Magnetic Resonance Elastography of Human Lung Parenchyma: Technical development, theoretical modeling and in vivo validation

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Introduction: Lung function and structure is determined by the dynamic balance between externally applied forces (prestress) and both parenchymal and surface film forces. In lung diseases, it is appreciated that perturbation of this balance is associated with disease type and severity [1]. Magnetic Resonance Elastography (MRE) is a phase-contrast MRI-based elasticity imaging technique that can quantify the shear moduli of soft tissues by imaging externally induced shear waves with synchronized bipolar motion-encoding gradient (MEG) waveforms [2]. While MRE has the potential to provide new insights into several lung diseases, the implementation of ^{1}H-based lung MRE has been slow and challenging, primarily due to low proton spin density and susceptibility induced signal losses resulting from the ultrashort T_2* of lung parenchyma (~ 1- 2 ms). The purpose of this work was to develop MRE for in vivo assessment of human lung parenchyma and to asses the ability of this method to measure the change in stiffness of the lung parenchyma at different respiration states.

Methods: **Pulse Sequence Development:** A spin echo ^{1}H Lung MRE pulse sequence was developed to provide both a short echo time (TE) to detect the pulmonary MR signal and enough motion sensitivity necessary to image propagating shear waves. The TE was reduced by first implementing fractional motion encoding [3] followed by splitting of the bipolar MEG waveform such that individual lobes were placed either side of the 180° RF pulse. With this configuration the unipolar MEG lobe after the 180° pulse ensures zero phase accumulation for static tissue as well as spoils magnetization created by the 180° pulse thereby allowing conventional crusher gradients flanking the 180° pulse to be removed. The modified pulse sequence is shown in Figure 1a. These modifications allowed the TE to be reduced from 43.6 ms (assuming a 20-ms bipolar MEG to encode 50-Hz motion) to 9.4 ms using two 2-ms MEG lobes.

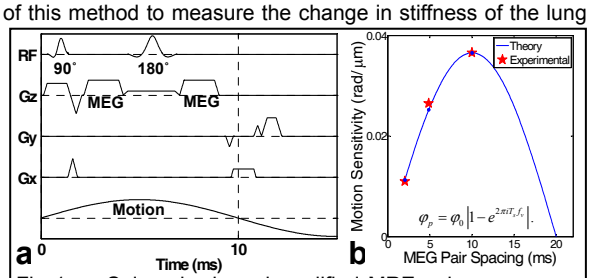

Fig 1: a. Spin echo based modified MRE pulse sequence with a TE of 9.4 ms. b. Motion sensitivity of split MEG with respect to MEG lobe spacing, the equation is provided.

Theory: The effect of these modifications on the motion sensitivity of the lung MRE pulse sequence was quantified by calculating the net motion sensitivity of pulse sequence Φ_p which is dependent upon the spacing of the two lobes and is given by $\varphi_p = \varphi_0 \left|1 - e^{2\pi i T_s f_v}\right|$, where Φ_o is the motion sensitivity of 1 trapezoidal MEG lobe (derived from frequency domain equations, in rad/μm, for example), T_s is the spacing between the MEG lobes and f_v is the frequency of vibration. The motion sensitivity is plotted as a function of T_s for a 50-Hz vibration in Figure 1b.

Experiments: All the experiments were conducted on a 1.5-T whole-body scanner (Signa Excite, GE Healthcare, Milwaukee, WI). Pulse sequence testing and experimental validation of the theory was performed on a cylindrical soft gelatin phantom where 50-Hz continuous vibrations were applied using a pressure-activated driver system and shear wave data were acquired with the modified pulse sequence using 2-ms MEG lobes. Wave data were obtained using three MEG lobe spacings: 2 ms (the traditional bipolar gradient spacing with both lobes before the refocusing pulse), 10 ms (the two lobes were separated by half the period of the motion) and 4.856 ms (the smallest possible spacing for the split MEG configuration with the current RF pulse constraints). The mean phase amplitude for each case was recorded and was normalized to the model using the bipolar gradient data. For in vivo human experiments, 10 healthy volunteers were recruited and were imaged according to our institutional review board guidelines. MRE data were obtained at two different levels of respiration, at residual volume (RV) and total lung capacity (TLC). Continuous 50-Hz waves were introduced into the lungs with the same driver system, with the passive driver placed on the chest wall anterior to the right lung. Imaging was performed with a custom-built 8-channel surface coil wrapped around the upper abdomen. Axial MRE acquisitions with 2-ms superior-inferior MEG lobes separated by 5.050 ms were used with the following imaging parameters: FOV=35 cm, 128x64 acquisition matrix, TR/TE = 200/9.4 ms, ±62.5 kHz bandwidth, 5 10-mm thick slices, and 4 time offsets. This resulted in a 21-sec breathhold for a singe phase offset. From the shear wave data, effective stiffness values were calculated using the local frequency estimation algorithm after directional filtering [4]. These data were corrected for lung density variations using MR volume data acquired at the two respiration states calibrated to 330 kg/m^3 density at RV. Density-corrected stiffness values were calculated as the product of relative densities and effective stiffnesses. The difference between RV and TLC stiffnesses was assessed with ANOVA using the software package JMP (JMP 8.0, Cary, NC).

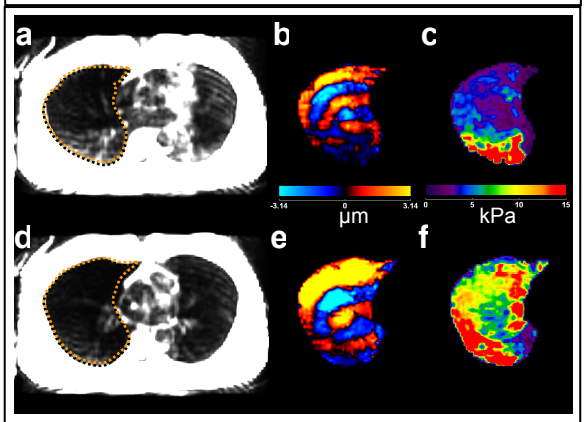

Figure 2: Human in vivo MRE data at residual volume (top) and total lung capacity (bottom). The shear wavelength is longer and effective stiffness is higher at TLC.

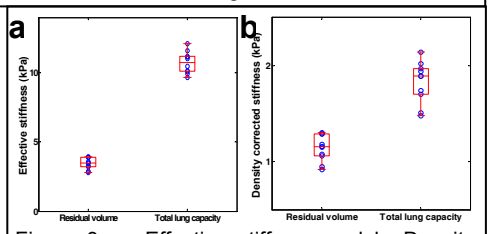

Figure 3: a. Effective stiffness and b. Density corrected stiffness of lungs were significantly higher at TLC than those at RV.

Results: Figure 1b shows the experimental motion sensitivity values obtained from the phantom experiments which agree well with the theoretical model. Figure 2 shows example lung MRE data from one volunteer, where the top and bottom rows show the data at RV and TLC, respectively. Figures 2b and 2e show wave images within the segmented right lung depicting the shear wave propagation. The wavelength is distinctively longer at TLC. Corresponding effective stiffness values are shown in 2c and 2f, and the stiffness at TLC is higher than at RV. Figures 3a and 3b show the effective stiffnesses and the density-corrected stiffnesses for all of the subjects and the values at TLC were higher for each subject than their corresponding RV stiffnesses. The mean values and the statistical analysis for the 10 volunteers are shown in Table 1.The difference in the stiffness values were statistically significant ($p < 0.0001$).

Table 1	RV	TLC	P value
μ_{eff} (kPa)	3.5	10.8	1.0e-15
μ_{dens_corr} (kPa)	1.1	1.8	9.8e-8

Conclusion: These data demonstrate that ^{1}H-based MRE is feasible within normal human subjects, providing a new potentially powerful in vivo tool for spatially resolving the elastic properties of lung parenchyma in patients with lung disease. Statistically significant differences in parenchymal stiffness at the TLC versus RV indicate that the change in shear stiffness of the lungs can be quantitated with this technique. Ongoing work includes increasing the clinical utility of the technique to allow full data acquisition of both lungs within normal breath-hold times.

Acknowledgements: NIH Grant EB07593, NIH EB 001981. **References:** 1. Suki et al., J Appl Physiol 98(5) : 1892-1899, 2005. 2. Muthupillai et al., *Science* 269: 1854-1857, 1995. 3. Rump et al., MRM 57(2) 388-395, 2007. 4. Manduca A et al., *Med Imag Anal.* 5: 237-254, 2001.