Original Investigation

Using Hyperpolarized ^{129}Xe MRI to Quantify the Pulmonary Ventilation Distribution

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Rationale and Objectives: Ventilation heterogeneity is impossible to detect with spirometry. Alternatively, pulmonary ventilation can be imaged three-dimensionally using inhaled ^{129}Xe magnetic resonance imaging (MRI). To date, such images have been quantified primarily based on ventilation defects. Here, we introduce a robust means to transform ^{129}Xe MRI scans such that the underlying ventilation distribution and its heterogeneity can be quantified.

Materials and Methods: Quantitative ^{129}Xe ventilation MRI was conducted in 12 younger (24.7 ± 5.2 years) and 10 older (62.2 ± 7.2 years) healthy individuals, as well as in 9 younger (25.9 ± 6.4 yrs) and 10 older (63.2 ± 6.1 years) asthmatics. The younger healthy population was used to establish a reference ventilation distribution and thresholds for six intensity bins. These bins were used to display and quantify the ventilation defect region (VDR), the low ventilation region (LVR), and the high ventilation region (HVR).

Results: The ventilation distribution in young subjects was roughly Gaussian with a mean and standard deviation of 0.52 ± 0.18, resulting in VDR = 2.1 ± 1.3%, LVR = 15.6 ± 5.4%, and HVR = 17.4 ± 3.1%. Older healthy volunteers exhibited a significantly right-skewed distribution (0.46 ± 0.20, P = 0.034), resulting in significantly increased VDR (7.0 ± 4.8%, P = 0.008) and LVR (24.5 ± 11.5%, P = 0.025). In the asthmatics, VDR and LVR increased in the older population, and HVR was significantly reduced (13.5 ± 4.6% vs 18.9 ± 4.5%, P = 0.009). Quantitative ^{129}Xe MRI also revealed altered ventilation heterogeneity in response to albuterol in two asthmatics with normal spirometry.

Conclusions: Quantitative ^{129}Xe MRI provides a robust and objective means to display and quantify the pulmonary ventilation distribution, even in subjects who have airway function impairment not appreciated by spirometry.

Key Words: Asthma; aging; albuterol.

INTRODUCTION

The distribution of ventilation is known to be nonuniform in healthy lungs (1–6), and this heterogeneity increases with age and disease. Ventilation heterogeneity is impossible to quantify using spirometry because it measures the lung as a single unit and is insensitive to pathology in the small airways—the so-called silent zone. Alternative approaches include using the multiple-breath nitrogen washout (MBNW) test to determine the distribution of specific ventilation (SV) (2,7), the lung clearance index (LCI) (8–11), or the multiple inert gas elimination technique (MIGET) to quantify the ventilation–perfusion relationship (6); however, none of these tests provides spatial information. Alternatively, imaging methods such as computed tomography (CT) delineate spatial changes in lung structures that may allow ventilation abnormalities to be inferred. However, CT does not directly measure ventilation and its radiation dose limits some longitudinal studies.

Recently, magnetic resonance imaging (MRI) techniques have emerged that enable direct detection of inhaled gases, such as oxygen (12–14), perfluorinated gases (15,16), and hyperpolarized (HP) ^{3}He (4,17,18). These techniques enable visualization of ventilation defects that have been shown to correlate with airway tone (4,19–21) and airway abnormalities (22). HP ^{3}He MRI readily depicts regional ventilation heterogeneity in patients with pulmonary obstructive diseases (23). More recently, ^{129}Xe gas has emerged as the most promising alternative to address dwindling supplies of ^{3}He (24–26). ^{129}Xe MRI appears to more readily detect ventilation defects than ^{3}He MRI (21,27) and has been used to visualize elimination of ventilation defects after bronchodilator administration (28).

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However, the analysis of ^{129}Xe MRI scans has yet to fully capture the entire pulmonary ventilation distribution. Most methods have focused on quantifying the ventilation defect percentage (VDP), the fraction of the lung with ventilation below an arbitrary threshold (29, 31). Although VDP quantifies the most severely affected lung units, its definition is not robust. Moreover, VDP does not report on lung units with mild to moderate impairment or increased ventilation. This finding has led to efforts to extend beyond the VDP, including heterogeneity (4,25,28). Recently, more sophisticated methods such as the hierarchical *k*-means clustering algorithm have been introduced (30) to derive five different ventilation levels from ^{3}He MRI and these levels were quantified in asthmatics (32). For ^{129}Xe MRI, our own group has recently introduced a method to rescale image intensity into four bins (31) and has shown VDP derived from such maps to be reproducible to ±1.52% (33). However, it has not yet been determined how these maps could be used to recover the pulmonary ventilation distribution.

Here, we present a novel approach to analyzing ^{129}Xe MRI scans that combines image histogram characterization and linear binning maps to more comprehensively map and quantify the underlying distribution of pulmonary ventilation. We illustrate its utility by detecting abnormalities in the scans from older normal subjects with normal spirometry. We subsequently characterize ventilation distribution differences in older and younger asthmatics, and illustrate the way in which it is altered by bronchodilator therapy.

METHODS

Subjects

We recruited 12 healthy young (18–30 years old) and 10 healthy older (50–70 years old) individuals who were nonsmokers, with FEV1 > 85% according to ethnically appropriate reference tables and FEV1/FVC > 0.7. We also recruited 9 younger (18–30 years old) and 10 older (50–70 years old) patients with mild intermittent asthma. Each subject provided informed consent to participate in the study protocol.

Image Acquisition

All magnetic resonance (MR) scans were performed on a 1.5-T EXCITE 15M4 MR system (GE Healthcare) using protocols described previously (31). Briefly, subjects were fitted in the supine position with a flexible chest coil (Clinical MR Solutions, Brookfield, WI) that was tuned to the 17.66-MHz ^{129}Xe frequency and proton blocked to permit acquisition of anatomical scans using the ^{1}H body coil. After the initial localizer and thoracic cavity scans (described subsequently), all subjects underwent ^{129}Xe ventilation MRI after inhaling a dose equivalent (DE) of 71 mL HP ^{129}Xe filled to 1 L total volume with helium buffer gas (34). Some asthmatics underwent additional ^{129}Xe ventilation MRI scans after four puffs of albuterol with lower DE = 24 mL, 10 minutes after the first ^{129}Xe MRI scan. Scan parameters (71 mL/24 mL DE) were fast spoiled gradient echo, field of view = 40/48 cm, matrix = 128 × (90–128)/64 × 64, slice thickness = 12.5 mm, bandwidth = 8.3 kHz, flip angle = 7°–10°, and repetition time/echo time = 8.1/1.9 ms; Slices were acquired in an anterior to posterior order (34). The ^{129}Xe gradient-echo ventilation images were analyzed in the context of a thoracic cavity image acquired of the same slices using a breath-hold ^{1}H steady-state free precession imaging sequence using the scanner's body coil. For this anatomical reference scan, subjects were in the same position as for ^{129}Xe MRI and inhaled a 1-L bag of room air. The ^{1}H images were then acquired with field of view = 40 cm, matrix = 192 × 192, slice thickness = 12.5 mm, flip angle = 45°, repetition time/echo time = 2.8/1.2 ms, and bandwidth = 125 kHz. All ^{1}H and ^{129}Xe MR images were reconstructed directly from the scanner and exported as 256 × 256 × 14 DICOM slices for analysis.

Image Analysis

Image analysis employed an extension of the method (31) we previously introduced to transform gray-scale ^{129}Xe MR images into maps that depict various levels of signal intensity. As illustrated in Figure 1, this method overcomes the lack of absolute MR signal scale (unlike Hounsfield units in CT) by analyzing the ^{129}Xe image in the context of a thoracic cavity mask and using the top percentile of intensities to rescale the image histogram to range from 0 to 1. In addition to correcting for the effects of vasculature and ^{129}Xe coil bias field, we applied two additional technical extensions. We now retain signal from the major airways before histogram rescaling, but remove it before quantitative reporting; these airways replenish fully with each breath and contribute the top percentile of intensities. Furthermore, we erode the thoracic cavity mask by 1 pixel to minimize false defects near the lung borders.

To establish an unbiased reference distribution, we first characterized the averaged rescaled ^{129}Xe intensity histograms from healthy young volunteers. Of the 12 younger volunteers scanned, images from 10 were deemed to exhibit no ventilation defects by visual inspection. From these subjects, an averaged rescaled intensity histogram was generated, and the mean and standard deviation (SD) of this histogram were used to define the threshold intensities for the ensuing six-bin maps. The mean of this distribution defined the boundary between bins 3 and 4, which were classified as the normally ventilated regions. Each bin was assigned a width of 1 SD. The lowest intensity bin was identified as the ventilation defect region (VDR), followed by the low ventilation region (LVR), while the highest two bins were combined to form the high ventilation region (HVR). These same definitions were then used to analyze all subsequent images by classifying each pixel into one of the six bins. In addition, the coefficient of variation (CV) of each rescaled distribution was calculated by taking the ratio of its SD to its mean. Each image was then displayed