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MAGNETIC RESONANCE ELASTOGRAPHY OF HUMAN LUNG PARENCHYMA: TECHNICAL DEVELOPMENT, THEORETICAL MODELING AND IN VIVO VALIDATION

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Abstract

Purpose—To develop a novel MR-based method for visualizing the elastic properties of human lung parenchyma *in vivo* and to evaluate the ability of this method to resolve differences in parenchymal stiffness at different respiration states in healthy volunteers.

Materials and Methods—A spin-echo MR Elastography (MRE) pulse sequence was developed to provide both high shear wave motion sensitivity and short TE for improved visualization of lung parenchyma. The improved motion sensitivity of this approach was modeled and tested with phantom experiments. *In vivo* testing was then performed on ten healthy volunteers at the respiratory states of residual volume (RV) and total lung capacity (TLC).

Results—Shear wave propagation was visualized within the lungs of all volunteers and was processed to provide parenchymal shear stiffness maps of all ten subjects. Density corrected stiffness values at TLC (1.83 ± 0.22 kPa) were higher than those at the RV (1.14 ± 0.14 kPa) with the difference being statistically significant ($p < 0.0001$).

Conclusion—¹H-based MR Elastography can noninvasively measure the shear stiffness of human lung parenchyma *in vivo* and can quantitate the change in shear stiffness due to respiration. The values obtained were consistent with previously reported *in vitro* assessments of cadaver lungs. Further work is required to increase the flexibility of the current acquisition and to investigate the clinical potential of lung MRE.

Keywords

lung elastography; mechanical properties; lung stiffness; magnetic resonance elastography; shear stiffness

INTRODUCTION

Lung disease is a significant global public health issue, accounting for approximately 7% of all deaths worldwide, with chronic respiratory diseases claiming the lives of over four million people annually (1). Within the United States alone, lung disease is the third leading cause of disease-related death and produces an economic burden of over \$154 billion a year (2). Successful strategies for reversing the increasing prevalence of lung diseases would

depend upon the development of imaging-based techniques in which information on the functional status of the lungs is elucidated as opposed to morphology alone.

Lung parenchyma is a prestressed mesh of connective tissue elements (3,4) in which elastin, collagen and proteoglycans are the main constituents. While it is appreciated that the individual mechanical properties of these structural components play a central role in lung function, this knowledge alone is insufficient to provide useful diagnostic and prognostic information on disease severity and extent (5). This is due in large part to the fact that lung diseases are typically associated with gross topographically heterogeneous changes to the mechanical properties of the parenchyma itself (5). A classic example is pulmonary fibrosis, in which the pulmonary parenchyma becomes stiffer due to both collagen deposition and concomitant changes in tissue architecture (6,7). In contrast, the loss of parenchyma, which is the hallmark of emphysema (8,9), results in reduced lung stiffness leading to hyperinflation and dynamic airway collapse. These examples serve to underscore the central role of both lung architectural and parenchymal mechanics in the pathogenesis of pulmonary disease and point to the current unmet clinical need to noninvasively quantify and resolve changes in the mechanical properties of lung parenchyma.

Because of the significance of lung parenchymal mechanical properties, numerous methods have been developed to assess these properties. Initial approaches involved quasistatic punch indentation testing, which have provided insight into the linear relationship between lung inflation pressure and shear modulus (10,11). Clinically, estimates of global bulk modulus derived from inspiration and expiration pressure-volume (PV) curves obtained by means of spirometry and esophageal manometry pulmonary function tests have provided important bedside information. However, they lack vital regional information on disease location and extent. CT provides excellent regional information on morphology, but it does not reveal any information with regards to regional tissue mechanical properties. MR-based radio frequency (RF) tagging methods have been successful at quantifying regional strain across the respiratory cycle (12) but do not quantify stress (i.e., load) and therefore do not provide insight into the underlying mechanical properties (i.e., elastic moduli) of the lung. What is thus needed is a method to quantify and spatially resolve the mechanical properties of the lung *in vivo*.

Recent developments using MR phase-contrast-based approaches to visualizing propagating shear waves have demonstrated that it is possible to spatially resolve the shear modulus of tissues *in vivo*. The technique, known as MR elastography (MRE, (13)), involves the application of time-harmonic external vibrations of frequencies in the range of 50 to 200 Hz into an object of interest using mechanical actuators (14) in synchrony with bipolar motion-encoding gradients (MEG) inserted into a standard MR pulse sequence. Displacements induced by propagating shear waves are encoded into the phase of the MR signal which is then processed to provide a spatially resolved image of the distribution of shear stiffness within the object.

While MRE has been successfully applied to solid organs such as the liver breast, brain and heart (15–19) the application of MRE for the quantification of lung parenchymal mechanical properties has been slow and challenging due to the inherently poor ^1H MR signal properties of the lung as a result of the decrease in physical density compared to solid organs and the effect of susceptibility induced signal losses (20,21). The use of contrast agents such as hyperpolarized gases with MRE have provided initial promising results (22,23). However, supply concerns (24,25) and the cost of the specialized hardware necessary to perform multinuclear (i.e. non- ^1H) MR imaging have limited the clinical utility of this approach. Recent animal ^1H MRE experiments have suggested that ^1H lung MRE can quantify the elastic properties of lung parenchyma (26) and reflect the relationship between shear

stiffness and inflation pressure observed using established punch indentation tests (27). We hypothesized that MRE can be extended to *in vivo* human lung imaging using ^1H -based MRE techniques and that changes of lung parenchymal shear stiffness due to physiological or pathological conditions can be quantitated. The purpose of this work was to develop MRE for *in vivo* assessment of human lung parenchyma and to test its ability to measure the change in stiffness of lung parenchyma at different respiration states.

METHODS

Pulse Sequence Modifications

The challenge of any *in vivo* implementation of lung MRE is to acquire an MR signal with sufficiently high signal-to-noise ratio such that shear-wave-induced displacements can be encoded into the phase of the MR signal. Gradient-echo and free induction decay pulse sequences can provide short echo times (TE) and hence high signal for anatomic and functional MRI of the lungs (e.g., ultra-short TE sequences, (28)). However, even using such sequences for MRE, with the addition of motion-encoding gradients (MEG), the TE will increase and the signal will significantly diminish due to T_2^* effects. Therefore, spin-echo-based imaging was pursued in this study. In one implementation of the spin-echo MRE sequence, a bipolar MEG with a duration of one period of the motion was placed on one side of the 180° radio frequency (RF) pulse. A schematic diagram of this pulse sequence corresponding to a harmonic motion of 50 Hz is shown in figure 1a. The bipolar MEG duration and the TE were 20 ms and 43.6 ms respectively. While spin-echo sequences are typically less sensitive to T_2^* signal loss in comparison to gradient echoes, the ultrashort T_2^* of lung parenchyma ($\sim 1\text{--}2$ ms) means that these sequences are also dominated by this signal loss, particularly at larger echo times (TEs). Thus, a major focus of the pulse sequence modifications described in the following sections has entailed the implementation of methods to reduce the TE of the sequence to minimize T_2^* signal loss.

Fractional Motion Encoding

The first step in reducing the TE was to implement fractional motion encoding (29,30), in which the duration of the MEG is less than a period of motion allowing the TE to be significantly reduced. As the MEG duration is reduced, the motion sensitivity of the acquisition is reduced as well. This loss in sensitivity can be tolerated or compensated for if this configuration can reduce the TE enough to produce significant MR signal. By fixing the duration of the MEG this implementation makes the TE independent of the frequency of vibration.

Split MEG

The TE of the pulse sequence was further reduced by splitting the single bipolar MEG initially present on the left side of the 180° RF pulse to two unipolar MEG lobes that were placed on either side of the 180° pulse (31). The net motion sensitivity or the net phase accrual of the two MEG lobes will depend upon their spacing and this dependence will be discussed in the theory section below.

MEG as Crusher Gradients

The final modification to the pulse sequence involved the use of the unipolar MEG lobes configuration to replace the crusher gradients typically placed on either side of the 180° RF pulse. In addition to ensuring zero phase accumulation for static tissue, the second lobe of the MEG also effectively spoils the signal from the free induction decay (FID) created by the imperfections in the refocusing pulse. This means that the crusher gradients that flank the 180° RF pulse in the unmodified spin-echo sequence (indicated by the arrow in figure

1a) is redundant and hence can be removed to reduce the TE even further. The modified spin-echo MRE pulse sequence with two 2-ms MEG lobes is shown in figure 1b and the TE of this sequence is 9.4 ms.

Theory

To appreciate the effect of the aforementioned changes in the spin-echo MRE pulse sequence on shear wave motion sensitivity, a mathematical analysis was performed. The motion sensitivity of the modified pulse sequence depends upon both the duration of the MEG lobes and the spacing between them. The phase in the transverse magnetization accrued due to motion of protons in the presence of a magnetic field gradient used as a motion-encoding gradient (MEG) is given by

$$\phi(T, \mathbf{r}) = \int_{t=-\infty}^{\infty} \gamma w(t) \mathbf{G}(t) \bullet \xi(t - T, \mathbf{r}) dt, \quad [1]$$

where $\phi(T, \mathbf{r})$ is the accrued phase at position $\mathbf{r}$ as a function of the time delay or offset between the motion and the MEG T , γ is the gyromagnetic ratio of the imaged protons ($2\pi \cdot 4257 \text{ rad} \cdot \text{s}^{-1} \cdot \text{G}^{-1}$ for water), $\mathbf{G}(t)$ is the vector MEG vector as a function of time, $\xi(t, \mathbf{r})$ is the vector motion as a function of time and $w(t)$ is a window function that limits the duration of the MEG. The motion sensitivity is often analyzed in the frequency domain via the temporal Fourier transform (FT) of $\phi(T, \mathbf{r})$, which yields

$$\Phi(f, \mathbf{r}) = \Xi^*(f, \mathbf{r}) \bullet [\gamma W(f) \otimes \Gamma(f)], \quad [2]$$

where $\Phi(f, \mathbf{r})$, $\Xi(f, \mathbf{r})$, $W(f)$, and $\Gamma(f)$ are the FT of $\phi(T, \mathbf{r})$, $\xi(t, \mathbf{r})$, $w(t)$, $\mathbf{G}(t)$, respectively, $*$ is the complex conjugate operation, $\bullet$ is the dot product operator, and $\otimes$ is the convolution operator. To determine the sensitivity of motion at a specific frequency of vibration f_v , the motion is represented by a plane wave:

$$\xi(t, \mathbf{r}) = \xi_0 \sin(2\pi f_v t - \mathbf{k} \bullet \mathbf{r}) \iff \Xi(f, \mathbf{r}) = \frac{i\xi_0}{2} \{ \delta(f + f_v) - \delta(f - f_v) \} e^{-\frac{if(\mathbf{k} \bullet \mathbf{r})}{f_v}} \quad [3]$$

where ξ_0 is the amplitude of the motion, $\mathbf{k}$ is the wave number, and $\delta(\cdot)$ is the Dirac delta function. The MEG is represented by a train of positive and negative trapezoids each with an amplitude of G_0 , duration T_g , and 0-to- G_0 rise time d . The Fourier transform of this waveform can be written as

$$\mathbf{G}(t) \iff \Gamma(f) = \sum_{m=\pm 1, \pm 3, \dots}^{\pm \infty} \frac{-2iG_0}{\pi m} \text{sinc}\left(\frac{md}{T_g}\right) \delta\left(f - \frac{m}{2T_g}\right). \quad [4]$$

The window function which truncates the MEG waveform is a boxcar function with a width of n trapezoids, given by

$$w(t)=\text{rect}\left(\frac{t-nT_g/2}{nT_g}\right) \Longleftrightarrow W(f)=nT_g \text{sinc}(nT_g f) e^{-\pi i f n T_g}. \quad [5]$$

For the motion sensitivity of 1 trapezoidal MEG, $n=1$ and

$$W(f)=T_g \text{sinc}(T_g f) e^{-\pi i f T_g} \quad [6]$$

Therefore, the frequency-domain representation of the accrued phase due to a trapezoidal MEG lobe is given by

$$\begin{aligned} \Phi(f, \mathbf{r}) &= \left[\frac{-\gamma T_g \mathbf{G}_0 \bullet \boldsymbol{\xi}_0}{\pi} \{ \delta(f+f_v) - \delta(f-f_v) \} e^{\frac{i f(\mathbf{k} \bullet \mathbf{r})}{f_v}} \right] \times \left[\text{sinc}(T_g f) e^{-\pi i f T_g} \otimes \sum_{m=\pm 1, \pm 3, \dots}^{\pm \infty} \frac{1}{m} \text{sinc}\left(\frac{md}{T_g}\right) \delta\left(f - \frac{m}{2T_g}\right) \right] \\ &= \left[\frac{-\gamma T_g \mathbf{G}_0 \bullet \boldsymbol{\xi}_0}{\pi} \{ \delta(f+f_v) - \delta(f-f_v) \} e^{\frac{i f(\mathbf{k} \bullet \mathbf{r})}{f_v}} \right] \times \left[\sum_{m=\pm 1, \pm 3, \dots}^{\pm \infty} \frac{1}{m} \text{sinc}\left(\frac{md}{T_g}\right) \text{sinc}\left(T_g f - \frac{m}{2}\right) e^{-\pi i (T_g f - \frac{m}{2})} \right]. \end{aligned} \quad [7]$$

At the frequency of vibration, the accrued phase can be expressed as the phasor

$$\Phi(f_v, \mathbf{r}) = \frac{i \gamma T_g \mathbf{G}_0 \bullet \boldsymbol{\xi}_0}{\pi} e^{i(\mathbf{k} \bullet \mathbf{r} - \pi T_g f_v)} \sum_{m=\pm 1, \pm 3, \dots}^{\pm \infty} \frac{1}{m} \text{sinc}\left(\frac{md}{T_g}\right) \text{sinc}\left(T_g f_v - \frac{m}{2}\right) (-1)^{(m-1)/2}. \quad [8]$$

The amplitude of the accrued phase $\phi(T, \mathbf{r})$ is given by

$$\phi_0 \equiv 2|\Phi(f_v, \mathbf{r})| = \left| \frac{2\gamma T_g \mathbf{G}_0 \bullet \boldsymbol{\xi}_0}{\pi} \sum_{m=\pm 1, \pm 3, \dots}^{\pm \infty} \frac{1}{m} \text{sinc}\left(\frac{md}{T_g}\right) \text{sinc}\left(T_g f_v - \frac{m}{2}\right) (-1)^{(m-1)/2} \right|. \quad [9]$$

If one trapezoidal gradient waveform is introduced into an imaging sequence for purposes of motion encoding, a second waveform with the same area but opposite polarity must typically be used as well to keep the 0th gradient moment for the imaging sequence zero. The resulting phase accumulation due to both of these waveforms will be the sum of the phases accrued from each MEG waveform separately. So, while the phasor from the first MEG is defined as

$$\Phi_1(f_v, \mathbf{r}) = \Phi(f_v, \mathbf{r}), \quad [10]$$

the phasor from the second MEG is given by

$$\Phi_2(f_v, \mathbf{r}, T_s) = -\Phi(f_v, \mathbf{r}) e^{2\pi i T_s f_v}, \quad [11]$$

where T_s is the temporal spacing between the start of the first and second MEGs. Therefore, the total phasor from this motion-encoding gradient pair of trapezoidal gradients is

$$\Phi_p(f_v, \mathbf{r}, T_s) = \Phi(f_v, \mathbf{r}) \left[1 - e^{2\pi i T_s f_v} \right]. \quad [12]$$

The amplitude of the accrued phase for the MEG pair is thus given by

$$\phi_p = \phi_0 \left| 1 - e^{2\pi i T_s f_v} \right|. \quad [13]$$

Phantom Study

All of the phantom experiments were performed with a 1.5-T whole-body scanner (Signa EXCITE, GE Healthcare, Milwaukee, WI) in combination with a single-channel transmit-receive birdcage coil. To evaluate the functioning of the modified pulse sequence and to validate the theoretical model of motion sensitivity, experiments were performed on a soft cylindrical phantom made up of 7.5% bovine gelatin (Sigma Life Sciences, MO, USA). Shear waves were induced in the phantom by vibrating the whole phantom with a pressure activated driver system (19). The phantom was placed on the passive driver as shown in figure 2a. When the active driver engine, connected to the passive driver through a connecting tube, generates the necessary vibrations, shear waves are induced into the gelatin due to the inertial effect at the walls of the container. Continuous harmonic shear waves of 50 Hz were induced within the phantom and were imaged with three MRE pulse sequence configurations:

1. Single 4-ms bipolar MEG before the 180° pulse (TE = 14 ms).
2. Two 2-ms unipolar MEG lobes placed around the 180° pulse with the smallest possible spacing (4.856 ms) with current RF pulse constraints (TE = 10 ms).
3. Two 2-ms MEG lobes placed around the 180° pulse separated by half the period of the motion (10 ms) (TE = 15 ms).

Other relevant parameters of the data acquisition included slice orientation = coronal, field of view (FOV) = 30 cm, slice thickness = 10 mm, acquisition matrix = 128×64, frequency-encoding direction = superior-inferior, motion-sensitizing direction = anterior-posterior, repetition time (TR) = 100 ms, gradient amplitude = 4 mT/m, and phase offsets = 4. The wave images obtained from these three experiments were compared with one another. The same amplitude of motion was used in all three cases, so the relative amplitude of the motion recorded in the phase images is indicative of the relative motion sensitivity of the three different pulse sequence configurations. The mean phase amplitude for each configuration was recorded, normalized to the model using the bipolar MEG data to verify agreement with the model and compared to one another to determine the relative sensitivity of each configuration.

In vivo Human Study

To test the *in vivo* feasibility of lung MRE and to assess its ability to differentiate changes in shear stiffness of lung parenchyma across the respiratory cycle, ten healthy volunteers with no diagnosed pulmonary pathologies were recruited. All of the experiments were performed after obtaining written consent in accordance with our institutional review board guidelines. The ten volunteers included 7 males and 3 females, with an average age of 29.6 years and an average height of 170 cm. The volunteers were all positioned in the scanner bore in a supine

position with their hands held over their head in a feet-first entry position as indicated in figure 2c.

Surface Coil Array

Signal detection was achieved using a custom-made receive-only surface coil array. The coil consisted of eight independent elements with each element laminated onto a fiberglass substrate. Figure 2b shows a picture of the coil array and the positioning of the coil on the subject is schematically indicated in figure 2c. The flexible nature of the coil design allowed individual elements to closely follow the contour of the volunteer's chest wall for a variety of body habitus.

Motion Induction

Shear vibrations were induced within the lungs using the pressure activated driver system (19) described for the phantom studies. Figure 2c schematically shows the location of the passive driver on the anterior chest wall of the subject positioned inside the receiver array. The driver was positioned anterior to the right lung so as to create shear waves in lung tissue that is devoid of cardiac tissue. Continuous vibrations of 50 Hz were used in this study since higher frequency vibrations are significantly attenuated and lower frequency vibrations have low spatial stiffness resolution. The passive driver delivers the longitudinal vibrations created by the active driver into the lung tissue where they undergo mode conversion generating shear waves (19) that can be imaged with the modified MRE pulse sequence.

Data Acquisition

Data were collected in the axial imaging plane with a 35-cm FOV, 128×64 acquisition matrix, superior-inferior motion-sensitizing direction, 0.6–0.8 fractional FOV, TR/TE = 200/9.4 ms, 4 mT/m MEG amplitude, five 10-mm slices with 1-mm spacing, and 4 phase offsets. Two 2-ms MEG lobes spaced 5.050 ms apart were used for motion encoding. The frequency-encoding direction was chosen to be in the right-left direction so that the artifacts created due to the cardiac motion would not significantly affect the lung signal. To reduce respiratory artifacts, data were acquired with breath holds of 21 seconds for a single phase offset. To verify the motion-encoding capability of the imaging sequence, data were acquired with and without motion for comparison at the forced expiration or residual volume (RV) state. This state was chosen since the tissue density and hence the pulmonary MR signal should be highest in that state.

To test whether MRE can differentiate the shear stiffnesses at different inspiratory levels, two sets of MRE data were acquired: first, at the residual volume (RV), where the volunteers were asked to hold their breath at forced complete expiration and secondly at total lung capacity (TLC) where the volunteers were asked to hold their breath at forced complete inspiration. The imaging parameters were the same as above.

Data Analysis

Shear wave images at RV and TLC acquired with the modified pulse sequence were phase unwrapped and processed using the local frequency estimation algorithm with spatio-temporal directional filters (with bandpass filter cutoff frequencies of 0.01 to 100 waves/FOV) to calculate shear stiffness maps (elastograms) of the lungs (32,33). This inversion algorithm estimates the shear stiffness using the equation $\mu = \rho V_s^2$ where μ is the shear stiffness and V_s is the speed of the propagating shear waves. ρ is the density of the tissue of interest which is usually assumed to be 1 g/ml. However, since the density of the lungs is far less than this, and changes during respiration, the calculated shear stiffness values are referred to here as effective stiffnesses ($\mu_{\text{effective}}$). The effective stiffness was estimated from

each slice using a single region of interest (ROI) containing visually detectable wave motion indicative of high phase SNR. The mean stiffness of the 5 slices was calculated at both respiration levels for each subject. To compare the stiffness estimates at the two levels of respiration, a two-tailed t-test with a significance (α) value of 0.05 was performed against the null hypothesis that there is no difference in mean stiffness using the software package JMP (JMP8.0, Cary, NC).

Lung Density Correction

To account for lung density changes in the estimation of shear stiffness, variations in physical density (which can range between 0.08 g/ml to 0.5 g/ml (34,35)) were calculated from lung volume measurements obtained from separate 2D multislice single-shot fast-spin-echo MR acquisitions at the two respiration states. From the calculated lung volumes, two different shear stiffness values were estimated according to how the lung density correction was performed. In the first method, the stiffness value, referred to as the mass-weighted stiffness ($\mu_{\text{mass\_weighted}}$, μ/mass), was calculated as the product of the effective stiffness and the inverse of the volume. With the second approach, the stiffness value, referred to as the density-corrected stiffness ($\mu_{\text{dens\_corr}}$), was calculated as the product of effective stiffness and the relative densities calibrated to a density value of 0.33 g/ml at the residual volume for each volunteer. These adjusted stiffness values were then compared at the two respiration states and their means were compared using analysis of variance.

RESULTS

Phantom Study

Results obtained from the phantom validation studies are shown in figure 3. In figure 3a, the theoretical net motion sensitivity of the modified pulse sequence is plotted against the spacing between the first and the second MEG lobe from the lowest possible MEG spacing without overlap (2 ms) to one period of the wave motion (20 ms). It can be seen that the sensitivity gradually increases as the spacing increases from 2 ms to half a period of motion (10 ms) and then decreases and reaches 0 at a full period of motion. The theoretical values for the three pulse sequence configurations used in the phantom study are indicated by the blue squares, where the bipolar MEG is treated as two unipolar lobes separated by a time interval equivalent to one lobe. Even increasing the spacing between the MEG lobes by 2.9 ms from the minimum duration increases the motion sensitivity by more than 200%. Thus, in theory, the split MEG configuration should have higher motion sensitivity in comparison to the bipolar MEG configuration, though it also has a lower TE. The magnitude image of the coronal imaging slice obtained from the MRE experiments is shown in figure 3b. One phase offset image obtained with the three pulse sequence configurations with the MEG lobes at 2 ms, 4.856 ms and 10 ms are shown in figures 3d, 3e and 3f respectively and a line profile (indicated in the figure) drawn through the center for these three datasets is shown in figure 3c. The wave data behaves as expected. The normalized experimental phase amplitude values are shown in figure 3c as the red stars and they agree well with the theoretical model.

In Vivo Human Study

Figure 4 shows typical lung MRE data obtained at the residual volume from one volunteer. Figure 4a shows the magnitude image obtained with the MRE pulse sequence using a grey scale window and level that shows the signal from the lung parenchyma. Cardiac artifacts are seen in the phase direction (A-P) in the magnitude image, however lung tissue devoid of these artifacts is easily visible. The boundary of the right lung is indicated with the dotted line. Figure 4b shows a single wave image from this acquisition with no applied external motion. Coherent phase is visible within the right lung and is also devoid of cardiac artifacts.

It can be appreciated that the phase signal within the lungs is noisy in comparison to the phase within other tissues such as muscle. A wave image of the lungs with the external motion present is shown in figure 4c, which, in comparison to figure 4b, illustrates the presence of shear waves in the abdominal muscle and the right lung. Phase aliasing can be seen at the anterior portion of the lung closer to the driver. Phase unwrapped data are shown in figure 4d, more clearly demonstrating the presence of shear waves (arrow).

Figure 5 shows MRE data obtained at the residual volume (top row) and the total lung capacity (bottom row) from the same volunteer. The top and the bottom row shows the data obtained at RV and TLC, respectively. It can be seen that the lung area is larger and the pulmonary magnitude signal is lower at the TLC in comparison to those at RV. Figures 5b and 5e show wave images within the segmented right lung depicting the shear wave propagation at the two respiration states. The wavelength is clearly longer at TLC. Corresponding effective stiffness maps are shown in 5c and 5f, and as expected the stiffness value at TLC is higher than at RV. The dotted line in the effective stiffness estimates indicates the region, based on the wave image, where the shear wave amplitude is good and the stiffness estimate is reliable.

Figure 6 is a plot of effective stiffness values for the 10 volunteers at the RV and TLC (blue circles). Box plots of the data with the median, 25th and 75th percentiles are also shown in the figure. The higher stiffness values at TLC in comparison to RV are evident. The data are provided in table 1. The mean and standard deviation of the stiffness at the RV was $3.45 \text{ kPa} \pm 0.41 \text{ kPa}$ while the stiffness estimates ranged from 2.8 to 3.94 kPa. The corresponding values at the TLC were $10.75 \text{ kPa} \pm 0.79 \text{ kPa}$, 9.67 and 12.1 kPa, respectively.

Figure 7 shows the lung volumetric data and the relative density values calculated at the RV and TLC. Figures 7a and 7b are 3D renderings of the manually segmented lungs. The lung volume is higher at TLC, as expected. Figure 7c shows the measured volumes in liters. The RV data ranged from 1.23 L to 3 L and the TLC data ranged from 2.79 L to 7.38 L. Figure 7d shows the relative density values obtained from these measured volumes calibrated to 0.33 g/ml. The relative densities at TLC were lower than at RV and ranged from 0.13 to 0.22 g/ml.

Figure 8 shows the mass-weighted stiffnesses and density-corrected stiffnesses for all the subjects. After correction for density variation, stiffnesses have decreased in comparison to the effective stiffness estimates, especially at TLC. Figure 8a shows the mass-weighted stiffnesses in units of $1/\text{ms}^2$. The values (mean $\pm$ standard deviation) at RV and TLC were 1.67 ± 0.6 and 2.57 ± 0.68 , respectively. Relative density-corrected values are shown in figure 8b and it should be noted that the stiffness scales differ between figures 8a and 8b. The data are provided in table 1. Again, density-corrected stiffness values were higher at TLC compared to RV.

Statistical analysis results for the three sets of stiffnesses at the two respiration states are provided in table 2. Statistical testing was done using an α value of 0.05. At this level, the difference in the stiffness is statistically significant in all three cases. However, the difference between the RV and TLC for the effective stiffness and the density-corrected stiffness values were more significant in comparison to that of the mass-weighted stiffness values.

DISCUSSION

Since its inception as a clinical diagnostic tool, MR imaging of the lung has had limited practical application due largely to the low signal-to-noise ratio of the MR signal of lung parenchyma (20,21,36). The application of MRE to the lung has encountered similar

limitations as well as unique challenges such as increased signal loss due to increased TE values necessary to accommodate MEG waveforms (26), and the inherent challenges of transmitting shear waves into the lung noninvasively through the intact chest wall. Although the use of exogenous contrast agents such as hyperpolarized noble gases have provided multiple orders of magnitude increase in the signal from within the lung (37), their widespread use and application have been hampered by equipment cost and supply constraints (25), thereby relegating their use to research purposes. This work describes the development of a ^1H spin-echo MRE pulse sequence for the specific application of spatially resolving the shear stiffness of lung parenchyma. Technical limitations associated with existing MRE pulse sequences have been overcome while preliminary testing in volunteers indicates that this technique can quantify parenchymal shear stiffness *in vivo* and that the values are consistent with established *in vitro* values.

In addition to the observed increase in stiffness of the lung parenchyma at TLC, it was also observed that the shear wave amplitude within the pulmonary parenchyma was higher at TLC than at RV. Typically, shear wave amplitude would be expected to be lower in stiffer tissue due to lower shear strains. We attribute this discrepancy to improved coupling of the mechanical driver with the lung tissue due to the expanded chest. It should also be noted that shear wave images obtained at TLC were typically noisier than those obtained at RV due to the reduced magnitude signal. However, since the inversion algorithm measures local spatial frequency content over several scales, the increase in wave amplitude and image noise will not affect the stiffness estimation significantly (33). Also, the regions of interest for the mean stiffness measurements were chosen to be in areas with high phase SNR.

In some cases, in addition to shear waves, the presence of bulk motion or longitudinal waves was observed and can be seen as very long wavelength waves within the phase-difference images. Since no spatial filtering or curl filtering to remove longitudinal waves was applied, these waves may have artificially increased the observed stiffness values. To reduce their effects, regions dominated by these waves were avoided in the calculation of the mean stiffness. Further, the density-corrected estimates of shear stiffness did not include corrections for gravity-induced changes in density throughout the lung (38). While this is expected to affect the wave propagation data and ultimately regional estimates of shear stiffness, this effect was not accounted for. This was because the density corrections were calculated based on entire lung volumes and were thus considered constant across the right lung imaged in this study.

A challenge with deriving estimates of lung shear stiffness by MRE or other techniques is that a gold standard for assessing this parameter does not exist. However, previous studies performed on cadaver lungs have indicated that there exists a relatively linear relationship between shear stiffness and transpulmonary pressure P_{TP} , $\mu = m P_{\text{TP}}$ (10,34,39) where μ is the shear stiffness and m the proportionality constant. While m typically ranges from 0.5 to greater than 1.0, it is generally appreciated that m is typically less than unity. Although transpulmonary pressures were not obtained in this study, if it is assumed that P_{TP} values of 1 cm H_2O and 25 cm H_2O correspond to RV and TLC, the expected shear stiffness values should be 0.07 kPa and 1.75 kPa respectively if m is equal to 0.7 (39). Comparing these data to the density-corrected values obtained in this study it can be seen that the value at the TLC is in agreement while the measured value at the RV is higher than predicted. There are several reasons that can explain this discrepancy. The aforementioned relationship was observed in *in vitro* lungs, where the lungs are completely deflated to 0 P_{TP} , while the *in vivo* lungs will be at residual lung capacity. In addition, the linear dependence on shear stiffness was obtained using quasistatic punch indentation testing while the MRE measurements were performed using a dynamic stress (in this case, 50-Hz motion), resulting in higher assessed stiffnesses due to viscoelastic and dispersive effects of the tissue. Further,

when the pulmonary vital capacity and RV/TLC ratio values were compared to expected values (40) based on age and height, the experimental values were much higher (0.52 RV/TLC ratio) than the expected value of 0.27 implying that the subjects did not reach RV or TLC. This discrepancy suggests that the assumed P_{TP} values for these respiration states are in error.

There were several technical compromises made throughout this work. The choice of MRE imaging parameters was based on the requirements of providing shear wave penetration throughout the lung while simultaneously limiting the TE to less than 10 ms and was not optimized on a subject-by-subject basis. In addition, stiffness calculations were performed from the displacement data acquired only in a small number of slices with motion encoding in the superior-inferior direction rather than using a fully sampled 3D displacement field, making several assumptions that include isotropy, local homogeneity, linearity and a planar shear wave propagating only within the imaging slices of interest (33). Despite these limitations, these data were consistent with previously reported *in vitro* assessments of lungs. Ongoing ^1H lung MRE developments include accelerated data acquisition schemes so as to enable acquisition of full 3D data within shorter breath hold times.

In conclusion, these data support the hypothesis that ^1H -based MR elastography can noninvasively measure the shear stiffness of pulmonary parenchyma *in vivo*. In addition, based on statistically significant differences between shear stiffness estimates at RV and TLC, the data indicate that the shear stiffness of lung can be quantitated at various phases of the respiratory cycle. It is thus apparent that ^1H lung MRE has the potential to be a powerful new tool for the diagnosis and monitoring of lung disease *in vivo*. Further work is required to increase the flexibility of the current acquisition and to investigate the clinical potential of MRE of the lungs.

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Figure 1.

(a) Conventional spin-echo MRE pulse sequence with a bipolar 20-ms motion-encoding gradient (MEG) on one side of the refocusing pulse with a TE of 43.6 ms. The synchronized sinusoidal motion is also schematically shown. (b) Modified MRE pulse sequence with two 2-ms MEG lobes placed on either side of the refocusing pulse with a TE of 9.4 ms. The crusher gradients (indicated with the arrow in (a)) were removed in the modified sequence.

Figure 2.

(a) Experimental phantom setup. The positioning of the cylindrical gel phantom on the passive driver is shown with the imaging slice indicated. (b) Custom-built 8-channel receiver coil array. (c) MRE experimental setup for the human volunteer study. Subjects were positioned supine, the passive driver was placed on the anterior chest wall and the receiver coil array wrapped around the driver and the upper abdomen.

Figure 3.

(a) Theoretical curve for motion sensitivity as a function of motion-encoding gradient (MEG) pair spacing (blue line). Note that maximum sensitivity is achieved when the spacing is equal to half the period of wave motion. Blue squares indicate theoretical values for MEG pair spacing at 2 ms, 4.856 ms and 10 ms. Red stars indicate experimental values which agree well with the theoretical values. (b) Magnitude image of the gelatin phantom. (c) Line profile comparison of the wave data shown in (d–f). Example wave data are shown with MEG pair spacings at (d) 2 ms (bipolar MEG), (e) 4.856 ms and (f) 10 ms. It can be seen that the shear wave amplitude increases with increasing MEG spacing.

Figure 4.

In vivo lung MRE data. (a) Magnitude image of a single axial slice with the right lung border identified by the dashed line. (b) Phase-contrast wave image with no applied motion. The image boundary is marked with the dashed line. Note that coherent phase information can be observed within the right lung. (c) Wave image with applied motion. (d) Phase unwrapped wave image where the presence of shear waves is clearly evident (arrow).

Figure 5.

Comparison of MRE data at residual volume (RV) and total lung capacity (TLC). (a,d) Magnitude images obtained at RV and TLC. The boundary of the right lung is marked with the dashed line. (b,e) Displacement image in units of microns with a pseudo-color scale, the dotted line marks the boundary of the lungs. (c,f) Corresponding effective stiffness estimates. The shear wavelength is longer and the effective stiffness is higher at TLC than at RV. The regions of interest shown in (c) and (f) indicate the regions where mean stiffness estimates were obtained for this subject.

Figure 6. Comparison of effective stiffness estimates at RV and TLC for all ten volunteers. The difference in shear stiffness between RV and TLC is statistically significant.

Figure 7.

(a) 3D rendering of the volume data obtained from one volunteer at residual volume (RV). (b) Volume data at total lung capacity (TLC). The higher volume at TLC is evident. (c) Volume data obtained from all the subjects. Note the large variability in estimated volumes. However, within individual subjects the TLC volume was always higher. (d) Corresponding relative density estimates calibrated to 0.33 g/ml. As expected, the values at TLC were all lower than 0.33 g/ml.

Figure 8.

(a) Mass-weighted stiffness estimates and (b) density-corrected stiffness estimates at residual volume (RV) and total lung capacity (TLC). Note the difference in scales for the two images. For each type of stiffness estimate, the mean values at the two respiration states were found to be significantly different.

Table 1

Calculated shear stiffness values

Subject	Effective Stiffness(kPa)		Volume (L)		Mass-Weighted Stiffness (1/ms ²)		Relative Density-Corrected Stiffness (kPa)	
	RV	TLC	RV	TLC	RV	TLC	RV	TLC
1	3.94	10.12	3.00	5.30	1.31	1.91	1.30	1.89
2	3.90	12.10	1.84	4.32	2.12	2.80	1.29	1.70
3	3.50	11.19	2.75	5.16	1.27	2.17	1.16	1.97
4	2.89	9.95	2.98	5.18	0.97	1.92	0.95	1.89
5	3.90	11.16	1.54	3.27	2.52	3.41	1.29	1.74
6	3.27	11.04	2.25	4.22	1.45	2.62	1.08	1.94
7	2.80	11.62	2.90	7.38	0.96	1.57	0.92	1.51
8F	3.59	9.67	2.52	3.76	1.42	2.57	1.18	2.14
9F	3.48	10.48	1.96	3.37	1.77	3.11	1.15	2.02
10F	3.23	10.16	1.23	2.79	2.62	3.64	1.06	1.48

F – Female volunteers

Table 2

Statistical analysis of stiffnesses

Stiffness	Respiration Level		t-test
	Residual Volume	Total Lung Capacity	P Value
Effective Stiffness $\mu_{\text{effective}}$ (kPa)	3.45	10.75	<1e-10
Mass-Weighted Stiffness $\mu_{\text{mass\_weighted}}$ (1/ms ²)	1.67	2.57	0.0046
Density-Corrected Stiffness $\mu_{\text{dens\_corr}}$ (kPa)	1.14	1.84	9.62e-8