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MR Elastography as a method for the assessment of myocardial stiffness: Comparison with an established pressure-volume model in a left ventricular model of the heart

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Abstract

Magnetic resonance elastography (MRE) measurements of shear stiffness (μ) in a spherical phantom experiencing both static and cyclic pressure variations were compared to those derived from an established pressure-volume (P-V) based model. A spherical phantom was constructed using a silicone rubber composite of 10 cm inner diameter and 1.3 cm thickness. A gradient echo MRE sequence was used to determine μ within the phantom at static and cyclic pressures ranging from 55 to 90 mmHg. Average values of μ using MRE were obtained within a region of interest and were compared to the P-V derived estimates. Under both static and cyclic pressure conditions, the P-V and MRE-based estimates of μ ranged from 98.2 to 155.1 kPa and 96.2 to 150.8 kPa, respectively. Correlation coefficients (R^2) of 0.98 and 0.97 between the P-V and MRE shear modulus measurements were obtained under static and cyclic pressure conditions, respectively. For both static and cyclic pressures, MRE-based measures of μ agree with those derived from a P-V model suggesting that MRE can be used as a new, non-invasive method of assessing μ in sphere-like fluid filled organs such as the heart.

Keywords

MRE; P-V relationships; gated MRE sequences; Cardiac MRE

Introduction

Up to 40% of patients with heart failure (HF) have normal systolic function and ejection fraction (1). In these cases, HF is thought to be caused by abnormal diastolic function (2), due in large part to increased left ventricular (LV) chamber stiffness (3) as a result of increased myocardial stiffness.

The current method for assessing myocardial stiffness is to measure the pressure-volume (P-V) relationship of the LV across the cardiac cycle (4–6) and then to calculate P-V-based metrics whose relationship to specific disease states is known. Changes in LV compliance (dV/dP), chamber stiffness (dP/dV) and wall stiffness obtained from P-V curves have been used for identifying cardiac diseases such as coronary artery disease, angina pectoris and acute myocardial infarction (4–6), and are considered the reference standard for diagnosing

diastolic dysfunction (3). However, a distinct disadvantage of this technique is the invasive method by which the P-V data is obtained (5,7), i.e. the insertion of a pressure catheter through the femoral artery into the LV. As a consequence, the widespread application of this established method for the diagnosis of HF has been hampered. What is needed is a non-invasive, direct in vivo measurement of myocardial stiffness, particularly in those HF cases with normal ejection fraction.

MR elastography (MRE; (8–15)) is a noninvasive technique capable of measuring the shear stiffness of soft tissues. MRE produces images of tissue response to propagating cyclic shear waves in the acoustic frequency range using phase-contrast MR techniques. External vibrations are introduced into the tissue in order to produce propagating shear waves which are synchronized with motion-encoding gradients (MEG) in the imaging sequence that encode the motion in the phase of the MR images. These wave images are then processed to obtain shear stiffness maps of the tissue under investigation.

While MRE has been successfully applied to static organs such as liver (11), breast (10,12), and brain (9), calculation of MRE-derived shear stiffness maps in tissue undergoing complex motion is yet to be demonstrated. Further, even if MRE-derived measures can be obtained under these conditions, their relationship to current, accepted (i.e. P-V based) measures is unknown. Therefore, the aim of this study is to evaluate a new MRI based method of calculating the shear modulus under both static and cyclic pressure conditions by means of comparison with a previously validated P-V based method. The hypothesis of this work is that MRE-derived measures of shear stiffness can be obtained under both static and cyclic pressure conditions and that these values, averaged over the volume of interest, correlate with those derived from an established and previously validated P-V based model.

Theory

Spherical Shell Inversion

Existing MRE methods for calculating shear modulus (μ) assume that the shear wave is propagating in a uniform, infinite medium (16). However, this assumption is not valid in the heart - a fluid-filled chamber with comparatively thin walls of finite volume. In order to account for these differences, a new model for estimating μ that includes both boundary effects and geometric considerations similar to those encountered within the heart is required. A model that approximates a propagating shear wave within the LV is that of a propagating wave front in a thin spherical shell. The equations of motion in an isotropic shell can be derived by applying Hamilton's variational principle (17) assuming small-amplitude midsurface deflections and nontorsional axisymmetric motion (i.e. no through-plane motion). Expressed in the polar coordinate system, the equation of flexural motion in the shell is described by Eq. [1], where a = shell inner radius, u = circumferential component of displacement, w = radial component of displacement, c_p = flexural plate speed ($c_p^2 = E/(1-\nu^2)\rho$), E = Young's modulus, ρ = density (assumed to be 1 g/cm³), ν = Poisson's ratio, $\beta^2 = h^2/12a^2$, h = thickness of the shell, and p_a = applied load (17,18).

$$\begin{aligned}
& \beta^2 \frac{\partial^3 u}{\partial \theta^3} + 2\beta^2 \cot \theta \frac{\partial^2 u}{\partial \theta^2} \\
& - [(1 + \nu)(1 + \beta^2) + \beta^2 \cot^2 \theta] \frac{\partial u}{\partial \theta} + \cot \theta (2 - \nu + \cot^2 \theta) \beta^2 - (1 + \nu) u \\
& - \beta^2 \frac{\partial^2 w}{\partial \theta^4} \\
& - 2\beta^2 \cot \theta \frac{\partial^3 w}{\partial \theta^3} \\
& + \beta^2 (1 + \nu + \cot^2 \theta) \frac{\partial^2 w}{\partial \theta^2} \\
& - \beta^2 \cot \theta (2 - \nu + \cot^2 \theta) \frac{\partial w}{\partial \theta} \\
& - 2(1 + \nu) w \\
& - \frac{a^2 \ddot{w}}{c_p^2} = - p_a \frac{(1 - \nu^2) a^2}{E h}
\end{aligned} \tag{1}$$

Because MRE is a phase-contrast technique that can encode displacements, MRE can be used to derive the displacement field (u, w) that can be used as the input into Eq. [1] to calculate E as long as the various derivatives of u and w are well behaved and p_a is known or can be approximated. The shear modulus of the material can then be calculated according to the relationship $\mu = E/2(1+\nu)$. This model is appropriate for small-amplitude vibrations with the wall volume remaining constant during the vibrations.

P-V-Based Assessment of Shear Stiffness

The current standard method for measuring μ within the heart is to obtain P-V curves of the LV throughout the cardiac cycle, which can then be used to derive a single, global estimate of μ within the myocardium calculated over the cardiac cycle. This model is derived based on the assumptions that 1) the LV geometry is spherical, and 2) the LV wall is incompressible (i.e., the wall volume remains constant throughout the cardiac cycle indicating the Poisson's ratio is 0.5 (19)) (4). Using the above assumptions, Young's modulus E can be derived and is represented by the following relationship:

$$E = 3\sigma_m \left[\left(1 + \left(\frac{V_w}{V} \right) \left(\frac{a^2}{a^2 + b^2} \right) \right) \left(1 + \left(\frac{V}{P} \right) \left(\frac{dP}{dV} \right) \right) - \left(\left(\frac{b^2}{a^2 + b^2} \right) \left(\frac{b^3 - a^3}{2R^3 + b^3} \right) \right) \right] \tag{2}$$

$$\sigma_m = P \left(\frac{V}{V_w} \right) \left(1 + \frac{b^3}{2R^3} \right) \tag{3}$$

where σ_m = stress at the mid-wall, V = volume of the chamber (i.e., LV cavity), V_w = volume of the wall (remains constant as the material is assumed to be incompressible), P =

internal cavity pressure (i.e., chamber pressure), a = inner radius of the shell, b = outer radius of the shell, $R = (a+b)/2$ (i.e., mid-wall radius) and dP/dV = chamber stiffness (4). While Eq. 2 is a simplified model for the heart, it is appropriate for any phantom setup with spherical geometry and nearly incompressible material.

Equation 2 states that if dP/dV and the parameters that define the geometry of the ventricle are known, then E and hence μ can be obtained. In the experiments described in this work, dP/dV was calculated from the slope of the least-squares straight line fit to data of P at various cavity volumes V , where P is the difference between the line pressure (from the pressure transducer) and atmospheric pressure. V and V_w are the inner volume of the sphere and volume of the wall respectively. V and V_w were calculated from the inner radius and outer radius of the magnitude images obtained from the MRE data acquired for the spherical shell inversion algorithm. The Young's modulus calculated from this method was converted to the shear stiffness μ using $\mu = E/2(1+\nu)$.

Methods

Experiment Setup

To model the LV, a hollow spherical phantom was constructed with silicone rubber (Wirosil, BEGO, Germany), with an inner diameter of 10 cm and thickness of 1.3 cm and ν of 0.45 (obtained from material testing). Figure 1 shows the experimental setup, which included the spherical phantom, pressure transducer, pulse plythsmograph, computer-controlled pump and electromechanical driver. A water-filled balloon was inserted into the phantom and connected to a computer-controlled pump. A pressure transducer (PX26-030GV, Omega Engineering, Inc., Stamford, CT) was connected along the tubing to measure the pressure in the phantom, and the plythsmograph was used to trigger the pulse sequence. An electromechanical driver connected to a function generator (33120A, Agilent Technologies Inc., Santa Clara, CA) was used to generate mechanical waves within the phantom. The MRE pulse sequence provided the trigger pulse to the function generator to synchronize the waves to the imaging sequence.

Image Acquisition

Cyclic Pressure Acquisition—All imaging was performed on a 1.5-Tesla MRI scanner (Signa, GE Health Care, Milwaukee, WI). Data acquisition was performed using the GRE MRE pulse sequence shown in figure 2. The pulse sequence is a conventional gradient moment nulled GRE sequence (to suppress flow and motion artifacts) with the addition of gradient moment nulled motion-encoding gradients that are synchronized to the source of the mechanical excitation.

Cyclic pressure changes within the phantom were induced by programming the computer-controlled pump with a sinusoidal waveform at a frequency of 1Hz (60 bpm). The maximum pressure within the phantom was then varied from 55 to 90 mmHg.

By gating the MRE sequence to the detected peak of the pulse plythsmograph waveform and initiating data acquisition after a predetermined delay, data were acquired at different pressure values by keeping the frequency of the pressure waveform constant and varying its maximum amplitude. Chemical presaturation was also used to saturate the water signal from within the phantom to reduce any residual flow-related artifacts (chemical shift of Wirosil is 290 Hz at 1.5 T). Imaging parameters included TR = 1000 ms, TE = 15.9 ms, flip angle = 30°, slice thickness = 10 mm, acquisition matrix = 256×64, FOV = 14 cm, excitation frequency = 200 Hz, 4 MRE phase offsets, and a motion-encoding gradient of 200 Hz (5 ms) was applied separately in the x and y directions to sample the in-plane motion.

During MRE acquisition, the waveform from the pressure transducer was digitized at a sampling rate of 1 kHz. Because the delay from the peak of the pressure waveform to initiation of imaging was known, the actual pressure inside the phantom was obtained from the measured pressure waveform using the value at the same delay time from the peak of the waveform.

Small-amplitude shear waves were introduced into the phantom by means of a small electromechanical tapper affixed to the top of the phantom. This device provided the applied load (p_a) and was modeled in Eq. 1 as a Gaussian function with a standard deviation of 0.005 radians and pressure amplitude of 10^5 Pa. The phantom at a particular phase of the pressure cycle was modeled as a static object undergoing small-amplitude vibrations from the tapper, which do not change the wall volume. The in-plane Cartesian components of motion measured using the GRE MRE pulse sequence were converted to circumferential and radial displacements by means of a polar co-ordinate transformation. The through-plane component of motion was neglected because Eq.1 assumes no torsional motion. To ensure that the derivatives in Eq. [1] were well behaved, especially for higher order derivatives, Savitzky-Golay filters (20) were applied which fit a least squares polynomial to the data.

Static Pressure Acquisition—MRE data were also acquired at fixed inflation pressures equal to the peak pressures of the dynamic pressure experiment: 55, 66, 70, 75, 80, and 87 mmHg. This was performed to quantitate any differences between shear stiffness values derived from the cyclic and static pressure conditions. The imaging parameters for the static pressure acquisitions were the same as those for the cyclic pressure acquisitions except that the TR was set to 150 ms.

Estimation of phantom volume—P-V based estimates of μ required calculation of the volume of the spherical phantom. In this experiment, V was calculated based on an estimate of the radius derived from a single-slice MR image through the center of the phantom at each pressure level. In order to verify the accuracy of this calculation, 3D GRE imaging was performed at three pressures; atmospheric, minimum (55 mmHg) and maximum (88 mmHg) to determine the percentage error in the volume estimation of the chamber and wall when compared to the single-slice estimate. The acquisition parameters included TR = 12.6 ms, TE = 2.7 ms, slice thickness = 2 mm, flip angle = 30°, acquisition matrix = 256×192, and FOV = 14 cm.

Statistical Analysis

Equations 2 and 3 predict that shear stiffness (μ) is linearly proportional to pressure (P). To determine the agreement between P and μ for both the P-V and MRE based approximations for μ , a least squares linear regression fit of μ to P was performed for the P-V and MRE-derived estimates of μ for the range of pressures sampled under both cyclic and static conditions.

Results

Before Eq. [1] can be used to estimate μ from MRE derived displacement fields, these displacements must be first converted from Cartesian to radial and circumferential displacement fields. Figure 3 shows an example of a radial displacement map of the phantom under cyclic pressure conditions at a single point of the pressure cycle corresponding to a pressure of 55.6 mmHg. This displacement and the corresponding circumferential displacement map were input into Eq. [1] to obtain the stiffness map shown. The mean stiffness was 96.2 ± 16.2 kPa within the region of interest (ROI) shown by the dotted line.

Cyclic pressure

A linear correlation was observed between stiffness estimates and inflation pressures for both MRE and P-V model under cyclic pressure conditions. Figure 4 is a plot of the shear stiffness versus inflation pressure under cyclic pressure conditions for both the MRE based (Eq. [1]) and P-V approach (Eq. [2]). The error bars in the figures represent ± 1 standard deviation (SD) of the MRE values within the ROI indicated in figure 3. The shear stiffness values ranged from 96–150 kPa at inflation pressures between 55 and 90 mmHg. The R^2 value between the P-V and MRE measurements was 0.97 for cyclic pressure conditions.

Static Pressure

Similar to cyclic pressure conditions, a high correlation was observed between shear stiffness and inflation pressure under static pressure conditions. Figure 5 represents the linear correlation between shear stiffness and pressure under static pressure conditions for both MRE and P-V model. The error bars in the figures represent ± 1 standard deviation (SD) of the MRE values within the ROI indicated in figure 3. The shear stiffness values ranged from 98–155 kPa at inflation pressures between 55 and 90 mmHg. The R^2 value between the P-V and MRE measurements was 0.98 for static pressure conditions.

Agreement was observed in stiffness estimates at different static inflation pressures between MRE and P-V approach. The relationship between shear stiffness obtained using the P-V model and the MRE-derived estimates during static pressure infusions is shown in figure 6. The R^2 value was 0.968 with a slope near unity.

Cyclic Pressure vs Static Pressure (MRE)

A good correlation of MRE-derived stiffness estimates were observed between cyclic and static pressure infusions. Figure 7 is a plot of cyclic versus static MRE-derived stiffness estimates at each of the six sampled inflation pressures. The R^2 value of 0.99 and slope near unity indicates very high correlation and correspondence between the stiffness estimates obtained under both cyclic and static pressure conditions.

Estimation of phantom volume

Volumes of the spherical shell measured from a single-slice and from a 3D volume at atmospheric pressure were 465 cc and 494 cc respectively, indicating an error estimate of 6%. Similarly, for 55 mmHg and 88 mmHg pressures the error in the volume estimate is 5.7% and 5.2%, respectively.

Discussion

In this study, excellent agreement between MRE-derived and P-V based measures of μ were obtained under both cyclic and static pressure conditions. Additional experiments (not shown) were conducted by modifying the phantom portion of the current setup, so that rather than having the phantom surrounded by air, the phantom was immersed in a water bath or was surrounded by a water-soaked sponge to mimic the in vivo environment of the heart. We found good agreement of the stiffness estimates with increase in pressure acquired using these alternative setups to those from the original setup described in this work. These results thus support the hypothesis that MRE-derived measures of μ can be obtained under both cyclic and static pressure conditions but with the advantage of not requiring invasive measures such as the insertion of a pressure catheter within the LV as required by the P-V based approach.

While MRE is an established method for measuring shear stiffness in soft tissues (8,12–15,21), it is yet to be validated as a method for assessment of μ within a moving organ such

as heart. Previous applications of MRE to measure myocardial stiffness (22,23), have only considered transient wave speed and do not produce any spatially resolved stiffness maps. The correlation demonstrated here between MRE-derived measures of shear stiffness for both cyclic and static pressure conditions suggests that MRE can also be applied in tissues or organs undergoing motion. While the technique shows great promise, significant work remains to transfer this methodology from phantom to in vivo studies. Essential steps necessary to move from phantom studies would be to increase acquisition speed in order to obtain data within a breath-hold as well as shear wave driver development in order to generate shear waves within the myocardium non invasively. As such, the work represents a proof of concept only.

The high correlation between the MRE and P-V based methods also suggests that the P-V model can be used as a reference method for future in vivo cardiac MRE studies. Successful in vivo implementation of a gated, cardiac MRE technique could become a useful diagnostic measure of effective myocardial stiffness. MRE can also potentially obtain spatially resolved stiffness maps noninvasively, while the P-V model is invasive and provides only global estimates of stiffness.

MRE is also not the only MR-based method for the assessment of tissue mechanical properties. Other MR-based methods for assessing the mechanical properties of the myocardium have included spatial modulation of magnetization (tagged) MRI (24) and strain-encoding MRI (25). However, as with their ultrasound counterparts (i.e. ultrasound elastography (26), these techniques are limited because they provide information about relative changes in mechanical properties, such as strain, but do not include any information about the loading and hence cannot be used to estimate absolute values of moduli (i.e. stiffness) (27). The model used in this study (i.e., Eq. 1) assumes an isotropic material, and if applied in the case of an anisotropic material, such as the myocardium, then μ should be interpreted as an isotropic effective shear modulus.

The MRE application demonstrated here is an extension of the MRE method from semi-infinite to bounded media that thus includes geometric considerations. While the inclusion of boundary conditions imposed by the finite geometry of the object has the potential to improve the accuracy of the MRE based estimates of μ , there are still several limitations. First, the stiffness measurements obtained using the inversion Eq. [1] require the estimation of several high-order derivatives, and as such are sensitive to noise. Estimating these high-order derivatives can also cause errors at the edges of the object. ROIs were drawn in the middle of the object to avoid any residual artifacts at the edges. Second, the phantom may have through-plane wave propagation effects, which would be inconsistent with the model governing Eq. [1]. Therefore, we believe that this motion may be the cause of systematic errors in the stiffness map shown in figure 3, which will be further investigated. Third, knowledge or an estimate of the loading function is required to solve Eq. [1]. In practice, for small amplitude vibrations, the estimate of this forcing function has a negligible impact of the final elastograms. Finally, wave source and interference effects cause artifacts in the elastograms at the top and bottom of the stiffness maps. Despite these limitations, the proposed technique provides a possible method for assessing effective myocardial stiffness, as the data is acquired at a particular cardiac phase, which makes the heart effectively static and the assumptions of constant wall volume and spherical geometry might support Eq.1.

Future work will extend the acquisition and inversion methodology to in vitro and in vivo cardiac tissue. Developments will include optimizing the MRE acquisition to reduce acquisition times (e.g., using parallel imaging techniques), refining the inversion to reduce noise sensitivity, and optimizing the resolution of the technique (e.g., to assess the regional stiffness of infarcted cardiac tissue).

In conclusion, the results of this study indicate that MRE estimates of μ agree with those obtained from a previously validated and established model for estimating global μ based measurement of the P-V relationship within the LV model across the pressure cycle for both static and cyclic pressure conditions. These results also indicate the possibility of in vivo measurements of stiffness with MRE throughout the cardiac cycle to diagnose various cardiac disease states with appropriate modifications of the existing pulse sequence. MRE based measures of myocardial stiffness may eventually provide localized and non-invasive assessments of cardiac tissue mechanical properties beyond the capabilities of current techniques.

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Figure 1. Experimental setup showing the connections between the driver, flow pump, pressure transducer and plythsmograph.

Figure 2.

A gradient echo MRE schematic pulse sequence indicating the RF pulse; X, Y, and Z gradients with flow-compensating gradients shown on X and Z; the first moment nulled MEG which can be applied along any axis; and the mechanical excitation.

Figure 3.

Radial displacement image (left) of the phantom obtained under cyclic pressure conditions using the GRE MRE sequence at a pressure of 55.6 mmHg and corresponding stiffness map (right) with a mean stiffness of 96.2 ± 16.2 kPa for a region of interest shown with the dotted line.

Figure 4.
Plot of MRE and P-V stiffness estimates versus pressure during cyclic pressure changes.

Figure 5.
Plot of MRE and P-V stiffness estimates versus pressure using static infusion pressures.

Figure 6. Correlation between shear stiffness measurements from the P-V method and MRE during static pressure infusions.

Figure 7.
Correlation between shear stiffness estimates obtained during cyclic and static pressure infusions using MRE.