Probing the regional distribution of pulmonary gas exchange through single-breath gas- and dissolved-phase $^{129}$Xe MR imaging

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Submitted 31 January 2013; accepted in final form 5 July 2013

Kaushik SS, Freeman MS, Cleveland ZI, Davies J, Stiles J, Virgincar RS, Robertson SH, He M, Kelly KT, Foster WM, McAdams HP, Driehuys B. Probing the regional distribution of pulmonary gas exchange through single-breath gas- and dissolved-phase $^{129}$Xe MR imaging. J Appl Physiol 115: 850–860, 2013. First published July 11, 2013; doi:10.1152/japplphysiol.00092.2013.—Although some central aspects of pulmonary function (ventilation and perfusion) are known to be heterogeneous, the distribution of diffusive gas exchange remains poorly characterized. A solution is offered by hyperpolarized $^{129}$Xe magnetic resonance (MR) imaging, because this gas can be separately detected from those remaining in the alveolar spaces and dissolved in its tissues. Early dissolved-phase $^{129}$Xe images exhibited intensity gradients that favored the dependent lung. To quantitatively corroborate this finding, we developed an interleaved, three-dimensional radial sequence to image the gaseous and dissolved $^{129}$Xe distributions in the same breath. These images were normalized and divided to calculate “$^{129}$Xe gas-transfer” maps. We hypothesized that, for healthy volunteers, $^{129}$Xe gas-transfer maps would retain the previously observed posture-dependent gradients. This was tested in nine subjects: when the subjects were supine, $^{129}$Xe gas transfer exhibited a posterior-anterior gradient of $2.00 \pm 0.74\%$/cm; when the subjects were prone, the gradient reversed to $1.94 \pm 1.14\%$/cm ($P < 0.001$). The $^{129}$Xe gas-transfer maps also exhibited significant heterogeneity, as measured by the coefficient of variation, that correlated with subject total lung capacity ($r = 0.77$, $P = 0.015$). Gas-transfer intensity varied monotonically with slice position and increased in slices proximal to the main pulmonary arteries. Despite substantial heterogeneity, the mean gas transfer for all subjects was $1.00 \pm 0.01$ while supine and $1.01 \pm 0.01$ while prone ($P = 0.25$), indicating good “matching” between gas- and dissolved-phase distributions. This study demonstrates that single-breath gas- and dissolved-phase $^{129}$Xe MR imaging yields $^{129}$Xe gas-transfer maps that are sensitive to altered gas exchange caused by differences in lung inflation and posture.

hyperpolarized $^{129}$Xe; dissolved phase; radial pulse sequence; supine; prone

THE INTRODUCTION OF HYPERPOLARIZED (HP) gas magnetic resonance (MR) imaging (MRI) over the last decade has enabled rapid, noninvasive, and relatively high-resolution three-dimensional (3D) imaging of pulmonary function in a single breath hold (36). The most well-developed clinical applications of HP gas MRI use the regional density of the isotope $^3$He to visualize regions of impaired ventilation, altered ventilation dynamics (13), and regional gas trapping (34) in the lungs. Furthermore, MRI of gaseous HP $^3$He in the pulmonary air spaces can be used to assess other aspects of lung biology, including pulmonary microstructure, by mapping the apparent diffusion coefficient of $^3$He (28) and $^2$O by mapping the MR relaxation of $^3$He (8). Unfortunately, because of its increasing cost and scarcity, $^3$He has not achieved widespread clinical dissemination. However, HP $^{129}$Xe MRI has recently been shown to be well tolerated in human subjects (7) and to display sensitivity similar to that of $^3$He to changes in ventilation (36) and pulmonary microstructure through diffusion-weighted imaging (20).

Additionally, HP $^{129}$Xe is advantageous, in that it is moderately soluble in the pulmonary tissues and capillary blood (~10% solubility). Because $^{129}$Xe follows the same physical gas-transfer pathway as $O_2$ to reach the red blood cells (RBCs) in the pulmonary capillary bed, $^{129}$Xe enables MRI of pulmonary function beyond the air spaces (3). Moreover, when $^{129}$Xe is dissolved in the blood-gas barrier tissues and the RBCs, its MR frequency shifts dramatically (several kHz at the magnetic field strengths commonly used for MRI). This frequency shift enables $^{129}$Xe atoms dissolved in the barrier tissues and RBCs to be separately detected from those remaining in the alveolar gas spaces (6). Although these “dissolved-phase” $^{129}$Xe atoms represent only ~2% of the total magnetization pool at any given instant, we and others recently demonstrated that it is possible to obtain a 3D image of the uptake of $^{129}$Xe gas in human subjects in a breath hold (3, 21). These initial dissolved-phase $^{129}$Xe images were characterized by strong gravitational gradients and notable isogravitational heterogeneity, even in healthy subjects (3). Hence, these findings suggest that $^{129}$Xe MRI is well suited to show regional pulmonary gas transfer. However, the physical origins of the dissolved-phase $^{129}$Xe signal are substantially different from more standard physiological approaches to measurement of gas transfer.

Inhaled $^{129}$Xe enters the pulmonary capillary beds by diffusion from the alveolar spaces, and these $^{129}$Xe atoms very quickly saturate the thin (~10-µm) alveolar septa on a time scale of ~150–200 ms (24). Imaging of these dissolved atoms employs selective, relatively large radio-frequency (RF) flip
angles (10–30°), and this rapidly depletes their signal. However, this dissolved magnetization is rapidly replenished by continuous diffusion of fresh HP 129Xe into the tissues from the alveolar gas spaces (3, 6). Hence, these combined properties of alveolar structure and a properly designed MR acquisition scheme ensure that dissolved 129Xe MR signal arises almost exclusively from the lung’s gas exchange tissues and contains virtually no contribution from the larger downstream vasculature. Moreover, as estimated by Cleveland et al. (3), ~40–50% of the dissolved 129Xe signal originates from the capillary blood, both RBCs and plasma, and the remainder from the adjacent lung parenchyma.

Like O₂ transfer, 129Xe gas transfer increases in regions where the well-perfused capillary bed is in contact with well-ventilated lung. By contrast, low dissolved 129Xe intensity can arise from poorly ventilated or well ventilated, but poorly perfused, regions of the lungs. However, unlike O₂ or CO, 129Xe does not bind chemically to hemoglobin. Thus 129Xe lacks the complexity of the reactive conductance component, and 129Xe transfer begins to resemble a spatially resolved measure of the membrane diffusing capacity. However, because 129Xe is an inert gas, it is essentially a perfusion-limited, and not a diffusion-limited, marker.

Because dissolved-phase 129Xe image intensity is affected by ventilation and perfusion, it cannot be interpreted in isolation. For instance, in our initial work, two separate images of the dissolved- and gas-phase HP 129Xe distributions were acquired from two separate 1-liter breaths of 129Xe (3). Unfortunately, the batch-to-batch polarization of 129Xe and the breath-to-breath distributions of an inhaled gas can vary substantially, especially when lung volumes are between functional residual capacity (FRC) and total lung capacity (TLC). Thus it was not possible to obtain an accurate estimate of the “source” gas-phase magnetization with use of this two-breath imaging approach, and only qualitative comparisons between images (and subjects) were possible.

A preferred approach for assessing the spatial distribution of dissolved HP 129Xe is to image gaseous and dissolved 129Xe in the same breath hold. Recently, such single-breath images of the gas- and dissolved-phase 129Xe were elegantly achieved by Mugler et al. (21), who took advantage of the chemical-shift “artifact” between dissolved- and gas-phase 129Xe. This study employed a Cartesian gradient-recalled echo sequence (21) with carefully tuned acquisition parameters, allowing the gas and dissolved phases to appear side-by-side in each image slice. Although this work provided important initial quantitative confirmation of the observed gradients in dissolved 129Xe images, it employed a relatively long echo time (TE), which sacrificed significant signal-to-noise ratio (SNR) because of the relatively short (~2 ms) T₂ of dissolved 129Xe (22). An additional complication is that the T₂ of the gas phase is ~10 times longer than that of the dissolved phase, which compromises quantitative comparisons at longer TEs.

Therefore, the first goal of this work was to develop a robust, 3D isotropic approach to image dissolved 129Xe in the resting lung, which would enable quantitative study of the 129Xe gas-transfer distribution. Our technical approach is designed to overcome specific limitations of the previously described gradient-recalled echo acquisition by use of a 3D radial acquisition scheme to alternatively excite the gas- and dissolved-phase 129Xe resonances. This approach permits acquisition with sub-millisecond TEs to counteract the signal losses due to the short dissolved-phase 129Xe T₂ (22). Moreover, this acquisition strategy is robust to motion (e.g., cardiac motion) (10) and to undersampling (29) and acquires 3D isotropic images of gas- and dissolved-phase 129Xe that are inherently coregistered. These distributions are then normalized, and the ratio of dissolved- to gas-phase signal intensity provides a unitless, but still quantitative, measure of regional 129Xe gas transfer. Moreover, these 129Xe gas-transfer maps reflect the extent of “matching” of the signal intensity distributions of gas-phase (a surrogate for ventilation) and dissolved-phase (a surrogate for diffusive gas exchange) 129Xe.

With a robust 129Xe gas-transfer acquisition in hand, our second goal was to develop a fundamental understanding of the physiologically relevant information provided by these images by performing 129Xe MRI of the lungs under a set of conditions that are known to alter the underlying pattern of physiological gas exchange. Thus 129Xe gas transfer was imaged in the supine and prone positions for all subjects. Such postural changes are known to alter the resting perfusion distribution (26) and diffusing capacity for O₂ (19). Moreover, our previous efforts to image the dissolved 129Xe distribution showed that the images were characterized by a strong postural gradient, which favored the dependent lung. We thus hypothesized that, upon development of a single-breath method of imaging 129Xe gas transfer, a postural gradient would be detectable in the individual 129Xe gas- and dissolved-phase distributions and that gravitational gradients would still be retained in the normalized 129Xe gas-transfer maps. Furthermore, we hypothesized that gradients in the gas and dissolved phases, as well as in 129Xe gas transfer, would reverse when subjects were repositioned from the supine to the prone position. Such imaging of the underlying variability of 129Xe gas transfer in healthy subjects provides a necessary platform to probe basic lung physiology and eventually understand the pathophysiologic changes that arise with the onset of pulmonary diseases.

Methods

Subject inclusion and exclusion criteria. Studies were approved by the Duke Institutional Review Board and conducted under US Food and Drug Administration Investigational New Drug Application 109490. Written, informed consent was obtained from all the subjects prior to the scan. All subjects (8 men, 1 woman) were ≥18 yr of age (average 45.6 ± 18.7), had a <5 pack-yr smoking history, had not smoked in the last 5 yr, and had no diagnosed pulmonary disorders. The body mass index for the subjects was 19–29.6 (average 24.3 ± 3.6). Subjects were excluded if they were unable to hold their breath for 16 s, had a history of cardiac arrhythmias, were pregnant or lactating, or had a respiratory illness within 30 days of MRI. At 1 h prior to MR studies, subjects underwent pulmonary function testing, including measures of TLC, which were used to interpret aspects of the MR images. TLC was calculated as the sum of residual volume, which was measured by body plethysmography, and vital capacity, which was measured by spirometry.

Xe polarization and delivery. Each subject received two 1-liter doses of xenon (isotopically enriched to 86% 129Xe; Linde Gases, Stewartsville, NJ) produced by rubidium vapor spin-exchange optical pumping (5) and cryogenically accumulated using a commercially available polarizer (model 9800, Polarean, Durham, NC). Xe was then thawed into a 1-liter ALTEF bag (Jensen Inert Products, Coral Springs, FL), and polarization (~8–10%) was determined using a
polarization measurement station (model 2881, Polarean). Prior to gas inhalation, subjects were instructed to inhale to TLC and exhale to FRC twice. They then inhaled the gas through 0.95-cm-ID Tygon tubing (Saint Gobain Performance Plastics, Akron, OH) and held their breath for a maximum of 16 s while the images were acquired. Throughout the imaging session, blood oxygenation and heart rate were monitored using a MR-compatible monitoring system (GE Healthcare, Helsinki, Finland).

**MR acquisition and work flow.** Studies were conducted on a 1.5-T scanner (EXCITE 15M4, GE Healthcare Waukesha, WI) equipped with a 2-kW broadband (8–70 MHz) amplifier for the multinuclear RF chain (CPC, Hauppauge, NY). Subjects were fitted in a quadrature 129Xe vest coil (Clinical MR Solutions, Brookfield, WI) tuned to 17.66 MHz and proton-blocked to permit 1H MRI of the thoracic cavity with the scanner’s body coil, with no change in body position. Single-breath gas- and dissolved-phase HP 129Xe images were acquired by collection of each radial view of k-space twice (Fig. 1).

First the transmit and receive frequencies were set on the gas-phase resonance (0 Hz) and then on the dissolved-phase resonance (+3,832 Hz). Imaging parameters included sinc pulse duration = 1.2 ms, TE/TR = 0.932/7.5 ms, matrix = 32 × 32 × 32, 1,001 rays for each frequency, gas flip angle = 0.5°, dissolved flip angle = 22°, bandwidth = 15.625 kHz, and field of view = 40 cm. k-Space data for each 129Xe resonance was reconstructed separately using a nonuniform fast Fourier transform algorithm (30). Prior to this study, dissolved 129Xe MRI acquisition parameters and, thus, image quality were rigorously optimized with regard to the frequency selectivity of the RF excitation (see Appendix). Radial 1H images of the thoracic cavity (breath hold = 16 s) were acquired using a 274-µs hard pulse, TE/TR = 0.336/2.4 ms, matrix = 64 × 64 × 64, 5,647 rays, 512 dummy pulses, flip angle = 5°, bandwidth = 15,625 kHz, and field of view = 40 cm.

The study work flow proceeded as follows: after a free-breathing localizer scan in the supine position, 1H radial thoracic cavity images were acquired after the subject had inhaled 1 liter of room air from a polyethylene bag starting from FRC. This was followed by administration of 1 liter of 129Xe for single-breath acquisition of both the gas- and dissolved-phase distributions. The subject was then transferred to the prone position with no change in the coil orientation, and a second, 1-liter single-breath scan of the gas- and dissolved-phase distributions was acquired. Finally, while the subject was still in the prone position, a second radial breath-hold 1H scan of the thoracic cavity was acquired.

**Image and statistical analysis.** The 1H images were used to confine the analysis of the HP 129Xe images to the thoracic cavity (36). To match the resolution of the thoracic cavity images, the dual-acquisition gas- and dissolved-phase 129Xe images were up-sampled from their native 32 × 32 × 32 matrix to a 64 × 64 × 64 matrix by bilinear interpolation using ImageJ 1.44p (National Institutes of Health, Bethesda, MD). The 1H and gaseous 129Xe images were then registered using a multiresolution, affine transformation, with joint entropy

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**Fig. 1.** Pulse sequence diagram for single-breath, 3-dimensional (3D) radial imaging of gas- and dissolved-phase 129Xe. A: pulse sequence diagram. A given ray of k-space was acquired after excitation of the gas phase (α = 0.5°), and then a second ray with an identical k-space trajectory was acquired after excitation of the dissolved phase (α = 22°). TR eff, repetition time to apply 2 successive radio-frequency pulses, one on the gas phase and one on the dissolved phase of 129Xe. B: 3D k-space trajectories for both resonances, which were reconstructed separately to yield the images.
as the cost function and a cubic-spline interpolation using the Image Registration Toolkit (31). Because these dual-acquisition gas- and dissolved-phase $^{129}$Xe images are inherently coregistered, this transformation also registered the dissolved-phase and $^1$H images. The thoracic cavity image was then segmented using the region-growing algorithm in 3DSlicer (36) to create a binary thoracic cavity “mask” (Fig. 2). This mask was manually segmented to remove the trachea and main stem bronchi and morphologically closed using a spherical structuring element (7-voxel diameter); then an additional filling operation in MATLAB R2011a (MathWorks, Natick, MA) was performed.

Both gas- and dissolved-phase images were normalized by the sum of their respective voxel intensities within the thoracic cavity mask (25), and the resulting normalized dissolved-phase images were divided on a voxel-by-voxel basis by the corresponding normalized gas-phase images to create the $^{129}$Xe gas-transfer maps. Images were analyzed for posterior-anterior signal intensity gradients by a linear regression (weighted by voxel count) of the mean signal intensity of each slice as a function of slice position. $^{129}$Xe gas-transfer maps and source images were further analyzed for heterogeneity by calculating the coefficient of variation (CV) for the whole lung.

The effects of subject posture on the uptake of HP $^{129}$Xe are illustrated in Fig. 4, which depicts coronal $^{129}$Xe gas-transfer maps from a second subject. When supine (Fig. 4A), this subject exhibited decreasing $^{129}$Xe gas-transfer values from the posterior to the anterior lung. However, when the subject was repositioned in the prone position (Fig. 4B), the gradient in $^{129}$Xe transfer reversed, with higher values in the anterior, now gravitationally dependent, lung and lower values in the posterior, now nondependent, lung. The $^{129}$Xe gas-transfer distributions for both positions are better appreciated when plotted as a function of slice position (Fig. 4C). In addition to quantitatively depicting gradient reversal, Fig. 4C shows the scale of $^{129}$Xe gas-transfer variability for this subject. With the subject supine, mean $^{129}$Xe transfer decreased 43% from the posterior to the anterior lung, but with the subject prone, $^{129}$Xe transfer

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**RESULTS**

**Signal intensity gradients.** Isotropic, single-breath gas- and dissolved-phase HP $^{129}$Xe images were successfully acquired in both postures for all nine subjects. Figure 3 shows a typical example of these images acquired from a 29-yr-old healthy male subject in the supine position. Similar to the trends observed in earlier studies (3, 21), axial slices from these images reveal that gas- and dissolved-phase signal intensities are greatest in the gravitationally dependent posterior lung and diminish in the anterior lung. Although gas- and dissolved-phase images individually exhibit gravitational gradients, these gradients persist in the normalized dissolved phase-to-gas phase ratio ($^{129}$Xe gas transfer) maps. Hence, the $^{129}$Xe gas transfer itself exhibits a gravitational gradient beyond what can be attributed simply to the gas-phase $^{129}$Xe distribution.

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**Fig. 3.** Representative single-breath, isotropic gas- and dissolved-phase images and the corresponding gas-transfer map, defined as the normalized dissolved-phase image-to-gas-phase image ratio.
increased 27% from the posterior to the anterior lung. However, in both postures, $^{129}$Xe transfer was nonmonotonic and increased markedly in slices isogravitational with the main pulmonary arteries. This increase was evident for seven of the nine subjects, with two other subjects displaying a gas-transfer plateau in the central regions of the lungs. The functional gradients for all subjects, as well as their demographics, are summarized in Table 1.

The population means of the gradients in $^{129}$Xe distribution for all subjects are summarized in Table 2 and Fig. 5. Gas-phase images exhibited a modest population-mean posterior-anterior gradient of $-1.92 \pm 1.73\%/cm$ for supine subjects that reversed significantly and diminished to $0.28 \pm 2.23\%/cm$ when the subjects were prone ($P = 0.042$). Dissolved-phase $^{129}$Xe images exhibited a larger posterior-anterior gradient of $-3.46 \pm 1.91\%/cm$ for supine subjects that also reversed significantly ($P = 0.0034$) to $2.18 \pm 2.47\%/cm$ when the subjects were prone. These gradients persisted in the $^{129}$Xe gas-transfer maps and also reversed significantly ($P < 0.001$) when subjects changed from the supine ($-1.99 \pm 0.74\%/cm$) to the prone ($1.94 \pm 1.14\%/cm$) position.

Heterogeneity analysis. In addition to gravitational gradients, gas-phase, dissolved-phase, and $^{129}$Xe transfer maps showed significant in-plane and overall heterogeneity. Whole lung heterogeneity, as measured by the CV, is summarized in Table 2 and Fig. 6. The population-mean CVs of the gas- and dissolved-phase $^{129}$Xe images were similar and not significantly impacted by posture ($P = 0.21$ for gas, $P = 0.22$ for dissolved, and $P = 0.45$ for $^{129}$Xe gas transfer). However, for both postures, the whole lung CVs of the dissolved-phase image were modestly higher than those of the gas-phase images ($P = 0.0001$ for supine and $P = 0.0028$ for prone). Interestingly, the CV of the normalized $^{129}$Xe gas-transfer maps relative to the gas- or dissolved-phase images alone was roughly 45% lower in both positions. Despite the pronounced spatial variation in the $^{129}$Xe gas-transfer maps, the $^{129}$Xe gas-transfer value averaged over the entire lung remained near unity for all subjects (see Table 1) and displayed no significant posture dependence: $1.00 \pm 0.01$ in the supine position and $1.01 \pm 0.01$ in the prone position ($P = 0.25$).

The distribution of gas transfer was also impacted by lung inflation. In the supine position, subjects with larger TLC tended to exhibit greater gas-transfer heterogeneity than those with smaller TLC. Because all subjects in this study received the same 1-liter volume of HP $^{129}$Xe (i.e., range 10.9–17.4% of TLC), subjects with larger lung volume underwent imaging at a lower degree of lung inflation. For supine subjects (Fig. 7A), $^{129}$Xe gas-transfer CV correlated significantly with TLC ($r = 0.77, P = 0.015$). However, in the prone position (Fig. 7B), these same subjects exhibited no correlation between CV and TLC ($r = 0.18, P = 0.64$). Notably, the polarization-corrected SNR (SNR/polarization) was not significantly different between postures ($P = 0.55$ for gas phase and $P = 0.42$ for dissolved phase). Thus TLC-dependent heterogeneity in the

Table 1. Subject demographics and postural gradients

<table>
<thead>
<tr>
<th>Subj No</th>
<th>Age, yr</th>
<th>TLC, liters</th>
<th>Gas</th>
<th>Dissolved</th>
<th>$^{129}$Xe Gas Transfer</th>
<th>Mean $^{129}$Xe Gas Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supine</td>
<td>Prone</td>
<td>Supine</td>
<td>Prone</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>9.16</td>
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<td>-5.30</td>
<td>-2.28</td>
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</tr>
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<td>2</td>
<td>60</td>
<td>8.05</td>
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<td>68</td>
<td>7.00</td>
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<td>-4.15</td>
<td>-2.32</td>
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</tr>
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<td>-4.84</td>
<td>-2.08</td>
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</tr>
<tr>
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<td>-1.36</td>
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</tr>
<tr>
<td>6</td>
<td>65</td>
<td>7.17</td>
<td>2.40</td>
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</tr>
<tr>
<td>7</td>
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</tr>
<tr>
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</tr>
<tr>
<td>9</td>
<td>33</td>
<td>7.96</td>
<td>-1.81</td>
<td>-5.30</td>
<td>-3.24</td>
<td>0.95</td>
</tr>
</tbody>
</table>

TLC, total lung capacity.
supine position does not appear to be explained by lower image SNR resulting from greater $^{129}$Xe dilution but, instead, reflects fundamental aspects of $^{129}$Xe gas-transfer distribution.

**DISCUSSION**

**Gravitational gradients.** The acquisition-and-analysis method described here accounts for the contribution of the gas-phase $^{129}$Xe distribution to the dissolved-phase $^{129}$Xe image, permitting quantitative regional mapping of $^{129}$Xe gas transfer. These maps corroborate our hypothesis that $^{129}$Xe gas transfer is heterogeneous in normal subjects and is subject to gravitational gradients that reverse with subject posture. Indeed, $^{129}$Xe gas transfer varies by 30–40% across the lung field. These single-breath $^{129}$Xe gas-transfer images show trends that are consistent with observations from other imaging modalities and experimental techniques that image tissue density (32) and perfusion (23, 25, 26) and provide a unique window on the regional variability of lung function in healthy subjects.

It is important to note that the $^{129}$Xe gas-transfer imaging signal arises from physical origins that are fundamentally different from established physiological measures of respiratory gas transfer. First, since $^{129}$Xe gas-transfer images are acquired in a single breath, they will report primarily on well-ventilated regions of the lung. Second, $^{129}$Xe gas-transfer signal arises almost exclusively from the alveolar septa, where diffusion from the alveolar spaces continuously replenishes the dissolved $^{129}$Xe magnetization. Given that the harmonic mean thickness of the barrier is $1\ \mu m(L)$ and the diffusion coefficient of $^{129}$Xe in the barrier is $0.33 \times 10^{-5} \text{cm}^2/\text{s} (D)$, $^{129}$Xe takes only $\sim 1.5$ ms [$t = (L^2/2D)$] to diffuse across the interstitial barrier and into the RBCs and only $\sim 150$ ms longer to saturate the septum (24). Furthermore, 40–50% of the dissolved $^{129}$Xe signal originates from the capillary blood, which transits through the capillary network in 0.75 s. Consequently, although $^{129}$Xe gas-transfer intensity is influenced by perfusion, it must closely reflect local capillary blood volume. Since local blood volume tracks with perfusion (18), $^{129}$Xe transfer imaging may be thought of as approximating local ventilation-perfusion matching. Hence, in this regard, $^{129}$Xe transfer MRI is a closer surrogate for studying the $O_2$ transfer pathway than other imaging modalities that infer this information indirectly through ventilation and perfusion metrics.

The postural gradients in $^{129}$Xe gas transfer in this study are consistent with tissue density, ventilation, and perfusion gradients reported by other imaging modalities, which are summarized in Table 3. For supine subjects, lung tissue density has been reported to exhibit a posterior-anterior gradient of $-4.33\%$/cm by CT (32) and $-4.9 \pm 1.9\%$/cm by MRI (14). By comparison, the mean $^{129}$Xe gas-transfer gradient of $-2.0 \pm 0.74\%$/cm for supine subjects was of the same sign but roughly half as large. This is because $^{129}$Xe transfer is affected by tissue density gradients, but these gradients also cause a gradient in the intrapleural pressure, which similarly increases ventilation in the dependent lung. Since $^{129}$Xe gas transfer is “ventilation-normalized,” $^{129}$Xe gas transfer exhibits a smaller gradient than the dissolved signal or tissue density alone. Comparison of $^{129}$Xe gas-transfer distribution with perfusion distributions measured by other modalities revealed a gravitational gradient that was of the same sign as, but somewhat smaller than, the perfusion gradient of $-3.10 \pm 1.50\%$/cm observed for supine subjects by single-photon-emission CT (SPECT) (25) and roughly half the $-4.40 \pm 3.20\%$/cm gradient reported by PET (23). However, the supine $^{129}$Xe gas-transfer gradient was very similar to the perfusion gradient reported by arterial spin labeling ($-2.10 \pm 4.32\%$/cm), albeit with reduced intersubject variability. For prone subjects, the $^{129}$Xe gas-transfer gradient was reversed and exhibited a positive slope of $1.94 \pm 1.14\%$/cm, which is comparable to the density gradient of $2.72\%$/cm measured by CT (32), as well as perfusion gradients of $2.70 \pm 1.50\%$/cm measured by SPECT (25) and $1.11 \pm 1.68\%$/cm.

**Table 2. Mean gradients and coefficients of variation**

<table>
<thead>
<tr>
<th>Posture</th>
<th>Gas Gradient, %/cm</th>
<th>Dissolved Gradient, %/cm</th>
<th>$^{129}$Xe Gas Transfer Gradient, %/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>$-1.92 \pm 1.73$</td>
<td>$-3.46 \pm 1.91$</td>
<td>$-2.00 \pm 0.74$</td>
</tr>
<tr>
<td>Prone</td>
<td>$0.28 \pm 2.23$</td>
<td>$2.18 \pm 2.47$</td>
<td>$1.94 \pm 1.14$</td>
</tr>
</tbody>
</table>

**Fig. 5.** Signal intensity and gas-transfer gradients for all subjects. Gas and dissolved phases showed a significant gradient reversal ($P < 0.001$, by F-test) when subjects were repositioned from the supine to the prone position ($P = 0.042$ for gas and $P = 0.0034$ for dissolved). The gradient in gas transfer also reversed significantly when subjects were repositioned from supine to prone ($P < 0.0001$).

**Fig. 6.** Population means for whole lung coefficient of variation (CV). Mean gas-transfer CV was almost half that of the gas- and dissolved-phase images. The CV was significantly higher for dissolved-phase than gas-phase images for both postures ($P = 0.0001$ for supine and $P = 0.003$ for prone). No significant posture-dependent change in CV was observed in gas-phase ($P = 0.22$) and dissolved-phase ($P = 0.21$) images or $^{129}$Xe gas-transfer maps ($P = 0.34$).
measured by arterial spin labeling MRI (26). However, it was less than half the perfusion gradient of 5.20 ± 4.30%/cm reported by PET (23). While perfusion and tissue density contribute significantly to the gas-transfer distribution, the differences in the gravitational gradients can be attributed to the sensitivity of the dissolved-phase signal to the capillary blood volume (not flow) and the tissue density primarily in the acinar region of the lung.

Although all subjects demonstrated a consistent trend of increasing $^{129}$Xe gas transfer from nondependent to dependent lung in both positions, this behavior was distinctly nonmonotonic and unique to each subject (Fig. 8). For example, when lung in both positions, this behavior was distinctly nonmonotonic. For example, when lung in both positions, this behavior was distinctly nonmonotonic.

Table 3. Comparison of $^{129}$Xe gas-transfer gradients with other modalities

<table>
<thead>
<tr>
<th></th>
<th>$^{129}$Xe Gas Transfer</th>
<th>ASL</th>
<th>PET</th>
<th>SPECT</th>
<th>Tissue Density CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>−2.00 ± 0.74</td>
<td>−2.10 ± 4.32</td>
<td>−4.40 ± 3.20</td>
<td>−3.10 ± 1.50</td>
<td>−4.33</td>
</tr>
<tr>
<td>Prone</td>
<td>1.94 ± 1.14</td>
<td>1.11 ± 1.68</td>
<td>5.20 ± 4.30</td>
<td>2.70 ± 1.50</td>
<td>2.72</td>
</tr>
</tbody>
</table>

Values are expressed as %/cm. ASL, arterial spin labeling (calculated using data in Ref. 26); PET, positron emission tomography (reported in Ref. 23); SPECT, single-photon-emission computed tomography (reported in Ref. 25); tissue density CT, tissue density computed tomography (reported in Ref. 32).
terns, the mean $^{129}$Xe gas-transfer ratio for all the subjects, regardless of posture, was $\sim 1$. This finding is noteworthy considering that $^{129}$Xe gas-transfer values in a given gravitational plane ranged from as low as 0.6 to as high as 1.4 and exhibited an even greater range at the voxel level. Much like the well-established ventilation-to-perfusion ratio, the $^{129}$Xe gas-transfer ratio appears to exhibit a wide range of values in healthy subjects and, yet, to retain nearly perfect “matching” when averaged over the entire lung. The substantial regional variability in $^{129}$Xe gas transfer suggests that the healthy lung at rest possesses significant “reserve capacity,” a notion that has also been put forth to explain why stereology-based estimates of pulmonary diffusing capacity consistently predict diffusing capacities that exceed the experimentally measured values (4, 37). In fact, pulmonary diffusing capacity of CO ($DL_{CO}$) is known to increase with cardiac output (15). Thus it could be intriguing to conduct $^{129}$Xe gas-transfer MRI in subjects undergoing exercise-induced or physiological stress, because these conditions should make the perfusion-dependent capillary bed filling more uniform and would be expected to result in correspondingly uniform $^{129}$Xe gas-transfer maps and to exhibit a narrower range.

**Technical aspects of radial $^{129}$Xe gas-transfer imaging.** Although not a primary focus of this work, the MR acquisition approach developed here represents a significant technical extension of prior human dissolved-phase imaging studies (3, 21). By employing a radial, center-out $k$-space trajectory, we enable submillisecond TE imaging that largely overcomes the short dissolved-phase $^{129}$Xe $T_2^*$ of $\sim 2$ ms (22) and retains greater SNR, despite the relatively modest $^{129}$Xe polarization ($\sim 8–10\%$). Furthermore, this 3D acquisition is intrinsically isotropic and robust against the undersampling of $k$-space (29), and the dense oversampling of the center of $k$-space ensures that the images are largely unaffected by the motion of the heart (10). This approach does require overcoming two challenges compared with the approach of Mugler et al. (21), who deliberately excited both phases together. The interleaved acquisition described here requires twice as many RF excitations and readouts to individually acquire each ray of $k$-space for gas- and dissolved-phase $^{129}$Xe, but the potentially longer acquisition time is offset by undersampling $k$-space and by using shorter TE afforded by the radial sequence.

A second challenge is the need to apply highly selective RF excitation pulses to avoid exciting the 50-fold larger gas-phase magnetization pool to minimize off-resonance artifacts. This requirement is confounded by the nonlinear response of the RF amplifiers used in MRI systems that tend to distort the prescribed shape of the selective pulse and cause undesired off-resonance excitation. As outlined in the **APPENDIX**, an adequate solution was developed by characterizing the off-resonance excitation profile of the scanner to empirically determine a pulse length and a power that minimizes off-resonant excitation while providing the large flip angle needed for dissolved-phase $^{129}$Xe MRI.

The interleaved radial acquisition approach outlined here is also well suited to aid in the interpretation of the underlying gas-exchange physiology. Creation of 3D images of both distributions in a single breath, with short TE, enables casting of dissolved- and gas-phase distributions into a unified map of $^{129}$Xe gas transfer. This approach for calculating regional $^{129}$Xe gas transfer has the further technical advantage of eliminating most coil-induced B$_1$ inhomogeneity, because to first order, it affects gas- and dissolved-phase $^{129}$Xe residing in a given image voxel equally. Moreover, the short TE enabled by radial imaging

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**Fig. 8.** $^{129}$Xe gas-transfer pattern for subjects 1–9.
Reduced SNR differences caused by the 10-fold longer $T_2^*$ of gas-phase relative to dissolved-phase $^{129}$Xe, which simplifies the quantification of $^{129}$Xe gas-transfer images.

**Conclusions.** This work has demonstrated the feasibility of acquiring 3D, isotropic images of gas- and dissolved-phase HP $^{129}$Xe in a single breath. This acquisition, coupled with appropriate normalization of the gas- and dissolved-phase $^{129}$Xe images, enables mapping of regional $^{129}$Xe gas transfer from air space to pulmonary blood and tissues, and, thus, provides a surrogate for studying the regional distribution $O_2$ transfer in the lungs. This study has confirmed our primary hypothesis that $^{129}$Xe transfer in the healthy lung at rest is heterogeneous and favors the gravitationally dependent lung. Although the distribution of $^{129}$Xe gas transfer can be characterized by a linear gravitational gradient that reverses when subjects are imaged prone, rather than supine, the posterior-anterior variation distribution is distinctly nonmonotonic, with particularly increased values in the plane of the main pulmonary arteries. In aggregate, this study points to the notion that healthy individuals possess a significant reserve capacity for gas transfer, which results in its heterogeneous distribution under basal conditions.

Given that $^{129}$Xe gas transfer from air space into blood follows the same pathway into the blood as $O_2$ and standard test gases such as $CO$, it is tempting to consider whether $^{129}$Xe reduce the $CO$ uptake and similarly reduce $^{129}$Xe gas transfer. Alveolitis, which may lower the alveolar surface area, will reduce $^{129}$Xe gas transfer in the healthy lung at rest is heterogeneous and favors the gravitationally dependent lung. Although the distribution of $^{129}$Xe gas transfer can be characterized by a linear gravitational gradient that reverses when subjects are imaged prone, rather than supine, the posterior-anterior variation distribution is distinctly nonmonotonic, with particularly increased values in the plane of the main pulmonary arteries. In aggregate, this study points to the notion that healthy individuals possess a significant reserve capacity for gas transfer, which results in its heterogeneous distribution under basal conditions.

However, a key difference with physiological gases is that $^{129}$Xe is a freely diffusible gas that binds only transiently to hemoglobin (33), meaning that, unlike $O_2$ or $CO$, $^{129}$Xe gas transfer does not involve a reactive conductance, nor is $^{129}$Xe gas-transfer MRI a measurement of physical $^{129}$Xe uptake. Rather, it is a measure of dissolved $^{129}$Xe magnetization in a pseudo steady state with magnetization in the air spaces and, to first order, should be purely perfusion-limited. This stands in contrast to a measurement such as $DL_{CO}$, which is diffusion-limited and is known to diminish in the presence of fibrosis or alveolitis (17). Under conditions of inflammation or increased barrier thickness, $^{129}$Xe gas transfer could actually increase, because more tissue is present to take up $^{129}$Xe. Hence, although the similarities between $^{129}$Xe gas transfer and $DL_{CO}$ are tantalizing, significant additional work must be done to fully characterize their relationships.

These limitations point to the future value of further separating the dissolved $^{129}$Xe signal into its parenchymal tissue and RBC components (6), the groundwork for which has been laid by the acquisition methodology introduced here. Recently, extraordinary progress in such separation was made by Qing et al. (27), paving a path toward direct imaging of conditions where increased thickness of barrier tissue impairs diffusive transport of $^{129}$Xe to the RBCs. As a final note, because $^{129}$Xe gas-transfer MRI uses no ionizing radiation, this single-breath imaging approach is well suited to repeated studies and could lead to a better understanding of pulmonary gas-exchange distribution in healthy subjects and individuals with pulmonary disease.

**APPENDIX**

**Minimizing off-resonance excitation.** As discussed by Cleveland et al. (3), production of dissolved-phase $^{129}$Xe images without off-resonance artifacts requires selective excitation of the dissolved $^{129}$Xe with a relatively large flip angle ($\sim 10–20^\circ$), without excitation of the much larger gas-phase $^{129}$Xe magnetization pool. This selectivity must be achieved using an RF excitation pulse that is sufficiently brief to limit the signal losses caused by the short $T_2^*$ ($\sim 2$ ms) of dissolved-phase $^{129}$Xe (22). Although the dissolved-phase $^{129}$Xe resonance frequency is separated from the gas phase by $\sim 3.8$ kHz at 1.5 T, avoidance of gas-phase excitation remains challenging because of the nonlinearity of the broadband RF amplifiers on most MRI scanners, which can cause significant gain-dependent warping of the desired RF pulse shape (2). Therefore, we empirically characterized the excitation

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**Fig. 9.** Characterization of off-resonant excitation. A: schematic showing the method used to map the off-resonance excitation pattern. To mimic selective dissolved-phase excitation using a 1-liter bag of HP $^{129}$Xe gas, 3-lobed sinc pulses of varying amplitudes (flip angles) were used to pulse 3.832 kHz above the gas-phase peak (on the RBC resonance). B: gas-phase signal intensity resulting from off-resonance excitation using various radio-frequency flip angles and pulse lengths. The 1,200-μs sinc pulse showed a reduction in the gas-phase excitation with a flip angle of $\sim 22^\circ$, and this pulse length and flip angle were chosen as optimum for all experiments.

*J Appl Physiol* • doi:10.1152/japplphysiol.00092.2013 • www.jappl.org
profile to identify the RF pulse duration and transmit power that
minimized unwanted gas-phase 129Xe excitation.

Characterization was performed by placement of a 1-liter ALTEF
bag containing HP 129Xe in the coil and application of RF excitation
pulses 3.832 kHz above gas-phase 129Xe resonance, where the 129Xe
RBC resonance would occur in vivo. Because the bag phantom
exhibits no dissolved-phase signal, any 129Xe signal results from
unwanted gas-phase 129Xe excitation and measures the degree of RF
pulse imperfection. The approach, which is illustrated in Fig. 9A, used
a three-lobe windowed sinc pulse, ranging in duration from 1 to 1.5
ms and swept over an 11- to 388-W range of RF power. As shown in
Fig. 9B, for pulses <1.2 ms, the gas-phase 129Xe excitation increased
with RF power before slightly decreasing at the highest powers.
However, for the 1.2-ms pulse, a narrow band of RF power exists
where gas-phase excitation is minimized. As the pulse duration was
increased to 1.4 ms, off-resonance excitation was somewhat diminish-
ished and the local minimum shifted to a lower power.

RF characterization was then repeated in three healthy volunteers
to confirm that the same optimum occurs in vivo. On the basis of these
tests, all dissolved-phase imaging results were acquired with a 1.2-ms
pulse. RF characterization showed that the gas-phase 129Xe excitation
was ∼20% of the dissolved-phase excitation and provided the optimal balance between
high-frequency selectivity needed to excite the dissolved-phase with-
out gaseous contamination and a short pulse length needed to combat
the short $T_2$ of dissolved 129Xe.

ACKNOWLEDGMENTS

The authors thank Gary Cofer for advice on pulse-sequence programming,
Jerry Dahlke for MR hardware expertise, and Sally Zimney for proofreading
the manuscript.

GRANTS

This work was funded by National Heart, Lung, and Blood Institute Grant
1R01 HL-105643 and partly by the Center for In Vivo Microscopy National
Institute of Biomedical Imaging and Bioengineering Grant P41 EB-015897.
Duke Clinical and Translational Science Award UL1 RR-024128 from the
National Center for Research Resources, and National Institute of Allergy and
Infectious Diseases Grant AI-081672.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.S.K., Z.I.C., and B.D. are responsible for conception and design of the
research; S.S.K., M.S.F., J.D., J.S., R.S.V., S.H.R., M.H., K.T.K., and B.D. performed the experiments; S.S.K. analyzed the data; S.S.K., M.S.F., Z.I.C.,
S.H.R., W.M.F., and B.D. interpreted the results of the experiments; S.S.K.
and Z.I.C. prepared the figures; S.S.K. drafted the manuscript; S.S.K., M.S.F.,
revised the manuscript; S.S.K., M.S.F., Z.I.C., J.D., J.S., R.S.V., S.H.R., M.H.,
K.T.K., W.M.F., H.P.M., and B.D. approved the final version of the manu-
script.

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