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In Vivo, High-Frequency Three-Dimensional Cardiac MR Elastography: Feasibility in Normal Volunteers

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Abstract

Purpose—Noninvasive stiffness imaging techniques (elastography) can image myocardial tissue biomechanics in vivo. For cardiac MR elastography (MRE) techniques, the optimal vibration frequency for in vivo experiments is unknown. Furthermore, the accuracy of cardiac MRE has never been evaluated in a geometrically accurate phantom. Therefore, the purpose of this study was to determine the necessary driving frequency to obtain accurate three-dimensional (3D) cardiac MRE stiffness estimates in a geometrically accurate diastolic cardiac phantom and to determine the optimal vibration frequency that can be introduced in healthy volunteers.

Methods—The 3D cardiac MRE was performed on eight healthy volunteers using 80 Hz, 100 Hz, 140 Hz, 180 Hz, and 220 Hz vibration frequencies. These frequencies were tested in a geometrically accurate diastolic heart phantom and compared with dynamic mechanical analysis (DMA).

Results—The 3D Cardiac MRE was shown to be feasible in volunteers at frequencies as high as 180 Hz. MRE and DMA agreed within 5% at frequencies greater than 180 Hz in the cardiac phantom. However, octahedral shear strain signal to noise ratios and myocardial coverage was shown to be highest at a frequency of 140 Hz across all subjects.

Conclusion—This study motivates future evaluation of high-frequency 3D MRE in patient populations.

Keywords

cardiac MRE; cardiac elastography; myocardial stiffness

Introduction

The biomechanical properties of myocardial tissue play an important role in cardiac function. Increased myocardial stiffness can cause poor diastolic filling, which can lead to

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heart failure symptoms even with a normal left ventricular (LV) ejection fraction (1). Abnormal stiffness of myocardial infarcts can also affect LV wall stress and the pattern of LV remodeling (2). Being able to measure myocardial stiffness noninvasively could serve as a valuable diagnostic tool. Currently, in vivo myocardial stiffness is inferred from pressure-volume relationships, which are invasive, highly technical (3), and rarely performed in clinical practice.

Several groups are investigating elastography approaches using both ultrasound and MR imaging techniques as an alternative noninvasive way to assess myocardial tissue stiffness (4–11). With elastography approaches, an external source generates shear waves in a tissue of interest. An imaging technique then measures the vibrational displacements in the tissue. Finally, the displacement field is converted into a stiffness map through mathematical techniques, collectively referred to as inversion algorithms (12). For both ultrasound and MR techniques, all of the components of elastography work best in organs that are near the body surface, where shear waves can easily penetrate, and in organs that are large compared with the wavelength of the introduced shear wave—which is a requirement for most inversion algorithms.

Elastography is exceptionally difficult in the diastolic left ventricular myocardium, which is surrounded by lung tissue and has a wall that is normally between 8-and 12-mm-thick (13). As a result, to date, only a limited number of publications have reported on cardiac elastography in human subjects (7,10,14–17). Song et al (10), using ultrasound elastography, reported shear wave speeds in seven healthy human volunteers to be 1.5660.36m/s in end diastole. However, their approach had the intrinsic limitations of ultrasound elastography, namely the inability to obtain a three-dimensional (3D) displacement field and a limited acoustic window. Elgeti et al attempted cardiac MR elastography (MRE), but did not acquire 3D displacement fields nor did they attempt to quantitate myocardial stiffness. Instead they used a low driving frequency of 24.13 Hz to reduce the effects of shear wave attenuation and used shear wave amplitudes as a surrogate for myocardial stiffness (7,14). Kolipaka et al (17) compared 18 normal volunteers with two obstructive hypertrophic cardiomyopathy (HOCM) patients using a vibration frequency of 80 Hz and using 2D inversions on two single slices. They reported that normal volunteers and obstructive HOCM patients, in end-systole, had an effective mean myocardial stiffness of $5.64 \pm 1\text{ kPa}$ and $14.5 \pm 2.2\text{ kPa}$, respectively. The authors report that only an effective stiffness value could be given because heart geometry and 3D wave propagation effects were not taken into account. The accuracy of these techniques in a complex geometry of the heart has still not been tested however.

Elastography of the left ventricular myocardium is challenging for several reasons. The complex geometry of the heart suggests that full 3D, three-sensitization displacement fields are required for accurate stiffness calculations. Because the myocardium is thinner than typical MRE shear wavelengths, waveguide effects dominate the wave propagation, and incorrect stiffness estimates will result if these are not accounted for. Accurate stiffness estimates can be obtained in principle by taking the curl of the displacement field (18), but at the expense of noise amplification, which may lead to an underestimation of stiffness if the signal-to-noise ratio (SNR) is too low. Higher vibrational frequencies suggest higher resolution (desirable in a thin object), but these attenuate more quickly and may yield low

amplitudes and SNR. Lower vibrational frequencies penetrate more readily, but have stronger waveguide effects, and the longer wavelengths suggest smaller spatial derivatives and thus less tolerance to noise. The feasibility of detecting shear wave frequencies greater than 80 Hz that have penetrated into the myocardium using existing MRE acquisitions and current shear wave driver technologies has not been established in human volunteers or large animal models. Therefore, it is not clear what driving frequencies are necessary to produce accurate cardiac MRE stiffness maps or what frequencies are capable of penetrating the myocardium in human subjects. Furthermore, quantitative validation of MRE with material testing has generally been performed in large homogenous phantoms using wavelengths much smaller than the dimensions of the phantom (18–21). The accuracy of MRE is not well understood in a complex cardiac geometry. Also, removing the contribution of the longitudinal wave by calculating and inverting the 3D curl field from the displacement maps has only been validated to a limited degree with analytic models and simple phantoms (22,23). It, too, has not been validated in a geometrically accurate phantom of the human left ventricle.

Therefore, the purpose of this study was to determine the necessary driving frequency for accurate quantitative 3D cardiac MRE to be performed in a geometrically accurate diastolic cardiac phantom and to determine the optimal vibration frequency that can be introduced in healthy volunteers. These outcomes will be pivotal in understanding the accuracy, feasibility, and potential role cardiac MRE may have in noninvasively measuring myocardial stiffness in human subjects.

Methods

Physical Heart Model

A two-chamber silicon heart phantom was used to test the accuracy of the MRE reconstruction algorithm. The heart phantom was custom manufactured (The Chamberlain Group, MA, USA) from a segmented electrocardiogram (ECG)-gated computed tomography image volume of a patient's heart in diastole (Fig. 1). From the same batch of silicon as the heart phantom, three cylindrical samples were poured for dynamic mechanical analysis (DMA), described in more detail below. The scan was of a 36-year-old female who was asymptomatic with hyperlipidemia but no other cardiac history. The computed tomography scan of the patient was performed on a Somatom Definition scanner (Siemens Medical Systems, Erlangen Germany) after 5mg of oral metoprolol, 0.4 mg of nitroglycerine sublingual, and intravenous injection of 80mL of Omnipaque 350 (GE Healthcare, Milwaukee, WI). Scan parameters were gantry rotation = 330ms, kVp = 100, mA = 451, field of view (FOV) = 200mm, collimation = dual source 64×0.6 , slice thickness = 0.75 mm, increment = 0.4 mm.

MRE of the Heart Phantom

MRE was performed on the heart phantom to determine how the accuracy of the stiffness measurements varied with vibration frequency. A slightly modified, commercially available, pneumatic active driver (Resoundant Inc., Rochester, MN) and a custom-built cardiac MRE passive driver were used to deliver sinusoidal vibrations to the phantom. The passive driver

was customized to work at higher frequencies and it was composed of a cylindrical drum with a 10-cm-diameter, 0.5-mm-thick, polycarbonate diaphragm with a 5-mm-deep cavity and a 5-mm solid acrylic backing (Fig. 2A). The improved vibration amplitude of the custom passive driver compared with the conventional liver MRE driver, as measured by an accelerometer, is shown in Figure 3. Furthermore, to deliver even more vibrational amplitudes at frequencies greater than 100 Hz, the active driver was connected to an alternative amplifier (Crown XLS2000, Harman, Elkhart, IN) that was capable of outputting five times the power of the commercially available active driver.

Imaging was conducted on a 1.5 Tesla (T) MRI scanner (Signa Excite, GE Healthcare, Milwaukee, WI) in an eight-channel head coil with a modified cardiac-gated, spin-echo, echo planar imaging (EPI) MRE sequence, with vibration frequencies of 80 Hz, 100 Hz, 140 Hz, 180 Hz, and 220 Hz; repetition time/echo time (TR/TE) = 1066–1256/42–58 ms; FOV = 28.8cm; 96×96 image matrix; eight contiguous 3-mm-thick axial slices; one to three motion-encoding gradient pairs on each side of the refocusing pulse and matched to the vibration frequency; alternating x, y, z, and 0 motion-encoding gradient directions; and four phase offsets spaced evenly over one vibration period. For image processing purposes, the image volume was reformatted to $256 \times 256 \times 21$ to give an isotropic resolution of 1.1mm. The zero motion-encoding gradient direction was subtracted from the other motion-encoding direction images to remove static phase components due to field inhomogeneity.

MRE postprocessing was implemented by taking the curl of the 3D displacement field and performing a 3D direct inversion (DI) of the Helmholtz equation on the resulting wave field. To avoid any inter-slice phase discontinuities, before taking the curl, a previously described high-pass filter approach was used (24), which involves subtracting a low-pass filtered version of each slice from the original slice. The low-pass filter used for this process was a 3×3 matrix of ones centered in an all zero 256×256 k-space matrix. Spatial derivatives were taken using a $3 \times 3 \times 3$ “jack-shaped” kernel and the magnitude of the complex shear modulus was the reported stiffness value for the MRE stiffness calculations, assuming a tissue density of 1g/cm^3 . The DI algorithm solved the Helmholtz equation by using a least squares estimation with the following cost function (25):

$$\hat{\mu} = \underset{\mu}{\operatorname{argmin}} \nabla^2 \vec{u} \cdot \mu + \rho \omega^2 \vec{u}^2 = -\rho \omega^2 [\nabla^2 \vec{u}]^\dagger \vec{u}$$

where, μ is the shear modulus, $\mathbf{u}$ is the 3D (3×1) displacement vector of a single voxel, ρ is the density, ω is the angular velocity, ∇^2 is the 3D Laplace operator, and $\dagger$ is the pseudo inverse. Before applying the inversion algorithm, the curl was smoothed with a $7 \times 7 \times 7$ quartic smoothing kernel (26) to reduce stiffness outliers due to noise. No phase unwrapping algorithm was used. Instead, the phase derivatives for the curl operator were calculated using the real and imaginary parts of the displacement data as previously described (27). The left ventricle of the heart phantom was semi-automatically segmented from the MRE magnitude images using a random walker segmentation algorithm (28). The left ventricle mask was then eroded by two pixels in all directions to reduce edge effects.

The classification of what wave amplitudes or SNR are sufficient for accurate results with existing MRE reconstruction algorithms is still an ongoing field of research. The octahedral shear strain SNR (OSS-SNR) has been suggested as the most appropriate SNR measure for MRE (29). Therefore, this was the method chosen to help quantify the shear wave quality throughout the left ventricle. However, the validity of OSS-SNR as a measure of inversion quality and the establishment of an OSS-SNR threshold for accurate inversions was derived for a finite element based inversion and the validity of OSS-SNR and an appropriate OSS-SNR threshold has not been established for DI. For this study, an OSS-SNR threshold was chosen by obtaining “no-motion” datasets at each vibration frequency and processing them through the same pipeline used throughout this study. A plot of the percentage of pixels with OSS-SNR above a range of thresholds was made for each “no-motion” dataset. The average threshold across all “no-motion” datasets that would eliminate 95% of all voxels over the entire volume was chosen as a cutoff. This threshold was found to be 1.6 for our current study parameters. The mean OSS-SNR was calculated for the curl wave fields and only voxels with $\text{OSS-SNR} > 1.6$ were included in the stiffness calculations.

DMA

Immediately after scanning the heart phantom, mechanical testing using a commercially available DMA device (RheoSpectris™ C500, QC, Canada) was performed on three 4.5-cm-long, cylindrical tube samples (9-mm inner diameter) from the same silicon pour as was used for the heart phantom. DMA was performed at the same frequencies as the magnetic resonance elastography experiments. The percent error between the MRE stiffness results and the mean DMA results ($100 \times (\text{DMA-MRE})/\text{DMA}$), was calculated at each frequency.

MRE in Healthy Volunteers

Cardiac MRE was performed on eight healthy volunteers to determine the highest possible vibration frequency capable of being detected in the myocardium. To establish a “no-motion” baseline measurement of noise, one volunteer was asked to return a second time and undergo a full MRE exam without the application of any vibrational motion. This study was approved by our institutional review board and the subjects were imaged after obtaining written informed consent. The passive driver was placed in direct contact with the volunteer's skin, just to the left of the sternum and superior to the xiphoid process (Fig. 2B). An elastic tension strap, connected to a polyvinyl gel backing, was attached to the back of the passive driver with Velcro to help improve coupling between the driver diaphragm and the volunteer's skin surface. The gel backing acted as a fiducial marker for driver positioning during the MRE examinations. To help avoid signal interference from shear wave vibrations, cardiac gating was performed by placing electrocardiography leads on the back of the left shoulder of the volunteers instead of on the chest. Volunteers were imaged head first in the supine position.

Imaging was performed on a 1.5T closed-bore MR imager (Optima MR450W; GE Healthcare, Milwaukee, WI) in an oblique orientation to obtain long-axis MRE images of the heart using the built-in, receive-only, body coil array (GEM anterior–posterior array, GE Healthcare, Milwaukee, WI). The same active and passive drivers were used in the volunteer study as described for the phantom experiment. Imaging was conducted using a flow-

compensated, cardiac-gated, spin-echo, single-shot EPI MRE sequence, with vibration frequencies of 80 Hz, 100 Hz, 140 Hz, 180 Hz, and 220 Hz; TR was matched to each volunteer's heart rate with electrocardiogram-gating, TE = 52–79 ms depending on frequency; FOV = 32 cm; 64×64 image matrix; parallel imaging acceleration factor = 2; five contiguous 5-mm-thick axial slices; one to two motion-encoding gradient pairs on each side of the refocusing pulse matched to the vibration frequency; alternating x, y, z, and 0 motion-encoding gradient directions; and four phase offsets spaced evenly over one vibration period. For image processing purposes the image matrix was reformatted to $256 \times 256 \times 20$ to give an isotropic resolution of 1.25 mm. Because this was the first study conducted in human subjects, images were acquired at the minimum delay possible in the cardiac cycle (~ 100 ms as described below) after the ECG trigger, which is believed to be the most reproducible phase in the cardiac cycle. It should also be noted that the TE times, when possible, were chosen to fall within the range of reported myocardial T2 values (55–72 ms) (30,31) to approach the maximum MRE phase SNR (32).

To minimize wave pattern variations from heart beat to heart beat, a finite wave-train of vibrational motion shorter than the cardiac cycle was used instead of trying to deliver continuous motion. The vibrational motion was triggered off the R-wave peak after a user defined delay (~ 25 ms in this study) and allowed to propagate in the tissue for 100 ms before the motion-encoding gradients to ensure the wave field would be both reproducible and would have enough time to propagate throughout the myocardium. The pulse sequence timing diagram is shown in Figure 4 for 140-Hz vibrations and F4 the number of cycles of the vibration and the motion-encoding gradients used at each frequency are summarized in Table 1. Also, to ensure the highest accuracy in T1 the phase subtraction and first harmonic wave estimations, each slice was acquired separately, with all motion-encoding directions and offsets collected in a single breath-hold of approximately 27 s (depending on the heart rate).

The same MRE postprocessing as described in the phantom experiments was implemented. The left ventricle of the heart was semi-automatically segmented and the octahedral shear strain signal-to-noise ratio (OSS-SNR) (29) was calculated on the curl wave fields. The left ventricle mask was eroded by two pixels in all directions to reduce edge effects. In the remaining volume, the mean stiffness was calculated from voxels with OSS-SNR values greater than 1.6. The mean OSS-SNR over the entire volume was also measured for each volunteer across all frequencies. Lastly, to evaluate the coverage of the shear waves across the entire heart, the percentage of voxels with OSS-SNR > 1.6 over the entire myocardial mask were calculated for each volunteer at each vibration frequency.

Results

MRE and DMA of the Heart Phantom

The out of plane (z-direction) component of the vector curl wave field, the corresponding elastograms (magnitude of complex shear modulus), and a map of the voxels with OSS-SNR > 1.6 obtained with cardiac MRE in the heart phantom are shown for each frequency in Figure 5. The DMA testing showed that the mean ($\pm$ standard deviation) magnitude of the complex shear modulus of the heart phantom was 4.1 ± 0.2 , 4.2 ± 0.2 , 4.4 ± 0.1 , 4.5 ± 0.1 ,

and 4.6 ± 0.1 kPa for vibration frequencies of 80 Hz, 100 Hz, 140 Hz, 180 Hz, and 220 Hz, respectively. The corresponding DMA values of the storage modulus (mean $\pm$ standard deviation) for the same frequency range was 4.1 ± 0.1 , 4.2 ± 0.1 , 4.3 ± 0.1 , 4.39 ± 0.08 , and 4.49 ± 0.07 kPa, respectively. Lastly, the loss modulus values (mean $\pm$ standard deviation) were 0.63 ± 0.07 , 0.70 ± 0.07 , 0.83 ± 0.08 , 0.94 ± 0.07 , and 1.04 ± 0.07 kPa, respectively. The magnitude of the complex shear modulus, the storage modulus, and the loss modulus calculated with MRE have been summarized in Table 2. Lastly, the percent difference between the DMA measurements and the mean and median MRE measurements in voxels with OSS-SNR > 1.6 are summarized in Table 2 and a comparison of the magnitude of the complex shear modulus between the DMA and the MRE results are plotted in Figure 6. The MRE results generally underestimate the DMA values, but as the vibration frequency increased the MRE measurements converged to the DMA results.

MRE in Normal Subjects

Long-axis magnitude images have been shown in Figure 7 to demonstrate that, in early systole, flow artifacts were not visible over the range of TE values (62–79 ms) and vibration frequencies (80–220 Hz) used in this study. The bright blood in these images suggests that the blood is receiving both the 90 and 180 degree excitation pulses, supporting the idea that the blood is relatively slow moving in the timeframe between these two pulses. The out of plane component (z-direction) of the vector curl field, the corresponding elastograms (magnitude of complex shear modulus), and a map of the voxels with OSS-SNR > 1.6 are shown in Figure 8 for a single volunteer over the 80–220 Hz frequency sweep (Supporting Video S1 of the curl of the wave data at all frequencies and in all motion encoding directions are available online). The percentage of voxels that remain in the “no-motion” and “motion” datasets as a function of OSS-SNR threshold for all frequencies are shown in Figure 9A. The shaded gray region depicts the separation point between the “motion” and “no motion datasets”. The dashed cross-hair indicates the OSS-SNR threshold of 1.6 where 95% of all “no motion” voxels are eliminated.

For this same subject, the difference between $|G^*|$ of “motion” and “no motion” and the ratio of $|G^*|_{\text{“motion”}}$ over $|G^*|_{\text{“no-motion”}}$ have been plotted as a function of frequency in Figure 9B. The OSS-SNR and the percent of voxels with OSS-SNR > 1.6 for all volunteer subjects over the entire frequency range are plotted in Figure 10A and Figure 10B, respectively. Lastly, the magnitude of the complex shear modulus for voxels with OSS-SNR > 1.6 are plotted in Figure 11. For Figures 10 and 11, the boxes correspond to the 1st and 3rd quartiles, the horizontal line in each box is the median value, the “X” corresponds to the maximum and minimum values, the small square in each box is the mean value, and the error bars (whiskers) represent a single standard deviation from the mean across all subjects. These plots show that at all frequencies except for 220 Hz it was feasible for at least one volunteer to have a mean OSS-SNR above 1.6. However, only the 140 Hz frequency had a median OSS-SNR over all subjects just over 1.6, and a mean OSS-SNR just below the 1.6 threshold, (square in box plot). The 140 Hz vibration frequency also corresponded to having the highest percentage of voxels with OSS-SNR > 1.6 .

Discussion

This study demonstrated that in a complex geometrically accurate diastolic cardiac phantom, accurate quantitative LV cardiac MRE stiffness maps can be obtained when driving at frequencies of 180 Hz and higher. In human volunteers, cardiac MRE displacement fields can be produced and imaged with mean OSS-SNR > 1.6 at frequencies as high as 180 Hz, allowing for stiffness maps to be generated with direct inversion algorithms.

In the cardiac phantom experiments (Figs. [4 and 5]), it was demonstrated that as the vibration frequency increases from 80–220 Hz the accuracy of the magnitude of the complex shear modulus measurements improved from 50% error down to only -0.7% error. The error at lower frequencies is due to the increasing effects of noise at longer wavelengths, because derivatives are smaller and third derivatives are required in curl + DI processing. This is a novel finding as quantitative validation of MRE with material testing has generally been performed in large homogenous phantoms using wavelengths small in comparison with the phantom dimension (19–21). Furthermore, removing the contribution of the longitudinal wave by calculating and inverting the 3D curl field from the displacement vector fields has only been validated to a limited degree with analytic models and simple phantoms (22,23), and not (to our knowledge) in a complex heart geometry. This is the first demonstration that 3D MRE can give accurate stiffness measurements for a 4.1–4.6 kPa, geometrically accurate, diastolic cardiac phantom, when the curl of the wave field is taken, and when driven at vibration frequencies of 180–220 Hz.

In the human volunteer experiments (Fig. 10A), it was shown that obtaining mean OSS-SNR values greater than 1.6 was feasible for all frequencies tested, except for 220 Hz. However, with the current driver set-up, Figure 10A and 10B suggest that a vibration frequency of 140 Hz may be the most robust frequency to obtain the highest OSS-SNR while covering the greatest tissue volume in the heart across different subjects. This may represent a balance between various competing factors, because higher frequency suggests increased wave attenuation, but also shorter wavelengths (thus higher spatial derivatives) and increased signal due to shorter echo-times. This may be one explanation why 140 Hz appears to be the optimal frequency to perform cardiac MRE with the current processing and setup.

Due to the numerous difficulties of performing DMA on cardiac tissue samples that can be meaningfully compared with in vivo tissue mechanical properties, the lack of any other reference standard for measuring in vivo cardiac tissue mechanical properties, and the lack of a reproducibility study, it is still unclear what the current accuracy of cardiac MRE is in human subjects. In Figure 11, the average mean stiffness value across all 8 subjects was found to be 1.2 ± 0.2 kPa, 1.9 ± 0.3 kPa, 3.8 ± 0.6 kPa, 5.2 ± 0.7 kPa, and 6.9 ± 0.7 kPa at 80 Hz, 100 Hz, 140 Hz, 180 Hz, and 220 Hz vibration frequencies, respectively. Figures 9B and 10A suggest that the most accurate stiffness estimates for our processing occurs at 140 Hz, which we expect to be the least biased by noise. Our values at 100 Hz and 140 Hz are similar to those reported by Song et al, but approximately two- to three-fold larger at higher frequencies. This may partially be explained by acquiring data at different phases in the cardiac cycle and partially due to the introduction of discretization errors at smaller wavelengths (180 Hz and 220 Hz). Our 80 Hz results do not agree with those reported by

Wasse-naar et al (33) who reported an end-systolic stiffness of 6.10 ± 1.38 kPa. One explanation for this could be differences in processing techniques, specifically with respect to our use of the curl and DI and their use of a local frequency algorithm for their inversion and a band-pass filter in place of the curl to remove the longitudinal component of their data. In our phantom study, we found a significant underestimate of stiffness with low frequencies when using the curl due to noise amplification. Figure 6 suggests that as we increase the driving frequency the accuracy of the stiffness measurements increases. However, in tissues, it is difficult to determine how much of this is due to wave dispersion, versus discretization errors, versus the inaccuracy of the current wave inversions. It is not in the scope of this study to differentiate the contributions of each one from the other, but this will need to be addressed in future studies.

If the stiffness of the heart is truly on the order of 7 kPa in early systole, this would suggest that even frequencies higher than 220 Hz or improved denoising techniques may be needed to obtain accurate stiffness estimates in this phase of the cardiac cycle. Large changes in myocardial stiffness are expected throughout the cardiac cycle, which according to the cardiac phantom experiments could result in a wide range of stiffness accuracies as well. This motivates future experiments involving phantoms of different phases in the cardiac cycle, and with stiffness values greater than the one used in this study. In patient studies, one strategy may be to use multiple frequencies to estimate the stiffness of the heart at different stages in the heart cycle. Furthermore, the phases of the cardiac cycle and the corresponding stiffness of the heart may also impact the amplitude of the propagating shear waves (14). Therefore, cardiac phase dependent vibration amplitudes may also need to be considered. In this study, a systolic cardiac phase was chosen in volunteers for reproducibility purposes, which may have resulted in lower vibrational amplitudes and longer wavelengths due to the tissue being stiffer at this point in the cardiac cycle. This may have resulted in lower OSS-SNR values than what may be obtained in diastole. Nevertheless, it was encouraging to see that for all frequencies up to and including 180 Hz at least one volunteer had an average OSS-SNR greater than 1.6 over the myocardial tissue (Fig. 10A).

This study had some limitations because it was the first attempt at performing 3D high frequency cardiac MRE in healthy human volunteers. The wave inversions and derivative operators (e.g., curl, Laplacian) that were used assumed tissue isotropy and local homogeneity, which are not true in the heart and may introduce dynamic errors at different phases in the cardiac cycle. In future studies, it may be beneficial to account for anisotropy (9) to improve both inversion algorithms and curl operators for stiffness calculation (34,35). Second, in this study, we relied on breath-holds around 27 s to acquire all phase encoding directions and phase offsets in a single breath-hold for each slice. This is a limitation that may make this technique impractical and will need to be optimized before performing this in patient populations. Also, as with any cardiac imaging technique that relies on user defined delay times to image a specific phase in the cardiac cycle, it would be challenging to image diastolic phase in patients with large beat to beat variations. Such cases would require the development of more advanced dynamic delay time approaches. A recent study in diffusion MRI (36) has reported that higher order cardiac motion (e.g., jerk) may affect image quality when TEs are on the order of 70 ms, which may need to be addressed in future MRE studies. A 5-mm isotropic acquisition resolution was used in the volunteer study to ensure high

signal-to-noise ratio and good shear wave detectability. This will need to be improved upon in future studies. In this study, an OSS-SNR threshold was used to exclude single voxels based on their OSS-SNR rather than as a global measurement. Although such thresholding does not make a noisy region more reliable, from the phantom experiments it was observed that applying such a threshold does reduce some of the bias introduced by noisy regions within a larger volume of interest and in turn does improve the accuracy of the mean stiffness estimate over the entire volume. Nevertheless, it would be beneficial to develop techniques to further increase the mean OSS-SNR over the entire myocardial volume.

Lastly, it should be emphasized that although lower frequencies resulted in large differences between DMA results and MRE results, it is still too early to know how these errors will manifest in diagnostic accuracy. Furthermore, the aim of this study was not to establish a baseline value of myocardial stiffness in vivo over a wide frequency range, but rather to determine the optimal frequency to perform cardiac MRE in humans. Future studies with a much larger population base, in combination with test re-test repeatability studies, and the development and evaluation of cardiac specific inversion algorithms are still needed. These results do, however, motivate further investigation into the application of higher frequencies in future 3D cardiac MRE studies.

Conclusions

This work is the first demonstration of the feasibility of cardiac MR elastography at frequencies greater than 80 Hz and up to 180 Hz in healthy human volunteers, which would allow for the use of direct inversion algorithms to produce stiffness maps of the heart. Although it is feasible to obtain a mean OSS-SNR value of greater than 1.6 at frequencies as high as 180 Hz, with the current technology, 140 Hz may be the most robust driving frequency in terms of tissue coverage and consistency of obtaining mean OSS-SNR values > 1.6 across multiple subjects. This is also the first study to show that a 3D direct inversion of the curl wave field can produce accurate stiffness measurements, within 5% error, in a 4.1–4.6 kPa geometrically accurate diastolic cardiac phantom, at frequencies of 180 Hz and greater. The results of this study motivate future development and evaluation of high-frequency 3D MRE in patient populations to help it become a viable clinical tool.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Photograph of MRE heart phantom setup.

Fig. 2.

A: Photograph of the cardiac MRE passive driver. **B:** An example of the cardiac MRE passive driver positioning on volunteers. During cardiac MRE exams the passive driver was placed in direct contact with the volunteer's skin just to the left of the sternum and superior to the xiphoid process.

Fig. 3.

A comparison of the frequency response of the custom-built cardiac MRE passive driver and the conventional liver passive driver under the same experimental conditions.

Fig. 4.

ECG-gated cardiac MRE spin echo EPI timing diagram for 140-Hz vibrations. The time starts from the ECG-trigger at the R-wave peak. The axis of the motion-encoding gradients was changed to sequentially acquire motion in all three directions and is shown as a dotted wave form. The user defined time delay (Δt) was set to minimum (~ 25 ms) for this experiment. RF, radiofrequency pulses; $G(x,y,z)$, gradient wave forms in each Cartesian direction; M, vibrational motion; SSP, spatial-spectral RF pulse; MEG, flow-compensated motion-encoding gradients; ET, EPI echo train.

Fig. 5. Z-direction curl wave images (top row), corresponding $|G^*|$ elastograms (middle row), and pixels with OSS-SNR > 1.6 (bottom row), obtained in the cardiac phantom. Vibrations were applied to the apex of the heart and are propagating upward.

Fig. 6.

A plot of the mean (open squares) and median (open triangles) MRE magnitude of the complex shear modulus measurements compared with DMA analysis (dashes). The error bars represent the standard deviation of the mean for both the DMA and MRE measurements.

Fig. 7.

Long-axis magnitude images of a volunteer's heart with no evidence of flow artifacts and bright (relatively slow moving) blood in early systole.

Fig. 8.

Z-direction curl wave images (top row), corresponding elastograms (middle row), and the elastogram pixels with OSS > 1.6 (bottom row), from a single volunteer over the complete 80-220Hz frequency range.

Fig. 9.

A: Voxels that remain after different OSS-SNR thresholds for “motion” (triangles) and “no motion data” (squares). The intersection of the two dashed lines indicate the 1.6 OSS-SNR threshold that corresponds to only 5% of the voxels in the “no motion” data to remain. All data from the “no motion” scans fall within the shaded gray region of plot. **B:** The absolute difference between the magnitude of the complex shear modulus of the “motion” and “no motion” data over the entire frequency range (left vertical axis with black line and open squares). The ratio of the complex shear modulus of the “motion” data over the “no motion” data as a function of frequency (right vertical axis with red line and circles).

Fig. 10.

Box and whisker plot of mean OSS-SNR (A) and the number of total voxels with OSS-SNR > 1.6 (B) across all subjects at each vibration frequency. The "X" corresponds to the maximum and minimum values. The error bars (whiskers) represent the standard deviation of the mean across all subjects. The dashed line in A represents the OSS-SNR threshold used in this study. The mean OSS-SNR from the "no motion" scan has been denoted by the red circles and the solid line.

Fig. 11.

Box and whisker plot of mean shear modulus across all subjects in voxels with OSS-SNR>1.6. The “X” corresponds to the maximum and minimum values. The error bars (whiskers) represent the standard deviation of the mean across all subjects.

Table 1
Summary of Imaging Parameters for Each Vibration Frequency^a

Frequency (Hz)	Burst count	Pre-encoding cycles	MEG cycle pairs
80	40	8	1
100	60	10	2
140	60	14	2
180	100	18	3
220	80	22	3

^aBurst count = the total number of vibration cycles played out for each frequency per ECG trigger; Pre-encoding cycles = the number of vibrational cycles applied before motion encoding; MEG cycles = the number of motion encoding gradients used on each side of the 180° RF pulse.

Table 2
Summary of MRE Elastogram Measurements in Cardiac Phantom and Their Difference with Respect to the Equivalent DMA Measurements^a

f (Hz)	MRE			% Difference (DMA- MRE)/DMA			
	Mean (median) G' (kPa)	Mean (median) G'' (kPa)	Mean (median) G* _s (kPa)	Mean (median) G' (%)	Mean (median) G'' (%)	Mean (median) G* (%)	
80	2.0 ± 0.6 (2.0)	0.0 ± 0.6 (0.2)	2.1 ± 0.5 (2.1)	52 (50)	93 (73)	50 (49)	
100	2.5 ± 0.7 (2.4)	0.0 ± 0.7 (0.1)	2.5 ± 0.8 (2.5)	41 (42)	99 (90)	40 (41)	
140	3.4 ± 1.0 (3.4)	0.2 ± 0.9 (0.3)	3.5 ± 1.0 (3.5)	20 (20)	72 (61)	19 (19)	
180	4.7 ± 1.5 (4.7)	0.5 ± 1.6 (0.4)	5.0 ± 1.5 (4.9)	-6.5 (-6.1)	50 (56)	-11 (-9.6)	
220	4.3 ± 2.1 (4.3)	0.5 ± 1.4 (0.4)	4.6 ± 1.8 (4.5)	5.0 (3.2)	52 (59)	-0.7 (1.6)	

^aG' = storage modulus; G'' = loss modulus; |G*| = magnitude of the complex shear modulus; f = frequency.