the Xe concentration ([Xe]) in the air spaces (9), and the time course of Xe accumulation in the lung periphery during breathing, measured with serial CT images, is the basis for the Xe-CT measurement of regional ventilation (4, 33).

Although Xe is an inert gas, it is moderately soluble in blood and tissue \( (18) \) and has been used clinically \( (7) \) as an inhaled anesthetic, \( \sim 30\% \) more potent than nitrous oxide \( (5, 12, 25) \). [Xe] values of 30–50% have been used to measure cerebral blood flow in human studies, but with reported sedating or other side effects when [Xe] >5% was used \( (5) \). Thus, while Xe-CT has the potential to measure regional human pulmonary ventilation, concentrations of \( \leq35\% \), with consequent reduced signal, are recommended. Krypton (Kr), another radiodense inert gas, has a lower attenuation effect than Xe gas, but may be a useful inhalation contrast medium with CT scanning (42). In addition, because Kr is much less soluble than Xe and has no documented side effects, we hypothesized that a Kr and Xe gas mixture would prove a better contrast medium than Xe gas alone, especially for human use.

In this study, we investigate how the use of low [Xe] affects the robustness of regional time constant determinations by comparing mean time constants and their coefficients of variation (CVs) and confidence intervals (CIs) at three [Xe] values \( (55\% \text{ Xe}, 40\% \text{ Xe}, \text{ and 30}\% \text{ Xe}) \) in healthy, anesthetized, mechanically ventilated animals. In addition, we test the repeatability of the Xe-CT method using 55% Xe. Finally, we determine whether inhaled Xe can be supplemented with Kr to bring the total radiodensity of the inhaled contrast agent to a level that reduces side effects while sufficiently elevating the signal-to-noise ratio of our ventilation measurements to provide detailed maps of regional ventilation in humans.

METHODS

Animal Preparation

All animal studies were performed within the guidelines for animal care adopted by the American Physiological Society and the National Institutes of Health. The University of Iowa Institutional Animal Care and Use Committee approved the animal use protocols in advance. Six sheep \( (70–90 \text{ kg}) \) were premedicated with 0.5 ml premixed solution of ketamine \( (75 \text{ mg/ml}) \) and xylazine \( (25 \text{ ml/ml}) \) and anesthetized with isoflurane via a nose cone. The trachea was intubated with a cuffed endotracheal tube \( (9.0 \text{ mm}) \). Deep anesthesia was subsequently maintained with pentobarbital sodium \( (5 \text{ mg/kg and 1–3 mg/kg iv hourly}) \) and as needed) and muscle relaxation with pancuronium bromide \( (0.1 \text{ mg/kg and 0.5–1 mg iv hourly}) \). After intubation, the sheep were mechanically ventilated \( (10 \text{ ml/kg, 20 breaths/min}) \) with a piston respirator (Harvard Apparatus, Holliston, MA). Pressure catheters

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sized that using a 30% Xe/30% Kr mixture would give a 33% three times more CT enhancing than Kr (Fig. 1). Thus we hypothesized a level that produces an acceptable signal-to-noise ratio. Xe is about Xe gas could be supplemented with Kr to bring the total radiodensity at functional residual capacity.

Previous investigators performing animal experiments have lower [Xe] values affect the robustness of the time constant determination. In lung parenchyma was semiautomatically segmented from the chest wall and mediastinum (16). Using the customized software “Time Series Image Analysis,” the lung was divided into 9 × 9 pixel regions of interest (ROI), and the mean density in each ROI was measured for each image in the series and plotted as a function of time (Fig. 2). The time constant for each ROI was calculated by fitting this washin curve to a single-compartment exponential model using a nonlinear least square curve-fitting procedure. The ROI potentially included major airways and blood vessels, and so were filtered by applying two criteria: summed squared residual (SSR) of the curve fit <150 (33), and ROI air fraction between 40 and 90% (14). Means and SDs of the time constants were obtained by combining results from the four simultaneously acquired slices per animal. The heterogeneity of the regional time constants throughout the imaged lung (all four slices) was assessed from the CV of the ROI data within the lung field, defined as the SD normalized by the mean value.

Stochastic model (Monte Carlo simulation). Because data from multiple ROIs from the same images are correlated in an unknown way, traditional descriptive statistical measures may underestimate their variance (33). We estimated CIs about individual ROI parameter estimates using a Monte Carlo (MC) simulation, as previously described (33). Briefly, this process uses “noise” extracted from the SSR of each curve fit to determine the variability of the various fitted parameters. The sources of noise in these CT data includes scanner-derived image variations, lung density change caused by slight variations in lung volume across the multiple respiratory gated time

**Image Specifications**

Imaging was performed using a high-speed multidetector row CT (MDCT) scanner (MX 8000 scanner, Philips) that acquired four simultaneous sections in 0.5 s. The volume-scan protocol used to locate the position of apical and basal slices, the scanning parameters were 100 mA, 120 kV, slice thickness of 1.3 mm, slice increment of 0.6, scan angle of 180, 225 mm field of view, and in-plane pixel size of 0.391 × 0.391 mm. For the multibreath Xe-CT axial scanning protocol, kV = 90, mA = 120, scan time = 0.5 s, slice thickness = 2.5 mm, field view = 226 mm, in-plane pixel size = 0.449 × 0.449 mm, and a “standard” (“B”) image reconstruction kernel was used.

**Xe-CT and Xe/Kr-CT Protocol**

Based on a previous study (4), we imaged the lung during the washin of the contrast gas mixture over a series of 40 consecutive breaths (7 baseline images breathing air followed by 33 images breathing Xe/O2 or Xe/Kr/O2) at a single axial location in the lung base with image acquisition gated to end expiration. At a respiratory rate of 10 breaths/min, the entire process took 240 s (198 s of washin).

**Protocol 1.** The purpose of this protocol was to investigate how lower [Xe] values affect the robustness of the time constant determination. Previous investigators performing animal experiments have used [Xe] > 50% to obtain higher signal-to-noise ratios. Due to the side effects of Xe gas, investigators performing human experiments have limited [Xe] to 35% or less. We chose [Xe] values of 55, 40, and 30% in random order, repeated in both supine and prone positions in six animals at a lung base location selected from the volumetric scan at functional residual capacity.

**Protocol 2.** The purpose of this protocol was to determine whether Xe gas could be supplemented with Kr to bring the total radiodensity to a level that produces an acceptable signal-to-noise ratio. Xe is about three times more CT enhancing than Kr (Fig. 1). Thus we hypothesized that using a 30% Xe/30% Kr mixture would give a 33% improvement in enhancement over 30% Xe alone and thereby produce an acceptable magnitude of signal. As above, a series of 37 consecutive end-expiratory gated axial CT scans was taken in the supine position in three animals at the same location in the lung base as that selected in other protocols.

**Protocol 3.** This protocol was performed to investigate the repeatability of the Xe-CT technique using 55% Xe, which should provide the highest signal-to-noise ratio and maximum contrast enhancement. The identical scan protocol as protocol 1 using 55% Xe was repeated in both supine and prone positions in six animals at the same location in the lung base as that selected in other protocols. The order of the repeated scan was randomly performed.

**Data Analysis**

**Time constant determination.** For each axial location, the lung parenchyma was semiautomatically segmented from the chest wall and mediastinum (16). Using the customized software “Time Series Image Analysis,” the lung was divided into 9 × 9 pixel regions of interest (ROI), and the mean density in each ROI was measured for each image in the series and plotted as a function of time (Fig. 2). The time constant for each ROI was calculated by fitting this washin curve to a single-compartment exponential model using a nonlinear least square curve-fitting procedure. The ROI potentially included major airways and blood vessels, and so were filtered by applying two criteria: summed squared residual (SSR) of the curve fit <150 (33), and ROI air fraction between 40 and 90% (14). Means and SDs of the time constants were obtained by combining results from the four simultaneously acquired slices per animal. The heterogeneity of the regional time constants throughout the imaged lung (all four slices) was assessed from the CV of the ROI data within the lung field, defined as the SD normalized by the mean value.

Because data from multiple ROIs from the same images are correlated in an unknown way, traditional descriptive statistical measures may underestimate their variance (33). We estimated CIs about individual ROI parameter estimates using a Monte Carlo (MC) simulation, as previously described (33). Briefly, this process uses “noise” extracted from the SSR of each curve fit to determine the variability of the various fitted parameters. The sources of noise in these CT data includes scanner-derived image variations, lung density change caused by slight variations in lung volume across the multiple respiratory gated time

![Image](https://example.com/image.png)

**Fig. 1.** Xenon (Xe) and krypton (Kr) concentration [delta computed tomography (CT)] vs. CT contrast enhancement at 80, 100, and 120 kV. Delta CT was measured in a Siemens Sensation 16 multidetector row CT (MDCT) scanner with Xe and Kr gases diluted in air contained in 500-ml syringes. At 80, 100, and 120 kV, contrast enhancement (delta CT) due to Xe was three to four times greater than the contrast enhancement of Kr. HU, Hounsfield units.

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equilibration with Xe; D₀, baseline density. The time constant for washin (τ) is indicated. τ, time; D₀, arrival time; Dᵣ, density after full equilibration with Xe; D₀, baseline density.

points, registration error, and cardiogenic motion serving to shift lung regions from time point to time point. This noise represents a statistical component that is added to a deterministic model, which is then analyzed statistically. To perform this MC simulation, the original idealized sampled time-attenuation curve to simulate the noise component of the CT-derived Xe tracer curve.

\[ D(t) = (D₀ + ε) + (Dᵣ - D₀)[1 - \exp\left(-\frac{(t - τ)}{τ}\right)] \]

where \( t \) is time, \( Dᵣ \) is density after full equilibration with Xe, and \( τ \) is the time constant for washin. This simulated “noisy” washin curve is repeated \( n \) times, each with newly generated stochastic noise terms, and each is curve fitted, generating \( n \) sets of fitted parameters. The distribution of these parameters defines the variability of curve fit results, which may occur, given the actual noise in the data.

Six ROIs (21 pixels × 21 pixels) in one slice were chosen for each sheep (3 ROIs each for left and right lungs), and the simulation algorithm was applied to each ROI. To determine the numbers of repetitions for this process needed to achieve a stable average mean time constant, as shown in Fig. 3. ROIs using five different noise levels (SSR: 20, 30, 60, 80, 100) were evaluated for 50–1,000 repetitions (27). As shown in Fig. 3, both the mean time constant and SE remained unchanged after 500 repetitions for all noise levels. Thus, in this study, we used 700 times iteration. The unbiasedness of the parameter estimates was confirmed by comparing the true value with a statistical estimator obtained by calculating the mean ± SD of three estimators for 700 repeated simulations with three different levels of noise and two nominal time constants when using both 55% Xe and 30% Xe (data not shown).

The MC simulation was used to define a CI for each time constant of each of the six selected ROIs. The 95% CI is determined by the time constant values at the 2.5th and 97.5th percentiles of the ordered results from the simulation. These CIs are conveniently expressed analogous as the CV (CV*), corresponding to one-half of the 95% CI/mean, to correct for differences in the means (33). Then increases in the CV* reflect wider CIs for individual measurements and indicate a loss of ability to detect regional differences.

Xe/Kr mixture. For analysis of Xe/Kr images, the mean density in each ROI (9 pixels by 9 pixels) within the imaged lung field was plotted as a function of time. The time points were fitted to the washin exponential curve using a nonlinear least square curve-fitting procedure. The magnitude of contrast enhancement caused by the 30% Xe/30% Kr mixture was obtained by calculating the difference between the baseline (D₀) and plateau (Dᵣ) of the fitted exponential curves. The same process was applied to three different Xe gas image data sets to measure the magnitude of the contrast enhancement. To test the robustness or sensitivity to noise of the time constant with the 30% Xe/30% Kr mixture compared with that with Xe-only studies (30, 40, and 55% [Xe]), the mean time constant and the CV* (half 95% CI/mean), obtained by MC simulation, were calculated (see Fig. 7).

Repeatability of the Xe-CT technique. For the analysis of repeated image data in both body postures in six animals, mean time constants were calculated and compared between the two repeated studies (see Fig. 10).

Statistical Analysis

Differences in means, CVs, half 95% CI/mean, and repeatability were tested by Student’s paired t-test (two-tailed) with a significance level of \( P < 0.05 \).

RESULTS

Figure 4 shows color maps of the time constants (s) and specific ventilation (1/min) for 9 × 9 pixel ROIs in both the supine (left) and prone (right) positions. The time constant is equal to the inverse of the local ventilation per unit volume (specific ventilation). The longer the time constant (lower specific ventilation), the more poorly the ROI is ventilated, and vice versa. In the supine position, longer time constants were located in the nondependent part of the lung, and shorter time constants were located in dependent lung regions, indicating that the lung was more ventilated in the dependent regions than in the nondependent regions in this posture. However, in the prone position, all of the time constants were evenly distributed, indicating that ventilation in the prone position was relatively uniform. These ventral-dorsal relationships agree well with those of previous studies (25) and provide a minimum physiological relationship, which should remain present in image data as [Xe] values are varied.

Plot of mean time constants vs. [Xe] for different body positions is shown in Fig. 5. The mean time constants obtained using 30, 40, and 55% Xe were not significantly different from each other. While the mean time constants for the prone
position and end-expiratory scanning mode were greater at each [Xe] compared with the supine position, these differences were not significant ($P > 0.05$). Tables 1 and 2 show mean time constants in the nondependent, middle, and dependent regions at all three different [Xe] values for both the supine (Table 1) and prone (Table 2) positions. Mean time constants for each of the three regions were not significantly different at the three different [Xe] values in either position. However, in all three different [Xe] values with the animals in the supine position, the mean time constants in the nondependent regions were significantly greater (less ventilation) than those in both the middle and the dependent regions. There were no significant differences between the middle and the dependent regions or between regions in the prone position (Table 2).

Figure 6 shows the whole lung CVs for the experimental data at three different [Xe] values in different body positions. For both body positions, the CV using 30% Xe is significantly greater than that with 40% Xe and 55% Xe, but the CV of 55% Xe is not significantly different from that with 40% Xe. Note that the increase in the CV using 30% Xe indicates greater heterogeneity of the measured time constants, despite no difference in the means (Fig. 5). In addition, the CVs at all three [Xe] values were smaller in the prone position than in the supine position, reflecting the fact that the prone position is less heterogeneous in the distribution of ventilation than the supine position due to gravity and lung geometry (17, 31, 38). CVs of time constants in the nondependent, middle, and dependent regions when using three different [Xe] values were calculated for the supine (Table 3) and prone (Table 4) positions. In the supine position, the CV of 30% Xe was significantly different from 40% Xe and 55% Xe in the nondependent region, but not in the middle and dependent regions. In the prone position, the CV of 30% Xe was significantly different from 40% and 55% Xe in the middle and dependent regions, but not in the nondependent region.
The mean time constant obtained with the 30% Xe/30% Kr mixture did not differ from those obtained using 30, 40, or 50% Xe alone. Using MC simulation, the half CI/mean for the six large ROIs per animal (n/H11005 3) was obtained for the Xe/Kr mixture and compared with those at three different [Xe] values (Fig. 7). The half CI/mean using the 30% Xe/30% Kr mixture was not significantly different from those using 50% Xe and 40% Xe, but all were significantly lower than values obtained using 30% Xe.

A signal-to-noise ratio was calculated by dividing the maximum contrast enhancement (Df-Do) by the curve-fit SSR at 55 and 30% Xe in both supine and prone positions and then matched on a ROI-by-ROI basis (Fig. 8). In both positions, SNR at 55% Xe was larger for the majority of ROIs than that at 30% Xe. Table 5 shows SSR normalized by Df-D0 at 55, 40, and 30% Xe in the supine position, indicating the goodness of fit of the compartment model for Xe washin, particularly with respect to the [Xe]. In the supine position, SSR/(Df-D0) was greater at 30% Xe than at 55% Xe, suggesting that the greater [Xe] is, the better Xe washin curve is fitted.

Figure 9 shows the effects of ROI size (11, 21, and 31 pixel squares) on the half CI/mean. At all three [Xe] values and for the Xe/Kr mixture, decreasing ROI size caused an increase in the width of the 95% CI, indicating a reduction in the ability to discriminate differences between values. In addition, the half CI/mean for 30% Xe was significantly greater than for 40% Xe, 50% Xe, and 30% Xe/30% Kr mixture at all three different ROI sizes.

Figure 10 shows the repeatability of the regional tracer washin measurement in terms of calculated time constants for different body positions in six animals using a [Xe] of 55%. Each symbol represents the original and repeated data for mean time constants, relative to the identity line. The slopes were 0.92 (R2 = 0.92) for supine and 0.96 (R2 = 0.90) for prone positions, respectively. There were no significant differences between the repeat time constant determinations.

DISCUSSION

Our laboratory has previously demonstrated the methods and assessed the accuracy of Xe gas in conjunction with MDCT imaging for the quantitative assessment of regional ventilation (4, 33, 37). The major finding of this study is that, in seeking to establish Xe-CT methods for use in humans, we observe that the CVs (inversely proportional to signal-to-noise) at 30% Xe are significantly increased compared with 40% Xe and 55% Xe, even though the average time constants at all three [Xe] values are not significantly different. This concentration effect was evident using both the raw data and MC simulations. As an alternative method for potential human use, the contrast enhancement of 30% Xe/30% Kr mixture was similar to that of 40% Xe, while its noise parameters were not significantly different between the three different xenon (Xe) concentrations. Significantly different (P < 0.05) between *nondependent vs. middle and †nondependent vs. dependent at the same Xe concentration.

Table 1. Average time constants in the nondependent, middle, and dependent regions when using three different Xe concentrations in the supine position

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>55% Xe</th>
<th>40% Xe</th>
<th>30% Xe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondependent*†</td>
<td>Middle*</td>
<td>Dependent†</td>
</tr>
<tr>
<td>1</td>
<td>141.1</td>
<td>49.13</td>
<td>35.33</td>
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<td>2</td>
<td>102.51</td>
<td>38.54</td>
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</tr>
<tr>
<td>3</td>
<td>38.53</td>
<td>18.78</td>
<td>15.88</td>
</tr>
<tr>
<td>4</td>
<td>42.30</td>
<td>24.61</td>
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</tr>
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<td>5</td>
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<td>6</td>
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<tr>
<td>Mean</td>
<td>72.37</td>
<td>32.82</td>
<td>36.68</td>
</tr>
<tr>
<td>SD</td>
<td>40.99</td>
<td>11.01</td>
<td>11.91</td>
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</tbody>
</table>

Mean time constants in each region were not significantly different between the three different xenon (Xe) concentrations. Significantly different (P < 0.05) between *nondependent vs. middle and †nondependent vs. dependent at the same Xe concentration.

Table 2. Average time constants in the nondependent, middle, and dependent regions at three different Xe concentrations in the prone position

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>55% Xe</th>
<th>40% Xe</th>
<th>30% Xe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondependent</td>
<td>Middle</td>
<td>Dependent</td>
</tr>
<tr>
<td>1</td>
<td>44.34</td>
<td>41.59</td>
<td>36.39</td>
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<tr>
<td>2</td>
<td>61.77</td>
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<td>25.30</td>
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<tr>
<td>Mean</td>
<td>48.70</td>
<td>36.81</td>
<td>30.90</td>
</tr>
<tr>
<td>SD</td>
<td>12.64</td>
<td>7.59</td>
<td>8.00</td>
</tr>
</tbody>
</table>

Mean time constants in prone position were not significantly different between regions or Xe concentrations.
different from those of 55% Xe and 40% Xe. The Xe-CT method was highly repeatable in both supine and prone positions.

Methodological Issues (MC Simulation)

In this study, we utilized MC simulation to investigate the sensitivity of the time constant to noise when using different [Xe] values. In performing the MC simulation, several factors that can affect the evaluation of CIs were considered.

First, the use of MC simulation to determine the CI for a model parameter is independent of the relationship between the parameter and the model's dependent variable(s), but considerations of noise are crucial to successful performance of MC simulation. Noise, modeled as a stochastic term in MC simulation, can be caused by multiple real sources: for example, lung motion during breathing, which can change the end-expiratory or end-inspiratory volume and lead to a change in tissue components in the ROIs; cardiac motion, which can have an influence on the lung tissue density by adjacent parenchymal motion or changes in pulmonary blood volume; and interscan variation in CT number in the ROI due to the measurement error within the scanner (23). Following Simon et al. (33), we simulated a Gaussian-distributed noise component to add a stochastic term to the $D_0$. The authors reported that noise was normally distributed ($P = 0.338$) by performing the Shapiro-Wilks test for normality. Eidelman et al. (8) used MC simulation to investigate the sensitivity to noise of each of the three parameters of the lung’s static pressure-volume curve: pressure, volume, and incompleteness of data. The effects of noise on pressure and volume were assumed to be Gaussian distributed. Won et al. (43) performed MC simulation to estimate the error in deconvolution-based regional pulmonary microvascular mean transit time measures. Images of a physical airway tree cast using electron beam CT were used to measure noise by subtracting the attenuation value (Hounsfield units) from the average of eight levels of images in each pixel, showing that the noise obtained was normally distributed with a mean of $-0.43$ and a SD of 3.93, based on the Kolmogorov-Smirnov test for normality.

Second, to evaluate the CI in the MC simulation in this study, 700 repetitions were used, a level determined by performing MC simulation with different data sets at five different noise levels and determining that minimal changes in time constant CIs were obtained above 500 repetitions. In contrast, Simon et al. (33) chose 100 repetitions based on the same type of analysis. The difference in repetition number between the two studies may be due to the number of parameters used in the MC simulation. Our study fitted four parameters, while Simon et al. used three. The larger the number of parameters, the more repetition is needed. In general, the accuracy of performance of MC simulation is improved by increasing the number of repetitions; this factor must be balanced with computational time.

Third, our study found that the parameter estimates were unbiased for two nominal time constants and at three different levels of noise when using 30% Xe and 55% Xe. As the level of noise increased, the SD values for all parameters increased, which agrees well with the results that Simon et al. obtained using 70% Xe (33). Compared with 50% Xe, the SD of $D_0$ and $D_t$ using 30% Xe remained relatively constant, but the SD of the time constant and arrival time increased. The increased SD of the time constant using 30% Xe corresponds to the increase of half CI/mean using 30% Xe. The decrease of mean arrival time and increase of SD of arrival time using 30% could be

Table 3. Coefficient of variation of time constants in the nondependent, middle, and dependent regions when using three different Xe concentrations in the supine position

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>55% Xe</th>
<th>40% Xe</th>
<th>30% Xe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondependent</td>
<td>0.36</td>
<td>0.45</td>
<td>0.52</td>
</tr>
<tr>
<td>Middle</td>
<td>0.31</td>
<td>0.47</td>
<td>0.52</td>
</tr>
<tr>
<td>Dependent</td>
<td>0.37</td>
<td>0.65</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Coefficients of variation (SD/mean) of time constant in three vertical lung regions in the supine position. Only *55% Xe vs. 30% Xe and †40% Xe vs. 30% Xe in the nondependent region were significantly different ($P < 0.05$).

Fig. 6. Coefficients of variation for time constant at different Xe concentrations in different body positions. Coefficient of variation at 30% Xe is significantly different from that at 40% Xe and 55% Xe in both body positions. *$P < 0.05$, 30% vs. 40 and 55%.
partly explained by 1) the physical property of Xe gas, meaning that less dense gas (30% Xe) may arrive earlier at ROI and increase variation of the arrival time compared with more dense gas (55% Xe), and 2) the fitting of the compartment model, meaning that the fit of the compartment model to noiser low-concentration Xe data.

Comparison of 55, 40, and 30% Xe

As a stable, nonradioactive, and inert gas, Xe has been used as a contrast agent for highly sensitive imaging modalities such as CT. The Xe-CT method has potential for use in humans (11, 13, 34), but its use is limited by the fact that Xe is an anesthetic ~30% more potent than nitrous oxide. A number of studies have reported increasing side effects of Xe inhalation at concentrations >30% (9, 24, 45). Thus it is important to determine the tradeoffs in the use of lower [Xe] values and potential alternatives. Previous works by others regarding X-ray CT assessments of regional pulmonary ventilation have assumed the kinetics of Xe tracer gas filling or clearing the alveoli to follow the monoexponential model described by Kety (20). Kety proposed a model of inert gas exchange applicable to gases with both high and low solubility in blood and tissue, assuming that the inhaled concentration of an inert gas is held constant and that alveolar ventilation is treated as a continuous process. For the special case of very low solubility in blood, Kety’s model can be described as a simple exponential function, and alveolar-specific ventilation (ventilation per unit air volume) can be calculated as the inverse of the exponential time constant. In this study, we distinguished the determination of the mean time constant for a region from the CI or variability about that time constant when using different [Xe] values, especially 30% [Xe] for potential human use. For a given time constant, as the CI about it increases, then the ability to determine differences between regional time constants, and thus the sensitivity of the measurement, diminishes.

In the whole lung, the average time constant using 30% Xe was not significantly different from that at 40% and 50% Xe, but both the CV and half CI/mean with 30% Xe were significantly different, greater than those at 40% Xe and 55% Xe, implying that the use of 30% Xe results in the loss of robustness or sensitivity due to increased influence of noise at low [Xe]. When analyzed in three vertical regions (nondependent, middle, dependent), the average time constants using three different [Xe] values were not significantly different among the vertical regions or between body postures. However, clear differences emerged for the CVs and half CI/mean. In the supine position, the CVs and half CI/mean of 30% Xe were significantly different between 30% Xe and 55% Xe. These results can be explained by considering both the vertical distribution of the time constant and the interaction of noise level and absolute value of the time constant on the half CI/mean of the time constant. The time constants are longer in the nondependent regions than in the middle and dependent regions, which means that middle and dependent regions are better ventilated than the nondependent region, in agreement with many previous studies of regional ventilation distribution (17, 25, 38). According to the result of MC simulation performed by Simon et al. (33), as the level of noise increases, the half CI/mean of the time constant increases to a greater degree for longer compared with shorter time.
constants. Therefore, in the supine region, the relative increase of noise level to signal using 30% Xe has a significant influence on the nondependent region with longer time constants. In the prone position, however, time constants are uniformly distributed, resulting in the uniform distribution of CVs using 30% Xe and 55% Xe, regardless of vertical position.

On the other hand, there are also possible factors that could reduce the sensitivity to noise using 30% Xe compared with 40 and 50% Xe. One such factor is the solubility of Xe in blood and tissue. Xe is moderately soluble in blood and tissue; it has an oil/water solubility ratio of 20.0 at 37°C (22). Uptake of Xe into blood and tissue will alter the density of the portion of the ROI that does not contain air. The measurement of cerebral blood flow using the Xe-CT method takes advantage of this phenomenon (7, 19, 29). This solubility of Xe gas has been considered one of the sources of error in the application of multibreath washin and/or washout protocols (39, 40). During washin, Xe is removed from the alveolar space by blood flow, delaying the rate of rise of density and lengthening the apparent time constant. Later in the washin phase, the increased density of recirculating blood and Xe in the lung tissue could elevate the mean density. During the washout phase, Xe gas accumulated in the peripheral tissues during the washin phase, then returns to the lung, delaying the fall in density and preventing a return to the previous baseline (3, 32, 35). Hence, solubility and uptake potentially influence both washin andwashout phases, and this effect would increase with increased exposure time and [Xe]. In a previous study (4), we proposed a new approach to minimize this phenomenon by choosing the optimal number of washin breaths and used that in this study. Because we minimized the exposure time, we believe it is unlikely that Xe uptake had an important role in reducing sensitivity to noise using 30% Xe (37).

ROI size has an additional effect on measurement robustness at all [Xe]. Not surprisingly, as region size falls, the half CI/mean increases (Fig. 9), indicating that the ability to distinguish differences between regional ventilation measurements is also reduced. Thus maneuvers that increase signal, such as increasing [Xe] or Kr supplementation, are important for improving spatial resolution as well.

Comparison of 30% Xe/30% Kr Mixture with Xe

While Kr (atomic number 36) is less radiopaque than Xe, it is considerably more radiopaque than air. Winkler et al. (42) suggested that Kr gas may be a useful inhalation contrast medium for CT chest scanning, particularly at lower peak kilovoltage values. Xe provides about threefold greater CT enhancement than Kr at all concentrations and kilovolt settings (Fig. 1). On the other hand, Kr is much less soluble in tissue and does not produce anesthetic side effects, avoiding the confounding effects of uptake and recirculation. Cullen and Gross (6) reported on three human subjects inhaling 80% Kr with oxygen from a closed system. Kr demonstrated no significant narcotic properties. Thus, while Kr may be an insufficient contrast agent alone, an appropriate combination of Xe and Kr gas could be used to supplement Xe. In this study, we chose a 30% Xe/30% Kr mixture as a contrast agent for human use, considering both the desired limitation of Xe gas to concen-
single animal in the supine position. Our study to test the repeatability of the Xe-CT method, although each only in a
Repeatability of Xe-CT Method
volumetric image of the lung air spaces with signal only from
seconds after a single breath of Kr and end up with a detailed
scanning, one could potentially image the whole lung in
et al. (37). Through the use of dual-energy imaging and spiral
concept of single-breath imaging was demonstrated by Tajik
yield images of regional gas distribution, which is related to the
single breath of gas coupled with dual-energy scanning can
imaging about the K-edge of Kr may make imaging via Kr
imaging via Kr might be less powerful than the single-breath
imaging about the K-edge of Xe gas (Fig. 1), and the time constants measured were not
different from those obtained with Xe alone. The half CI/mean
using the 30% Xe/30% Kr mixture was not significantly
different from that of 55% Xe and 40% Xe in both body
postures, indicating that this mixture can provide a robust
measurement while avoiding the side effects of high [Xe].
Further investigation will be needed to verify the measurement
of pulmonary regional ventilation using a Xe and Kr mixture in
humans. Recent work by Porra et al. (30) has shown that
dual-energy imaging at either side of the K-edge of Xe gas
yields exquisitely detailed images of the gas distribution in the
lung. It is of great interest to determine whether dual-energy
imaging about the K-edge of Kr may make imaging via Kr
alone practical. Such dual-energy imaging is possible by CT
with the use of two X-ray guns on a single gantry, available
commercially as recently announced by Siemens (Somatom
Definition, Siemens AG, Erlangen, Germany). In theory, a
single breath of gas coupled with dual-energy scanning can
yield images of regional gas distribution, which is related to the
regional ventilation, particularly if a tidal breath is used. This
concept of single-breath imaging was demonstrated by Tajik
et al. (37). Through the use of dual-energy imaging and spiral
scanning, one could potentially image the whole lung in
seconds after a single breath of Kr and end up with a detailed
volumetric image of the lung air spaces with signal only from the
inhaled gas.

Repeatability of Xe-Kr CT

Tajik et al. (37) and Simon et al. (33) have both shown good
repeatability of the Xe-CT method, although each only in a
single animal in the supine position. Our study to test the
repeatability of Xe-CT technique was performed in six animals
in both prone and supine positions; it showed that the average
time constants obtained in original and repeated images were not
significantly different for any of these conditions (P > 0.05).
Based on the greater proximity of the slope to 1 and the higher r²
value, the prone position shows better repeatability than the supine position in both scanning modes, which could
be explained by the same factors that render the distribution of ventilation in the prone position more uniform than in the
supine position. Marucci et al. (25) reported that the vertical
gradient of ventilation was responsible for 37% of the total
variance in the distribution of ventilation supine, but there was
no contribution of gravity in the prone position. Hoffman and
colleague (14, 15) found a significant vertical gradient of air
content (3.3% air/cm at functional residual capacity) in the
supine position, but a minimal gradient (~0.36% air/cm) in the
prone position. Other studies found similar gradients of sub-
pleural alveolar size (44), pleural pressure (41), and alveolar
volume by PET (38) in the supine position, but no or minimal
gradient in the prone position.

Other Considerations for Human Applications

The use of functional imaging techniques in humans requires
maximization of the risk-to-benefit ratio to the subject, including
risks of radiation and tracer exposure and benefits from the
diagnostic information gained. This study is focused on reduc-
tion of exposure to the tracer while maximizing the signal and
quality of the ventilation data, and to address these issues we
used an imaging protocol designed for optimal image quality.
Radiation dose reduction is a separate complex issue, involving
not only CT technique but the number and timing of images,
reconstruction methods, and other technological approaches.
However, maximizing the inhaled tracer signal quality is a
requisite step in this overall optimization process.

Summary

Our results indicate that MDCT-based measurements of
regional ventilation using inhaled Xe continue to correctly
identify the mean time constant of a ROI as [Xe] is reduced,
but at the cost of decreased signal-to-noise ratio and wider CIs
about that value. This effectively reduces the robustness of the
measurement, making it more difficult to discern differences in
measured regional ventilation. Adding Kr to acceptably low-
dose Xe reduces noise and restores the sensitivity of the
measurement, and thus the Xe/Kr mixture poses a promising
alternative to the use of Xe alone for measuring regional
pulmonary ventilation in humans.

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