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Magnetic resonance Elastography of the Lung parenchyma in an *in situ* porcine model with a non-invasive mechanical driver: Correlation of Shear Stiffness with Trans-respiratory system Pressures

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Abstract

Quantification of the mechanical properties of lung parenchyma is an active field of research due to the association of this metric with normal function, disease initiation and progression. A phase contrast MRI-based elasticity imaging technique known as magnetic resonance elastography (MRE) is being investigated as a method for measuring the shear stiffness of lung parenchyma. Previous experiments performed with small animals using invasive drivers in direct contact with the lungs have indicated that the quantification of lung shear modulus with ¹H based MRE is feasible. This technique has been extended to an *in situ* porcine model with a noninvasive mechanical driver placed on the chest wall. This approach was tested to measure the change in parenchymal stiffness as a function of airway opening pressure (P_{ao}) in 10 adult pigs. In all animals, shear stiffness was successfully quantified at four different P_{ao} values. Mean ($\pm$ std error of mean) pulmonary parenchyma density corrected stiffness values were calculated to be 1.48 (± 0.09), 1.68 (± 0.10), 2.05 (± 0.13) and 2.23 (± 0.17) kPa for P_{ao} values of 5, 10, 15 and 20 cm H₂O respectively. Shear stiffness increased with increasing P_{ao} , in agreement with the literature. It is concluded that in an *in situ* porcine lung shear stiffness can be quantitated with ¹H MRE using a noninvasive mechanical driver, and that it is feasible to measure the change in shear stiffness due to change in P_{ao} .

Keywords

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

Introduction

Normal lung can be considered as a prestressed mesh of connective tissue elements (1,2) in which function is dictated by the communication of mechanical properties across the continuum of scales from microscopic to macroscopic. This continuum enables the transmission of force from the level of the whole lung down to the single cell and is regulated by means of feedback mechanisms that influence extracellular matrix composition and lung mechanics, thereby maintaining a mechanical equilibrium between the applied

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force and the prestress of the supportive matrix (3). In addition, it is generally appreciated that lung connective tissue is a non static structure that undergoes continuous breakdown and remodeling that is in part modulated by mechanical forces (3). Perturbation of the balance between applied force and the matrix prestress by, for example disease processes, initiates additional feedback mechanisms resulting in remodeling of parenchymal tissue which in turn alter the mechanical properties of the lung. Evidence for the relationship between change in parenchymal mechanical properties and pathologic processes can be found in a variety of lung diseases (4). For example, within the fibrotic lung, parenchymal stiffness increases with the degree of fibrosis (5,6) while in asthma it has been demonstrated that disease severity (i.e. increased degree of broncho-constriction) is associated with an increase in parenchymal shear modulus (μ) (7). In contrast, the lung becomes mechanically weaker with the degree of emphysema, due primarily to the remodeling of collagen fibers (8,9). As a result of these associations, methods to quantify lung mechanical properties have significant potential for diagnosis as well as monitoring of disease progression and response to therapies.

Early attempts to quantify the mechanical properties of lung parenchyma involved direct mechanical testing, most notably by means of punch indentation testing (10,11). While these methods have provided a wealth of data on the intrinsic mechanical properties of the lung, their clinical utility is limited due to the ex vivo nature of the measurement technique. A more common clinical approach is to obtain estimates of lung bulk modulus derived from inspiration and expiration pressure-volume (PV) curves obtained by means of esophageal manometry and spirometry-based pulmonary function tests (12). While this method provides an important diagnostic metric, spirometry based estimates are global and thus void of regional lung mechanical information. Computed tomography (CT) is frequently used to visualize fibrosis, although it does not reveal any information with regards to regional tissue mechanical properties of the lung. Despite attempts to develop CT-based composite physiological indices to predict disease severity, the correlation of these indices with extent of fibrosis has been at best moderate and generally lacks sufficient specificity to distinguish disease types (13-15). MR-based radio frequency (RF) tagging methods have been successful at quantifying regional strain across the respiratory cycle (16). However because these techniques do not quantify stress (i.e. load) they do not quantify the underlying mechanical properties (i.e elastic moduli) of the lung. What is thus needed is a method to quantify and spatially resolve the intrinsic mechanical properties of the lung in vivo.

Recently, a new phase contrast MR imaging based technique called magnetic resonance elastography (MRE, (17-19)) has been developed to quantitatively map the regional mechanical properties of soft tissues by calculation of regional shear stiffness. With this technique, time-harmonic external vibrations of frequencies in the range of 50 to 200 Hz are introduced into an object of interest using mechanical actuators. With the use of motion-encoding gradients (MEG) inserted into standard MR pulse sequences, the resultant shear wave propagation is mapped into the phase of MR images. Shear stiffness is then spatially resolved by processing the phase data that are essentially temporal snapshots of the propagating shear waves by mathematical inversion algorithms (20,21). The result of which is a map of the regional distribution of shear stiffness, most commonly referred to as an elastogram.

The application of MRE for the quantification of lung parenchymal mechanical properties is an ongoing and active area of research. However, its implementation has been slow and challenging due to the inherently poor ^1H MR signal properties of the lung itself including a decrease in physical density compared to solid organs and the effect of susceptibility induced signal losses (22-24). Researchers have investigated the use of contrast agents like hyperpolarized helium to address the decreased signal-to-noise ratio of lung tissue with

promising results (25,26). However, this approach has its limitations, including the need for dedicated expensive hardware required to perform multinuclear (i.e. non ^1H) MR imaging and more recently the global supply constraints associated with ^3He (27,28). Although reported animal ^1H MRE experiments have demonstrated initial feasibility, within the context of human lung MRE these studies are not applicable due to the fact that these studies involved using an invasive needle shear driver in direct contact with the lungs post expiration (29). In this study we hypothesized that shear waves can be induced, visualized and therefore that the stiffness of lung parenchyma can be quantitated in a large animal with a non-invasive driver and that the changes in shear stiffness either due to physiological or pathological changes can be monitored with ^1H MRE. The purpose of this work was to test this hypothesis in an in situ porcine model with a noninvasive mechanical driver placed on the chest wall and to test the ability of this technique to measure the stiffness of the lung parenchyma as a function of airway opening pressure [P_{ao}]

Methods

Experimental setup

A total of ten adult male pigs (average weight 42 kg) were imaged in accordance with our institutional animal use and care committee guidelines. All ten animals were recruited from a larger study designed to quantify the time course of the elastic properties of myocardial infarcts that were induced by the occlusion of circumflex coronary artery. Before imaging for our study, all animals were euthanized by administration of a solution of sodium pentobarbital, isopropyl alcohol, and propylene glycol (Sleepaway®, Fort Dodge, Iowa) so as to eliminate artifacts arising from cardiac and respiratory motion as well as ensuring that a constant airway opening pressure and lung volume could be maintained. To minimize the effects of post expiration changes in lung parenchymal properties, all data were obtained within an hour after the death of the animals.

All the experiments were performed with a 1.5-T whole-body scanner (Signa EXCITE 14.0, GE Healthcare, Milwaukee, Wisconsin). The animals were positioned in a supine position in a custom-made cradle within the scanner bore as shown schematically in figure 1a. An air line was introduced into the trachea of the pig to enable controlled inflation (and deflation) of both the lungs. The air line was continuous with a pressure sensor (Freescan Semiconductor, Austin, Texas), located outside the scanner room and was connected to the in-room medical air source, thereby enabling the inflation (or deflation) of the lungs to any desired airway opening pressure. For this study, the respiratory system was inflated to four different pressures ($P_{\text{ao}} = 5, 10, 15$ and $20 \text{ cm H}_2\text{O}$) and the pressure values maintained for a typical experiment are shown in figure 2a.

Magnetic Resonance Elastography

MRE was performed at the four airway pressure values using a non invasive pressure-activated passive drum driver placed on the anterior body wall of the pig as shown in figure 1. The passive driver was connected to an active driver engine that creates the required vibrations within the animal through a connecting tube between the two. Longitudinal vibrations transmitted to lung tissue from the passive driver undergo mode conversion, generating shear waves within the lung that are imaged using the MRE pulse sequence. In this particular study, continuous vibrations at 100 Hz were applied.

Four coronal slices that included both the lungs within each slice were acquired using a modified spin echo based MRE pulse sequence schematically shown in figure 2b. A bipolar motion encoding gradient pair (10 ms duration for the motion of 100 Hz) used in a conventional MRE pulse sequence was split into two unipolar gradient lobes (of 5 ms

duration each) and were placed one on each side of the 180° refocusing pulse to reduce the echo time (TE). In this particular work, the MEG lobes were placed on the slice selection gradient to sensitize the motion in the anterior-posterior direction. Changing the temporal relationship between the MEG and the motion, four temporal images (phase offsets) spaced equally over the period of wave motion were acquired. Other typical imaging parameters included field of view (FOV) = 34 cm, acquisition matrix = 128×64, frequency-encoding direction = superior-inferior, repetition time/echo time (TR/TE) = 200/16 ms, gradient amplitude = 4mT/m and slice thickness = 10 mm.

Data Analysis

Shear wave induced displacement images acquired with the MRE pulse sequence were processed using the local frequency estimation algorithm (LFE) with spatio-temporal directional filters to calculate shear stiffness maps of the lungs (20,30). Essentially 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 wave speed of the propagating shear waves. ρ is the density of the tissue of interest and the inversion algorithm assumes the density of the tissue to be 1000 kg/m³. While this is a good assumption for most of the soft tissues, it is not the case within the lung since the density of the lungs is less than this value. Thus, values of shear stiffness that were not corrected for this density difference were denoted as effective stiffnesses ($\mu_{\text{effective}}$). Preprocessing of the data involved phase unwrapping to remove the aliased phase information and band pass filtering (with cutoffs of 5 – 50 waves/FOV) to remove the low spatial frequency longitudinal waves and high frequency noise. $\mu_{\text{effective}}$ values were estimated for the four slices in all the ten animals and mean values within the lung regions (segmented using thresholding) with visually detectable wave amplitudes were calculated and compared for the different airway pressures.

Lung Density Correction

The density of air-filled lungs is far less than that of water and other soft tissues (can range from 80 kg/m³ to 500 kg/m³ (31,32)) and varies with respiratory system pressure. Since tissue density affects shear wave propagation, it needs to be incorporated into the elastogram calculation thereby providing a more accurate estimate of shear stiffness. To achieve this, density values were approximated by measuring the mean signal intensity of the lung parenchyma at each P_{ao} and calibrating these values to the previously reported density value of 240 kg/m³ for a trans-pulmonary pressure (P_{tp}) of 5 cm H₂O (31). P_{tp} values defined as the difference between P_{ao} and lung surface or pleural pressure (P_{pl}) were estimated from the P_{ao} values by assuming normal chest wall recoil properties. Specifically, it was assumed that P_{pl} increased from -5 cm H₂O at end expiration to + 10 cm H₂O at maximal lung inflation. To validate our density calculation approach, the estimated density values were compared to the density value obtained at a different pressure from previously published studies (190 kg/m³ for 15 cm H₂O P_{tp} , (31)). Two different values of density corrected stiffnesses were obtained based on the density correction values applied that included: 1) density correction values obtained from each individual animal ($\mu_{\text{dens-corr,indiv}}$) and 2) mean density correction value averaged over all ten animals ($\mu_{\text{dens-corr,mean}}$). Stiffness values based on both density correction methods were compared for all ten animals as a function of airway pressure.

To compare the mean value of stiffnesses for the different airway pressure groups, analysis of variance (ANOVA) was performed against the null hypothesis that there is no difference in their mean as a function of P_{ao} with a significance (α) value of 0.01 using the software package JMP (JMP 8.0, Cary, NC).

Results

Effective Stiffness

Figure 3 is an example of typical wave propagation patterns observed in situ. Figures 3(a)-(d) show the magnitude images of a particular slice at airway pressures of 5 cm H₂O, 10 cm H₂O, 15 cm H₂O and 20 cm H₂O respectively. A positive relationship between P_{ao} and lung volume is observed. In addition, the signal intensity of lung parenchyma is significantly lower than that of the surrounding tissues and decreases with the increasing airway pressures due (mainly) to the reduced proton density (i.e. increased air volume and constant tissue mass). Even though the magnitude signal within the lungs is low, coherent phase information with quantifiable shear wave amplitudes are observable in all cases. Figures 3(e)-(h) show the displacement (in micrometers) of the segmented lung tissue obtained from their respective phase contrast images for the four pressure values. This displacement is in the through plane direction with the shear waves propagating medially from the lateral chest wall. A visible increase in shear wavelength with increasing pressure is observed and is indicated by the arrows. Figures 3(i)-(l) are the effective stiffness maps (in kPa) as obtained from the LFE algorithm for the different airway opening pressures, overlaid on the magnitude images shown in the top row. From these data it is evident that the stiffness values increase with the increase in the P_{ao} .

Figure 4 is a plot of mean effective stiffness value of the four slices for all the ten animals versus inflation pressure and demonstrates that increasing airway pressure increases effective parenchymal stiffness. Even though it is observed that the variance of $\mu_{\text{effective}}$ increases as P_{ao} increases, the positive correlation between the two parameters is evident. These values are listed in table 1. Statistically, one-way ANOVA of this data provided an F ratio of 24.80 and a p-value of 7.037×10^{-9} underlining the strong correlation of $\mu_{\text{effective}}$ with the P_{ao} .

Lung Density Estimation

Figure 5(a) shows the values of the densities approximated for the ten animals based on the magnitude signal values obtained from the MRE data. Since relative density values were calibrated based on the magnitude signal intensity at 5 cm H₂O airway pressure, all density estimates at this pressure have the value of 240 kg/m³. It can be seen that as P_{ao} increases the estimated densities decrease. Even though there is variability between animals, the general negative trend is maintained in all, indicating that this method of density approximation is valid. Figure 5(b) shows the mean density value for all the ten animals (blue line) and the values reported in the literature (red line), demonstrating a good agreement between these two datasets (31).

Density Corrected Stiffness

Figure 6 shows the density corrected shear stiffness values obtained by multiplying the estimated densities and the effective stiffness values. Figures 6a and 6b show the stiffness values obtained using the densities from the corresponding individual pigs ($\mu_{\text{dens-corr,indiv}}$) and using the mean density values of the ten pigs ($\mu_{\text{dens-corr,mean}}$) respectively. It can be seen that with the correction for density variation, stiffness values have decreased in comparison to the effective stiffness estimates, especially for higher pressure values. If the observed increase in the shear wavelength and hence the $\mu_{\text{effective}}$ with respect to P_{ao} was only due to the density change, density corrected shear stiffness values would be independent of P_{ao} . However, the presence of a strong positive correlation between the density corrected stiffness and P_{ao} is still evident. This relationship is more clearly illustrated in the mean values for the two sets of density corrected stiffnesses that are also shown in the figure. Comparing these two sets of stiffness estimates, it can be seen that though there were minor

differences between the individual data points, the mean values were very similar, as can be observed in table 1. This indicates that use of representative density values for the calculation of $\mu_{\text{dens-corr}}$ values might be sufficiently accurate. ANOVA was performed on both stiffness estimates versus P_{ao} , and were found to be statistically highly significant (with an α of 0.01). The statistical P values were calculated to be 7.63×10^{-4} and 1.34×10^{-4} for the $\mu_{\text{dens-corr,indiv}}$ and $\mu_{\text{dens-corr,mean}}$ respectively.

Discussion

A limitation of ^1H lung MRI is the low magnitude of the MR signal, which can clearly be seen in Figures 3(a) – (d). Despite the low signal-to-noise ratio of the MR magnitude data, the phase difference data into which the shear wave displacements are encoded demonstrate the presence of propagating shear waves (Figures 3(e) - (f)). However, the phase difference data was noisy due to the low magnitude signal, and hence the LFE algorithm (20), that is relatively insensitive to noise, was used for the calculation of μ . These data also demonstrate that shear wave amplitudes increase with increasing inflation pressure. This counter-intuitive behavior can be attributed to the improved contact pressure between the driver and the pig due to the increase in the volume of the lungs and the thorax at the higher pressures resulting in improved coupling of the vibration of the passive driver to the lungs. However, because the applied inversion algorithm calculates the local spatial frequency content, the increased vibration amplitude will not affect the stiffness calculation. Thus, despite these limitations these data demonstrate that in situ ^1H lung MRE is technically feasible.

A fit of both sets of density corrected stiffness data against P_{tp} (estimated from the P_{ao} , expressed in kPa) with a linear model provided the equations $0.8287 P_{\text{tp}} + 0.9245$ and $0.908 P_{\text{tp}} + 0.9144$ with R^2 values higher than 0.98 for $\mu_{\text{dens-corr,indiv}}$ and $\mu_{\text{dens-corr,mean}}$ respectively. Previously published values for lung shear modulus based on punch indentation testing, depending upon animal species, range between 0.5 - 0.9 times the transpulmonary pressure (11,31,33,34). It can be seen that the slopes of the MRE-derived shear stiffness estimates versus inflation pressure for all animals in this study are within the expected range. However the intercepts of these relationships differ from previously reported values (34), and this difference is probably due to the differences in experimental methods. In this work, dynamic shear waves are imaged at 100Hz, while previously reported values were derived from quasistatic punch indentation testing. The viscoelastic nature of lung results in a frequency dependent relationship between the propagating shear wave and the mechanical parameters, explaining the observed deviation. In a recent study using ultrasound based surface wave method, the dynamic shear wave speed for a 100 Hz wave in an ex vivo lung was estimated as 1.83 m/s at 4.1 cm H_2O P_{tp} , which agrees well with our results of 2.49 m/s at 5.7 cm H_2O P_{tp} (35). In addition, longitudinal wave speed values calculated from our data assuming a Poisson's ratio (ν) of 0.43 ranged from 7.13 m/s at P_{ao} of 5cm H_2O to 10.12 m/s at P_{ao} of 20 cm H_2O and were within the range of previously published values in the literature (11,31,36).

A challenge with the approach described in this work is to accurately estimate the physical density of the lung. Although more complex models exist as well as the fact that calculation of physical density of the lungs is an active field of research by itself (37-39), the simple density estimation technique using the MRE magnitude images provided a straight forward method to correct for both density differences between lung and solid organs as well as accounting for the difference in physical density due to inflation pressure. Ultimately, clinical implementation of this technique will require accurate calculation of lung density both globally and locally using other MR-based approaches.

The use of a longitudinal driver placed on the skin above the rib cage is an effective noninvasive method of generating shear waves within the lungs. A challenge of this technique is that the wave field generated within the lung is complex and includes both the longitudinal waves and the shear waves of interest propagating in a multitude of directions. This implies that the wave field cannot be fully characterized by acquiring and analyzing data in individual 2D slices with displacements encoded along only one of the three possible orthogonal directions (frequency, phase or slice encoding) as was performed in this study. The 2D shear wave analysis used in this work makes the assumptions that only shear waves are present in the data and that they are propagating wholly within the selected imaging slice. Any deviation from these assumptions results in bias in the shear stiffness values. However, displacement information at the different pressures was acquired only in a single direction of motion in this study due to the time constraint of one-hour post-expiration window and the use of a classic spin-echo based MRE sequence that necessitates a relatively long repetition time.

While one direction of motion is theoretically sufficient under certain assumptions (such as isotropy and local homogeneity), these include the assumptions that the material is incompressible or that the longitudinal waves have been removed from the data in some way. The best way to remove the effect of longitudinal waves is to take the curl of the data, but this would require full 3D data with all 3 directions of motion. With our data, spatial band pass filtering is the only viable alternative. The relatively low value of Poisson's ratio for lung (0.43, (11)) means that the ratio of longitudinal to shear wave speeds ($\sqrt{2(1-\nu)/(1-2\nu)}=2.85$) is significantly lower than that for solid organs. This convergence of wave speeds makes separation of shear and longitudinal waves with band pass filtering difficult. However, with the choice of the motion application direction (AP) and the imaging slice orientation (coronal) for this study, the longitudinal waves travel primarily orthogonal to the slice (through plane, thus having a lower in plane spatial frequency) and the shear waves travel latero-medially within the slice (with higher spatial frequency), allowing for reasonable isolation of these wave components based on spatial band pass filtering. The contribution of longitudinal waves cannot be completely eliminated with this method, resulting in a potential source of error leading to higher shear stiffness values. Additionally, any obliquity between the wave propagation direction and imaging slice orientation leads to bias in the estimation of shear wavelength and hence the shear stiffness. Further research acquiring 3D/3-axis displacement and perhaps multi-frequency data will help characterize the complex wave fields completely, reduce the experimental bias and improve the accuracy of the shear stiffness estimation.

The porous architecture of the lung parenchyma and the vibration of air present in the alveolar sacs during MRE can potentially affect the shear wave propagation within the lungs (40). Considering the difference in the microscopic nature of the alveolar sacs and the macroscopic scale of shear wave propagation, the contribution of poroelasticity was ignored in this work, potentially introducing another source of bias. Further, even though the experiments were performed as soon as the animals were euthanized, the presence of trapped air, atelectasis, blood clots and/or the post mortal changes could affect the results too. Finally, there is a potential that some of the lungs used in this study were not completely normal due to the fact that the host animals were all obtained after occlusion of one of the main coronary arteries and imaged several weeks thereafter, providing the potential for cardiopulmonary effects such as pulmonary hypertension to affect the estimates of shear modulus (41,42). Despite this, it is assumed that these effects are not significant for the purpose of this study. However, it will be beneficial to perform this study in normal healthy animals to ascertain absolute stiffness values of porcine lungs. Once normative values of

shear stiffness are determined, MRE of diseased pigs with suspected mechanical property modifications could be studied to assess the diagnostic potential of this technique.

Conclusions

The data presented in this work indicate that it is feasible to noninvasively obtain estimates of parenchymal shear moduli in an intact chest of animals whose lung size and volume approximates that of humans. While additional challenges are needed to be addressed including but not limited to acquisition times of the order of a breath hold (tens of seconds) and the reduction of flow and cardiac motion artifacts, the close agreement between P_{ao} and shear stiffness suggests that MRE has the potential to be a noninvasive in vivo method for assessment of parenchymal shear stiffness in humans. These data provide motivation for further experiments to develop and test the ability of MRE for the assessment of lung diseases in animal models and eventually in vivo human clinical applications.

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References

1. Stamenovic D. Micromechanical foundations of pulmonary elasticity. *Physiol Rev.* 1990; 70(4): 1117–1134. [PubMed: 2217556]
2. Wilson TA, Bachofen H. A model for mechanical structure of the alveolar duct. *J Appl Physiol.* 1982; 52(4):1064–1070. [PubMed: 7085408]
3. Suki B, Ito S, Stamenovic D, Lutchen KR, Ingenito EP. Biomechanics of the lung parenchyma: critical roles of collagen and mechanical forces. *J Appl Physiol.* 2005; 98(5):1892–1899. [PubMed: 15829722]
4. Faffe DS, Zin WA. Lung Parenchymal Mechanics in Health and Disease. *Physiol Rev.* 2009; 89(3): 759–775. [PubMed: 19584312]
5. Goldstein RH, Lucey EC, Franzblau C, Snider GL. Failure of mechanical properties to parallel changes in lung connective tissue composition in bleomycin-induced pulmonary fibrosis in hamsters. *Am Rev Respir Dis.* 1979; 120(1):67–73. [PubMed: 88916]
6. Ebihara T, Venkatesan N, Tanaka R, Ludwig MS. Changes in Extracellular Matrix and Tissue Viscoelasticity in Bleomycin-induced Lung Fibrosis. *Temporal Aspects. Am J Respir Crit Care Med.* 2000; 162(4):1569–1576. [PubMed: 11029378]
7. Salerno FG, Ludwig MS. Elastic moduli of excised constricted rat lungs. *J Appl Physiol.* 1999; 86(1):66–70. [PubMed: 9887114]
8. Kononov S, Brewer K, Sakai H, Cavalcante FS, Sabayanagam CR, Ingenito EP, Suki B. Roles of mechanical forces and collagen failure in the development of elastase-induced emphysema. *Am J Respir Crit Care Med.* 2001; 164(10 Pt 1):1920–1926. [PubMed: 11734447]
9. Ito S, Ingenito EP, Brewer KK, Black LD, Parameswaran H, Lutchen KR, Suki B. Mechanics, nonlinearity, and failure strength of lung tissue in a mouse model of emphysema: possible role of collagen remodeling. *J Appl Physiol.* 2005; 98(2):503–511. [PubMed: 15465889]
10. Lai-Fook SJ, Hyatt RE, Rodarte JR. Elastic constants of trapped lung parenchyma. *J Appl Physiol.* 1978; 44(6):853–858. [PubMed: 670008]
11. Lai-Fook SJ, Wilson TA, Hyatt RE, Rodarte JR. Elastic constants of inflated lobes of dog lungs. *J Appl Physiol.* 1976; 40(4):508–513. [PubMed: 931871]
12. Gibson GJ, Pride NB. Lung distensibility. The static pressure-volume curve of the lungs and its use in clinical assessment. *Br J Dis Chest.* 1976; 70(3):143–184. [PubMed: 791334]
13. Wells AU. High-resolution computed tomography in the diagnosis of diffuse lung disease: a clinical perspective. *Semin Respir Crit Care Med.* 2003; 24(4):347–356. [PubMed: 16088556]
14. Wells AU, Nicholson AG, Hansell DM, du Bois RM. Respiratory bronchiolitis-associated interstitial lung disease. *Semin Respir Crit Care Med.* 2003; 24(5):585–594. [PubMed: 16088575]

15. Simon BA, Christensen GE, Low DA, Reinhardt JM. Computed Tomography Studies of Lung Mechanics. *Proc Am Thorac Soc.* 2005; 2(6):517–521. [PubMed: 16352757]
16. Chen Q, Mai VM, Bankier AA, Napadow VJ, Gilbert RJ, Edelman RR. Ultrafast MR grid-tagging sequence for assessment of local mechanical properties of the lungs. *Magnetic Resonance in Medicine.* 2001; 45(1):24–28. [PubMed: 11146481]
17. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. *Science.* 1995; 269(5232):1854–1857. [PubMed: 7569924]
18. Asbach P, Klatt D, Hamhaber U, Braun J, Somasundaram R, Hamm B, Sack I. Assessment of liver viscoelasticity using multifrequency MR elastography. *Magn Reson Med.* 2008; 60(2):373–379. [PubMed: 18666132]
19. Mariappan YK, Glaser KJ, Ehman RL. Magnetic resonance elastography: a review. *Clin Anat.* 2010; 23(5):497–511. [PubMed: 20544947]
20. Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, Felmlee JP, Greenleaf JF, Ehman RL. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. *Med Image Anal.* 2001; 5(4):237–254. [PubMed: 11731304]
21. Van Houten EE, Miga MI, Weaver JB, Kennedy FE, Paulsen KD. Three-dimensional subzone-based reconstruction algorithm for MR elastography. *Magn Reson Med.* 2001; 45(5):827–837. [PubMed: 11323809]
22. Bergin CJ, Glover GH, Pauly JM. Lung parenchyma: magnetic susceptibility in MR imaging. *Radiology.* 1991; 180(3):845–848. [PubMed: 1871305]
23. Morris AH, Blatter DD, Case TA, Cutillo AG, Ailion DC, Durney CH, Johnson SA. A new nuclear magnetic resonance property of lung. *J Appl Physiol.* 1985; 58(3):759–762. [PubMed: 3884578]
24. Shioya S, Christman R, Ailion DC. An in vivo NMR imaging determination of multiexponential Hahn T2 of normal lung. *Magnetic Resonance in Medicine.* 1990; 16(1):49–56. [PubMed: 2255237]
25. Goss BC, McGee KP, Ehman EC, Manduca A, Ehman RL. Magnetic resonance elastography of the lung: technical feasibility. *Magnetic Resonance in Medicine.* 2006; 56(5):1060–1066. [PubMed: 17036283]
26. Maître, X.; Sinkus, R.; Santarelli, R.; Sarraçanie, M.; Dubuisson, R.; Boriassé, E.; Durand, E.; Darrasse, L.; Bittoun, J. In vivo lung elastography with hyperpolarized helium-3 MRI. *Proceedings 17th Scientific Meeting, International Society for Magnetic Resonance in Medicine; Honolulu.* 2009 April; p. 6
27. David K. DOE begins rationing helium-3. *Physics Today.* 2010; 63(6):22–25.
28. Cho A. Helium-3 Shortage Could Put Freeze On Low-Temperature Research. *Science.* 2009; 326(5954):778–779. [PubMed: 19892947]
29. McGee KP, Hubmayr RD, Levin D, Ehman RL. Feasibility of quantifying the mechanical properties of lung parenchyma in a small-animal model using (1)H magnetic resonance elastography (MRE). *J Magn Reson Imaging.* 2009; 29(4):838–845. [PubMed: 19306407]
30. Manduca A, Lake DS, Kruse SA, Ehman RL. Spatio-temporal directional filtering for improved inversion of MR elastography images. *Medical Image Analysis.* 2003; 7(4):465–473. [PubMed: 14561551]
31. Jahed M, Lai-Fook SJ. Stress wave velocity measured in intact pig lungs with cross-spectral analysis. *J Appl Physiol.* 1994; 76(2):565–571. [PubMed: 8175564]
32. Rice DA. Sound speed in pulmonary parenchyma. *J Appl Physiol.* 1983; 54(1):304–308. [PubMed: 6826415]
33. Ganesan S, Man CS, Lai-Fook SJ. Generation and detection of lung stress waves from the chest surface. *Respir Physiol.* 1997; 110(1):19–32. [PubMed: 9361149]
34. Hajji MA, Wilson TA, Lai-Fook SJ. Improved measurements of shear modulus and pleural membrane tension of the lung. *J Appl Physiol.* 1979; 47(1):175–181. [PubMed: 468657]
35. Zhang X, Qiang B, Hubmayr RD, Urban MW, Kinnick R, Greenleaf JF. Noninvasive ultrasound image guided surface wave method for measuring the wave speed and estimating the elasticity of lungs: A feasibility study. *Ultrasonics.* 2010

36. Butler JP, Lehr JL, Drazen JM. Longitudinal elastic wave propagation in pulmonary parenchyma. *J Appl Physiol.* 1987; 62(4):1349–1355. [PubMed: 3597210]
37. Theilmann RJ, Arai TJ, Samiee A, Dubowitz DJ, Hopkins SR, Buxton RB, Prisk GK. Quantitative MRI measurement of lung density must account for the change in T(2) (*) with lung inflation. *J Magn Reson Imaging.* 2009; 30(3):527–534. [PubMed: 19630079]
38. Togao O, Tsuji R, Ohno Y, Dimitrov I, Takahashi M. Ultrashort echo time (UTE) MRI of the lung: Assessment of tissue density in the lung parenchyma. *Magnetic Resonance in Medicine.* 2010; 64(5):1491–1498. [PubMed: 20574988]
39. Hachenberg T, Lundquist H, Tokics L, Brismar B, Hedenstierna G. Analysis of lung density by computed tomography before and during general anaesthesia. *Acta Anaesthesiologica Scandinavica.* 1993; 37(6):549–555. [PubMed: 8213018]
40. Perrinez PR, Kennedy FE, Van Houten EE, Weaver JB, Paulsen KD. Magnetic resonance poroelastography: an algorithm for estimating the mechanical properties of fluid-saturated soft tissues. *IEEE Trans Med Imaging.* 2010; 29(3):746–755. [PubMed: 20199912]
41. Hales CA, Kazemi H. Small-Airways Function in Myocardial Infarction. *New England Journal of Medicine.* 1974; 290(14):761–765. [PubMed: 4815222]
42. Gray BA, Hyde RW, Hodges M, Yu PN. Alterations in lung volume and pulmonary function in relation to hemodynamic changes in acute myocardial infarction. *Circulation.* 1979; 59(3):551–559. [PubMed: 761336]

Figure 1.

(a) Schematic diagram of the experimental setup showing the positioning of the pig within the magnet bore, the air line and the pressure activated driver system. (b) Zoomed in image of the passive driver (indicated by the arrow) positioned on the anterior chest wall of the pig. The connecting tube linking the passive driver and the active driver can also be seen.

Figure 2.

(a) A plot of the P_{ao} values against time during a typical MRE experiment, indicating that the pressure values were stable during the experiments. (b) Spin echo based modified MRE pulse sequence diagram. The motion encoding gradient lobes (of 5ms duration) are indicated by the arrows. Schematic of the applied motion is also shown.

Figure 3. MRE results. (a-d) Magnitude images, (e-h) a single phase offset image, and (i-l) elastograms overlaid on the magnitude images, for the four airway opening pressures. The shear wavelength increases with the P_{ao} and is indicated with the arrows. Also, the increase in the effective stiffness with the increasing pressures is easily evident in the bottom row.

Figure 4.

Effective stiffness values calculated with the local frequency estimation algorithm for the ten animals are shown in blue circles and the mean values for the four P_{a0} are shown by the red line. The effective stiffness values are directly proportional to the P_{a0} values.

Figure 5.

(a) Plot of individual density values against P_{ao} , density of the lungs is inversely proportional to P_{ao} . (b) Mean density values for the ten animals are shown in blue, and the slope of this line is similar to the literature data (red line).

Figure 6.

Density corrected stiffness values calculated using the (a) density values obtained from the corresponding pigs and (b) mean density value for the ten animals. Even though there are differences in the individual data points, both the stiffnesses are strongly correlated with P_{ao} as seen from the plot of the mean values shown in red lines.

Tabulation 1

Shear stiffness Vs Airway opening pressures

Stiffness (kPa) Mean ($\pm$ std error)	Airway Opening pressure (P_{ao}) cm H ₂ O				ANOVA	
	5 cm	10 cm	15 cm	20 cm	F ratio	P value
$\mu_{\text{effective}}$	6.18 (0.36)	7.81 (0.48)	10.41 (0.66)	12.55 (0.70)	24.80	7.04e-9
$\mu_{\text{dens_corr,indiv}}$	1.48 (0.09)	1.68 (0.10)	2.05 (0.14)	2.23 (0.17)	7.039	7.63e-4
$\mu_{\text{dens_corr,mean}}$	1.48 (0.09)	1.69 (0.1)	2.05 (0.13)	2.22 (0.12)	9.053	1.34e-4