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Advances and Future Direction of Magnetic Resonance Elastography

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Abstract

The mechanical properties of soft tissues are closely associated with a variety of diseases. This motivates the development of elastography techniques in which tissue mechanical properties are quantitatively estimated through imaging. Magnetic resonance elastography (MRE) is a non-invasive phase-contrast MR technique where shear modulus of soft tissue can be spatially and temporally estimated. MRE has recently received significant attention due to its capability in non-invasively estimating tissue mechanical properties, which can offer considerable diagnostic potential. In this work, recent technology advances of MRE, its future clinical applications, and the related limitations will be discussed.

Keywords

Mechanical Properties of Tissues; Tissue Stiffness; MR Elastography; Clinical Applications of MR Elastography; MR Imaging.

1. Introduction

It is well known that many diseases are associated with alterations in tissue mechanical properties^{1,2}. For example, the aortic wall with an aneurysm can be significantly stiffer than the normal aortic wall due to over expression of collagen and calcification^{3–8}. In liver cirrhosis, the diseased liver becomes fibrotic and less compliant when compared to a healthy liver⁹. Many malignant breast cancers are also distinctively stiffer than benign tumors or normal surrounding fibroglandular tissue¹⁰. Palpation is an effective method in diagnosing a variety of diseases, but it is only applicable to superficial tissues and is a qualitative method. These opportunities for diagnostic improvement motivate the development of elastography techniques in which tissue mechanical properties are quantitatively estimated through imaging^{11–13}.

MRE is a non-invasive phase-contrast MR technique where shear modulus of a soft tissue can be spatially and temporally estimated^{1,2,14,15}. Earlier sections have explained the diagnostic value of MRE and its applications in different organs. In this review, recent development and advances in MRE will be summarized. We will mainly focus on the advancement of the MRE driver, pulse sequences, fast imaging techniques, and inversion algorithms followed by a brief discussion on different MRE applications that may offer great clinical utility in the future.

2. MRE Driver System

The mechanical excitation required for MRE application can be categorized into two groups: external drivers and internal drivers. An external driver system uses a non-physiological source to produce the mechanical wave, while an internal driver system uses physiological motion within the subject, such as cardiovascular motion, as the main source of mechanical excitation.

Active drivers can be electromechanical, piezoelectric-stack, or pneumatic^{1,16–19}. Because of its simplicity and patient comfort, pneumatic driver systems have recently been widely used in MRE research. Pneumatic driver systems with low-frequency excitation (60–200 Hz) have been used in studying the stiffness of brain²⁰, liver²¹, myocardium²², aorta of hypertensive animal model²³, and abdominal aortic aneurysm²⁴. Due to the compressibility of air, a pneumatic driver is limited by its inability to efficiently generate strong high-frequency harmonic waves, leading to significant wave attenuation²⁵. High-amplitude and high-frequency harmonic waves are beneficial to achieve higher spatial resolution of MRE measurements with deep penetration. For example, in prostate MRE studies, conventional surface MRE drivers can encounter challenges in achieving sufficient wave penetration at high frequencies needed for studying the prostate gland due to strong attenuation. For this reason, Chopra et al. developed a transurethral driver for prostate MRE in which a piezo-ceramic actuator was used to vibrate the transurethral device that was advanced into the subject to generate high frequencies²⁶. Future developments in the MRE driver design may focus on developing a noninvasive driver system that uses incompressible medium at higher frequencies and amplitudes for wave propagation as an alternative to the pneumatic medium.

Physiological motion, such as cardiac activity, can be used as an internal vibration source for MRE. Sinkus et al. estimated the shear modulus of the interventricular septum by imaging the shear wave propagation induced by aortic valve closure (AVC)¹⁷. Recently, Clough et al. performed aortic MRE on 8 healthy volunteers and 15 patients with hypertension using AVC as the wave generating source²⁷. One of the advantages of intrinsically induced mechanical waves is that it does not suffer from the insufficient wave penetration encountered with an external driver when imaging small, deep regions of interest with high frequency. However, synchronizing the intrinsic vibration to the motion-encoding gradient (MEG) can be challenging. Moreover, any valve defects can result in improper excitation for wave generation.

3. MRE Sequences

3.1 Gradient-Recalled-Echo, Spin-Echo, and Echo-Planar-Imaging MRE Sequences

Gradient-recalled-echo MRE (GRE-MRE) and spin-echo MRE (SE-MRE) sequences are frequently employed in a variety of MRE studies. Compared to GRE-based MRE sequences, SE sequences are less affected by T2* decay due to the refocusing mechanism of spin echoes, making the technique an excellent option for cardiac²⁸, vascular²⁹, liver (with iron overload)³⁰ and lung MRE³¹.

Echo-planar-imaging MRE (EPI-MRE) sequences is another popular technique employed in various MRE studies. In EPI acquisition, multiple k-space lines are acquired after a single excitation, significantly shortening the total acquisition time. Non-cardiac-gated EPI sequences are frequently used in liver and brain MRE research. Recently, Dong et al. developed a cardiac-gated SE-EPI sequence for rapid in-vivo aortic MRE²⁹. In this sequence, a first-moment-nulled 1–2–1 MEG was employed to avoid aortic flow-induced spin dephasing (See Figure 1). Similar aortic stiffness and higher first harmonic amplitudes were observed in SE-EPI MRE images when compared to a conventional retro-gated GRE-MRE sequence, demonstrating advantages in imaging patients with high body mass index. Moreover, EPI-MRE sequences with rapid readout can provide shorter scan time compared to conventional GRE or SE sequences. Additional acceleration in image acquisition is desired to provide patient comfort, shorten breathhold duration, and avoid motion artifacts. Therefore, fast MRE sequences and rapid MRE acquisition techniques are the main focus of future MRE development. Below are a few MRE acquisition techniques that are currently under investigation.

3.2 Sample Interval Modulation-Magnetic Resonance Elastography

To sensitize tissue displacement along different directions, a MEG is applied in slice-, readout- and phase-encoding directions via three separate scans. Sample interval modulation-magnetic resonance elastography (SLIM-MRE) was recently proposed to simultaneously encode three-directional tissue displacement into the phase of MR signal, significantly improving MRE efficiency and shorten the total acquisition time^{32–34}.

This is achieved by applying MEG along three encoding directions at the same time with different MEG starting times. To perform SLIM-MRE, the starting time for the j th direction (i.e., slice-, read- and phase-direction) at n th phase offset should be

$$S_{j,n} = \frac{1}{f} \text{modulo} \left\{ \frac{jn}{N}, 1 \right\}, \quad n = 0, 1, 2, \dots, N-1 \quad (\text{Eq. 1})$$

where N is the total number of phase offsets. Figure 2(a) displays the arrangement of MEGs with respect to the mechanical vibration for eight phase offsets. Finally, by applying Fourier transform on the acquired phase offsets ϕ_n , the complex tissue displacement information for each encoding direction can be fully recovered from different harmonics to calculate stiffness.

Klatt et al. performed in-vivo brain SLIM-MRE technique in healthy volunteers³⁴. Similar quantitative mechanical properties estimates were observed when compared to those obtained using conventional MRE scheme. However, SLIM-MRE is 2.5 times faster than conventional MRE. Figure 2(b) and (c) demonstrates the comparison between SLIM- and conventional MRE results in a volunteer.

Kearney et al. proposed to use MEGs with varying initial phases in SLIM-MRE to avoid the temporal shifting of MEG in creating different phase offsets, decreasing the achievable echo time (TE) in SLIM-MRE³⁵. Recently, Sui et al. proposed quadrature motion encoding (QuME) for spin-echo based MRE to shorten the TE in SLIM-MRE³⁶. Unlike SLIM-MRE, different phase offsets are achieved via modulating the amplitudes of two MEGs in QuME. Compared to the method by Kearney et al., QuME does not affect MEGs' moment nulling between encoding steps.

3.3 Diffusion and Diffusion Tensor Imaging MRE Sequences

Biological tissues, such as myocardium, spine, skeletal muscle, and brain white matter, exhibit anisotropic properties where the biomechanical properties vary in different spatial directions³⁷. Moreover, it was found that the anisotropy and diffusion properties can be altered by abnormalities in tissues, such as in liver, muscle, and white matter^{38–40}. Characterizing the anisotropic properties of soft tissues using diffusion tensor imaging (DTI) can be beneficial for (1) providing additional information in early diagnosis of diseases, (2) treatment monitoring, and (3) developing more accurate computational biomechanical models for MRE inversion. Therefore, combining MRE with diffusion imaging can provide complementary information about tissue mechanical properties, as well as about structural characteristics.

Performing MRE and diffusion scans in separate scans within one protocol can be time-consuming and limits its future application in clinical practice. Diffusion-MRE (dMRE) was proposed in which MRE and diffusion weighted imaging (DWI) images were simultaneously acquired⁴¹. The general principle of this technique is that harmonic vibration will introduce coherent phase shift (i.e., the MRE information), which can be encoded into the phase of MR signal while the diffusion-induced incoherent intravoxel dephasing (i.e., the diffusion information) will primarily affect the intensity of the MR magnitude image. Thus, it is feasible to encode both MRE and diffusion information into complex MR signal.

Recently, this technique has been extended further to simultaneously perform DTI and MRE (DTI-MRE)⁴². In DTI-MRE, the motion/diffusion-sensitizing gradients were applied with specific amplitudes, timings, and directions to encode MRE and diffusion information into the phase and magnitude of MR signal, respectively. Figure 3 demonstrates the DTI-MRE sequence with 12 gradient directions and gradient waveforms. Comparison between separate DTI/MRE and the proposed simultaneous DTI-MRE yielded similar results in in-vivo mice brains as shown in Figure 4. The DTI-MRE technique reduced the total scan time by/up to 50% when compared to the conventional, separate DTI/MRE acquisitions.

4. Accelerated MRE

One of the key elements in making MRE a more robust and clinically applicable technique in the future is its imaging speed. Although fast imaging techniques, such as sensitivity encoding (SENSE)⁴³ and generalized auto-calibrating partial parallel acquisition (GRAPPA)⁴⁴, have been proposed for conventional MR imaging where the magnitude images are of great interest, MRE is a phase-contrast imaging technique where the phase images contain the useful information. Therefore, there is an urgent need for developing a tailored fast-imaging strategy including both MR pulse-sequence and reconstruction development that explores the uniqueness of MRE data structure.

Two novel methods have been recently proposed for accelerating MRE measurements: compressive sensing (CS)^{45,46} and simultaneous multi-slice acquisition (SMS)⁴⁷. The k-space data is under-sampled in CS, while multiple slices are acquired at the same time in SMS with/without in-plane under-sampling.

4.1 Compressed Sensing MRE

Ahmad et al. proposed a CS technique named composite regularization with constant magnitude (CRCM) to recover phase images for estimating the shear stiffness of myocardium from under-sampled MRE data⁴⁸. In this method, the sparsity of the stiffness map in non-decimated wavelet domain was explored. In addition, as a phase-contrast imaging technique, the magnitude images of MRE measurements should not significantly vary across four phase offsets. Thus, this unique feature of MRE was used as prior knowledge for accurate stiffness map recovery in CRCM. Figure 5 displays the stiffness map reconstructed from fully sampled, GRAPPA (R=10) and CMCR (R=10) datasets. Compared to GRAPPA, CRCM maintained the accuracy of the recovered stiffness map while allowing high acceleration rates.

Bayesian method for magnetic resonance elastography using approximate message passing (BEAM) is another tailored CS technique for accelerating MRE proposed by Ebersole et al⁴⁹. In this method, transform sparsity of the stiffness map and magnitude consistency across different phase offsets were employed as prior knowledge for complex image recovery from highly under-sampled k-space data. In BEAM, iterative message passing algorithm was used to increase the computational efficiency. Figure 6(a) demonstrates the performance of BEAM under different acceleration rates for in-vivo liver MRE. Compared to GRAPPA with acceleration rate of 1.4, which is the current gold standard in clinical practice, BEAM was capable of accurately estimating the liver stiffness using only 20% of the scan time of that of GRAPPA acquisition. Figure 6(b) displays the Bland-Altman analysis between GRAPPA and BEAM for all volunteers with R=6.

4.2 Simultaneous Multi-Slice MRE

Simultaneous multi-slice acquisition (SMS) is another fast imaging technique that has the potential to accelerate MRE. This method largely relies on the total number of receiver coils available and their complex sensitivity profiles in spatial domain for separating simultaneously acquired slices⁴⁷. To excite multiple slices, sinusoidal modulation can be

applied to the RF pulse in the time domain. Guenther et al. has demonstrated the feasibility of SMS-MRE in gel phantom and in-vivo brain scans⁵⁰. In the study, multiband acquisition with Controlled Aliasing In Parallel Imaging Results In Higher Acceleration (CAPIRINHA) was employed for fast and SNR-efficient MRE measurements⁵¹. Good correlation was observed between conventional sequential multi-slice scans and SMS multi-slice scans. Similar wave structures were observed between conventional sequential and SMS-MRE multi-slice scans of in-vivo brain scans in two volunteers.

Recently, the SMS technique has been combined with in-plane acceleration (i.e., under sampling of k-space of each slice) to further shorten the imaging time of hepatic MRE. Majeed et al. proposed a novel SMS method by which 4 slices of diagnostic liver MRE data can be acquired within a single breath-hold (~16 sec)⁵². In this method, SMS has been applied together with GRAPPA using an established rapid MRE sequence⁵³. Figure 7 (a) compares a sequential multi-slice acquisition to a SMS acquisition in a healthy volunteer. For all volunteers, a strong linear correlation and excellent ($R^2 = 0.9$) agreement was observed between conventional and SMS methods (See Figure 7 (b)).

5. MRE Inversion

The process in which tissue shear modulus is calculated from the measured MRE displacement data is called MRE inversion. A variety of inversion algorithms have been proposed based on different assumptions. Simplified computational model under certain assumptions can result in estimation errors. Direct inversion (DI), multi-model DI (MMDI) and local frequency estimation (LFE) are examples of popular inversion algorithms. LFE derives shear modulus by estimating the spatial wavelength of the induced shear waves through lognormal filters in Fourier domain⁵⁴. This method has been employed in many pre-clinical studies and proved to be a robust method in the presence of noise.

5.1 Equation of Motion and Helmholtz Equation

An acoustic wave propagating in an infinite, homogeneous, viscoelastic, and isotropic medium can be described by the following equation:

$$-\rho\omega^2\mathbf{u} = \mu\nabla^2\mathbf{u} + (\lambda + \mu)\nabla(\nabla\cdot\mathbf{u}), \quad (\text{Eq. 2})$$

Where ρ is the density of the medium, $\omega = 2\pi f_{\text{mech}}$ is the mechanical frequency in *rads/s* $\mathbf{u}$ is a vector indicating the displacement field, μ is the shear modulus corresponding to shear deformation and λ is the second Lamé's constant corresponding to longitudinal deformation. Due to the incompressible nature of soft tissue, $\nabla(\nabla\cdot\mathbf{u})$ becomes a small value that is negligible. Thus, the second term on the right hand side is sometimes discarded, resulting in Helmholtz equation:

$$-\rho\omega^2\mathbf{u} = \mu\nabla^2\mathbf{u}. \quad (\text{Eq. 3})$$

It is important to notice that several critical assumptions have been made in deriving Equation 3.

5.2 Assumption1: Infinite Medium

In the Helmholtz equation, the medium is assumed to be infinite. For most soft tissues in which MRE has been performed (e.g., aorta, heart, and spinal cord), the media are bounded in which the propagating mechanical wave becomes complicated due to the relatively small dimensions and the geometry of the object⁵⁵. Additionally, in bounded media, the equation of motion presented in Equation 2 will no longer hold and thus, new equations of motion that take geometry of the medium into account are needed.

Kolipaka et al. proposed mathematical inversion algorithms that are capable of resolving shear stiffness from flexural waves in bounded media⁵⁶. In this study, geometry of beam, plate and spherical shell was investigated and taken into account in deriving the resulting stiffness using geometry-specific equations of motion. Stiffness obtained from MRE measurements, finite element modeling and mechanical testing were compared, demonstrating good agreement.

5.3 Assumption 2: Homogeneous Medium

The Helmholtz equation assumes medium homogeneity, which is not true in a majority of soft tissues. For instance, many breast tumors have significantly different texture and mechanical properties from the surrounding healthy tissues. Consequently, this simplification will lead to estimation errors at or near the boundaries between different regions¹⁵. In addition, by assuming homogeneous medium, the spatial resolution in the resulting elastogram will be mainly limited by the local window size used for stiffness estimation.

A novel implementation of a variational formulation was proposed by Romano, et al. to determine material mechanical properties in an inhomogeneous elastic medium⁵⁷. Different FEM inversion methods have also been recently proposed in which local homogeneity is not assumed^{58–67}. In general, these methods can be grouped into two categories: (1) iterative methods^{58–64} and (2) direct methods^{65–67}. Iterative methods derive stiffness iteratively via minimizing a cost function, which is usually chosen to be the difference between the calculated and measured displacements, while direct methods estimate shear modulus directly from the measured displacement data.

Van Houten et al. proposed an overlapping subzone iterative FEM inversion technique that is capable of recovering tissue mechanical properties at a resolution of MR pixel size⁶². In this technique, overlapping subzones are defined and processed in a hierarchical order determined by progressive error minimization. More specifically, mechanical properties are derived in each pre-defined subzone by minimizing the difference between the measured tissue displacement and the calculated displacement that is corresponding to the mechanical properties in each iteration. This inversion technique has been tested in simulated data with 15% noise and proven to distinguish inclusions as small as ~4 mm in diameter.

5.4 Assumption 3: Isotropic Medium

The third assumption of the Helmholtz equation is isotropic medium. This assumption is not valid in tissues such as white matter, skeletal muscle and myocardium where the tissue mechanical behavior in the direction that is parallel to fiber orientation is significantly different from those in perpendicular to the fiber direction³⁷.

A transversely isotropic model was proposed by Sinkus et al. in estimating anisotropic and viscous properties of breast tissue using MRE⁶⁸. This model was capable of describing anisotropic shear stiffness parallel to fibers. In-vivo results of breast lesions from two patients demonstrated enhanced anisotropic and viscous properties and a preferred fiber orientation.

Papazoglou et al. proposed shear wave group velocity inversion to quantify the anisotropic shear stiffness of human skeletal muscle⁶⁹. In this method, group wave velocity was obtained by automatic analysis of wave-phase gradients on a spatial-temporal scale. Subsequently, two shear moduli (i.e., one parallel and one perpendicular to the muscle fiber) were derived via analyzing the directional dependence of shear wave speed.

Ramano et al. proposed waveguide elastography in which DTI and MRE were used to derive the anisotropic elasticity tensor of white matter tracts in human brain⁷⁰. DTI was employed to delineate the fiber directions, while spatial-spectral filtered MRE data was used to track the propagation of shear waves at specific angles to the fiber orientations. Waveguide analysis was then performed to estimate anisotropic stiffness tensor⁷¹. Figure 8 displays the waveguide elastography in corticospinal tracts (CSTs). Using a similar method, Ramano et al. observed reduced anisotropic shear moduli polarized parallel and perpendicular to the CSTs in 14 amyotrophic lateral sclerosis patients⁷².

Recently, Miller et al. studied the relative detectability of tissue anisotropic properties from MRE⁷³. In this work, a FEM-based inversion method was proposed in which anisotropic material properties were estimated by iteratively minimizing the ground truth and the estimated displacement resulted by the material properties under iteration. This method was evaluated in an isotropic physical gel phantom with known properties and an anisotropic left ventricular (LV) finite element model with a histology-derived fiber field. Transverse and fiber Young's moduli, shear modulus and damping coefficient were well identified using the proposed method.

5.5 Assumption 4: Negligible Longitudinal Term $(\lambda + \mu)\nabla(\nabla u)$

In the Helmholtz equation, $(\lambda + \mu)\nabla(\nabla u)$ is discarded due to the incompressible nature of soft tissue which leads to negligible $\nabla(\nabla u)$. However, this can be controversial. This is because λ resulted by longitudinal waves can be of large magnitude, compensating the small magnitude of $\nabla(\nabla u)$.

Curl processing was proposed by Sinkus et al. to remove the effects of the longitudinal wave and thus, completely eliminate $(\lambda + \mu)\nabla(\nabla u)$ term from Equation 2^{68,74}. Applying curl operator to the acquired MRE displacement data yields

$$-\rho\omega^2 \nabla \times \mathbf{u} = \mu \nabla^2 (\nabla \times \mathbf{u}), \quad (\text{Eq. 4})$$

Where $\nabla \times \mathbf{u}$ is the curled displacement data. Subsequently, MRE stiffness can be correctly derived from Equation 4. Curl processing has been incorporated into various inversion algorithms, such as finite element method⁷⁵ and direct inversion⁶⁸. Promising results in different applications were observed. Manduca et al. studied the waveguide effects in simulated cardiac MRE data using FEM and reported that inversion without curl processing resulted in biased stiffness values⁵⁵. Moreover, it was observed that 3D inversion on curl-processed MRE data yielded more accurate stiffness estimation when compared to 2D inversion with curl processing, suggesting the importance of 3D MRE inversion.

Equation 4 involves taking 3rd-order spatial derivatives of the acquired data, making signal-to-noise (SNR) ratio a critical concern in the success of applying the curl operator. For low SNR data, an MRE inversion technique that is robust to noise is needed to avoid noise amplification caused by taking higher-order spatial derivatives.

Dong et al. proposed Helmholtz inversion using unconstrained optimization for MRE⁷⁶. In their work, the cost to be optimized is a function of both the displacement data and pursued stiffness. Two regularization terms are used to measure (1) the deviation of the reconstructed displacement $\mathbf{u}$ from the measured (noisy) displacement $\mathbf{u}_0$, and (2) the sparsity of the reconstructed stiffness μ in non-decimated wavelet domain. Figure 9 demonstrates the performance of LFE and the optimization method in a physical phantom with added Gaussian noise.

5.6 Neural Network Inversion (NNI)

Recently, Murphy et al. studied the feasibility of estimating stiffness using an artificial neural network (ANN)⁷⁷. In this work, a feed-forward neural network model with 3 hidden layers of 24 neuron units per layer was used. NNI is data-driven and trained to accurately estimate the stiffness. Therefore, MRE inversion using neural networks can potentially avoid practical issues that are encountered in conventional inversion methods, such as making various assumptions and simplifications, partial volume effect, noise, etc. Preliminary results in simulation, liver, and brain suggested that ANN-stiffness estimates were highly correlated to direct inversion results and more resistant to noise than an algebraic DI approach. Figure 10 demonstrates the comparison between MMDI and NNI results in liver MRE.

6. Future MRE Applications

6.1 Brain MRE

One of the most promising future clinical applications of MRE is estimating the mechanical properties of brain. Although conventional MRI has demonstrated success in imaging the anatomical structure of brain in clinical practice, non-invasively studying the mechanical properties of brain is still an area of considerable research interest². The stiffness variation of human brain tissue is known to be associated with different abnormalities, such as

multiple sclerosis (MS), Alzheimer's disease (AD) and brain tumors, making MRE a potential clinical tool in detecting and monitoring brain diseases.

Wuerfel et al. studied 45 MS patients using single-shot EPI MRE sequence with multi-frequency vibration⁴⁰. Significant decrease in cerebral viscoelasticity in MS patients was observed when compared to age-matched healthy volunteers. In a recent study conducted by Murphy et al., 7 probable AD patients, 14 Pittsburgh Compound B (PIB)-normal control subjects and 7 PIB+ normal control subjects were recruited for brain MRE²⁰. Decrease in brain stiffness was observed in AD patients when compared to age- and gender-matched control subjects (See Figure 11).

Romano et al. performed traumatic brain injury (TBI) study using mixed-model inversion (MMI) where fractional anisotropy (FA) was used as a threshold to determine if an isotropic or anisotropic inversion should be employed⁷⁸. Figure 12 demonstrates the comparison of white matter stiffness of the thalamus region between a healthy and moderate TBI patient.

In another study by Murphy et al., 13 patients with meningioma were recruited for brain MRE before surgical removal of the tumor⁷⁹. Both MRE-derived tumor stiffness alone and ratio of tumor stiffness to surrounding tissue stiffness was found to be significantly correlated to the surgical findings. Figure 13 displays an example of brain MRE stiffness measurements in two patients with different tumor properties. Pepin et al. reported significant decrease in MRE-derived tumor stiffness within 4 days of chemotherapy treatment in a mouse model while there was no appreciable volume change of the tumor, suggesting brain MRE can be a new imaging biomarker in assessing early tumor response to chemotherapy⁸⁰. Recently, Yin et al. and Kalra et al. performed preoperative assessment of tumor stiffness and tumor-brain adhesion in patients with vestibular schwannoma using a MRE-based method^{81,82}. MRE-derived octahedral shear strain (OSS) measurements at the tumor-brain interface was used to quantify the degree of adhesion (See Figure 14). Preliminary results showed a good correlation between preoperative assessment of tumor and surgical findings. In another study, brain stiffness in normal volunteers were compared against pseudotumor patients and showed that pseudotumor patients have significantly higher stiffness compared to normals⁸³.

6.2 Cardiac MRE

The elasticity of myocardium largely determines the capability of heart function, which is well known to be associated with a variety of cardiovascular diseases, such as myocardium infarction^{84,85}, diastolic dysfunction⁸⁶, hypertrophic cardiomyopathy⁸⁷, and hypertension⁸⁸. This gives rise to the significant interest of studying the mechanical properties of myocardium, a potential clinical application of MRE.

Recently, the reproducibility of cardiac MRE has been studied by Wassenaar et al. in 29 healthy volunteers⁸⁹. It was observed that cardiac MRE-derived stiffness is reproducible with myocardial stiffness changing cyclically across the cardiac cycle. Moreover, myocardial stiffness is significantly higher during end-systole (ES) compared to end-diastole (ED). In a study conducted by Kolipaka et al., MRE was employed as a method for the assessment of effective myocardial stiffness in pigs throughout the cardiac cycle²² and its comparison to

invasive LV pressure. A good correlation was observed between invasively measured LV pressure and MRE-derived effective stiffness with $R^2 = 0.84$.

Elgeti et al. measured shear wave amplitudes using cardiac MRE for diagnosis of diastolic dysfunction in 30 patients⁹⁰. Significantly lower shear wave amplitude (SWA) values in patients with diastolic dysfunction was observed with an inverse correlation to disease severity, demonstrating that LV SWA can provide image contrast to myocardial relaxation abnormalities. Mazumder et al. performed a series of animal studies involving (1) hypertensive model that creates heart failure with preserved ejection fraction (HFpEF)^{91,92} and (2) myocardial infarction (MI) in pigs⁹³. Myocardial stiffness increased in animals with hypertension (HFpEF) and MI when compared to normal controls. Figure 15 and 16 demonstrates an increase in myocardium stiffness in hypertension and MI porcine models, respectively. Recently, Arani et al. also demonstrated that myocardial stiffness is significantly higher in cardiac amyloidosis patients compared to normal controls²⁸.

Romano et al. and Mazumder et al. used waveguide MRE to assess the anisotropic stiffness of myocardium^{94,95}. Mazumder et al. demonstrated the anisotropy of the myocardium, indicating higher stiffness coefficients in systole compared to diastole and that longitudinal coefficients have significantly higher stiffness compared to shear stiffness coefficients⁹⁵. In the future, estimating anisotropic stiffness of the myocardium might play an important role in diagnosing and developing different therapeutic agents for treating systolic- and diastolic dysfunction-based diseases.

6.3 Aortic MRE

It is well known that the mechanical properties of the aorta are associated with a variety of cardiovascular comorbidities, such as atherosclerosis, aortic aneurysm, hypertension and aging-related vascular degeneration^{96–99}. Moreover, aortic stiffening is an indication of elevated risk of cardiovascular events^{100–102}, making aortic stiffness an important factor in understanding and diagnosis of cardiovascular diseases. For example, aortic (arterial) stiffness increases with hypertension, which diminishes the buffering capacity of the vasculature to the heart pulsatility, leading to end-organ damage eventually. Additionally, in aortic aneurysms determining the rupture potential based on stiffness estimation is very important to avoid sudden death. Therefore, studying aortic stiffness can potentially enable early detection as well as appropriate intervention of such events prior to any severe damage, resulting in more desirable treatment outcome.

In a preliminary study by Woodrum et al., a GRE MRE sequence with multiple mechanical vibration frequencies were used to estimate Young's modulus-wall thickness product ($E * t$) in a vessel model¹⁰³. The results suggested that vascular wall elasticity could be quantitatively measured by MRE.

Excellent reproducibility of the aortic MRE was observed by Kenyhercz et al.¹⁰⁴. In this work, a retrospectively pulse-gated GRE MRE sequence was applied to study the reproducibility as well as aortic stiffness across the cardiac cycle in 20 healthy volunteers. Aortic stiffness changed across the cardiac cycle with significantly higher ES stiffness compared to ED stiffness.

Damughatla et al. estimated aortic stiffness using MRE and compared the results to the MRI-based pulse wave velocity (PWV) in 21 healthy volunteers¹⁰⁵. Both MRE stiffness and PWV stiffness increased with age. However, poor linear correlation was found between MRE-derived stiffness and PWV-derived stiffness.

Kolipaka et al., Dong et al. and Woodrum et al. studied the influence of systemic arterial hypertension on aortic stiffness in volunteers, in-vivo and ex-vivo porcine aortas, respectively^{23,106,107}. Higher aortic stiffness within hypertensive aortas was observed in all studies. Figure 17 displays the elevated aortic stiffness in a hypertensive patient compared to a normotensive control. In hypertensive porcine model, moderate Spearman's correlation ($\rho=0.52$, $p=0.046$) was observed by Dong et al. between mean arterial pressure and effective aortic stiffness.

Evaluating the rupture risk of an abdominal aortic aneurysm (AAA) using the aortic MRE is another promising application of significant clinical interest. Currently, AAA diameter is the gold standard in assessing rupture risk. AAA with diameter $>5.5\text{cm}$ is considered high-risk. However, multiple studies have observed that small AAAs ($<5.5\text{cm}$) also frequently rupture, arguing that diameter is a poor metric in assessing rupture potential^{108–110}. Compared to AAA diameter, AAA stiffness is able to provide critical information about (1) the overall mechanical integrity of AAA, (2) the aortic wall microstructure and (3) the extracellular matrix (ECM) remodeling process, and thus potentially provides more accurate rupture risk evaluation^{4,5,24}.

Dong et al. studied the feasibility of AAA MRE in a porcine model using a retrospectively pulse-gated GRE sequence with 70Hz mechanical excitation generated through a pneumatic driver^{111,112}. Significantly higher aortic stiffness was observed in the AAA when compared to normal aorta. Recently, the same group compared MRE-derived AAA stiffness to burst testing results in 5 Yorkshire pigs¹¹³. It was observed that the aortic stiffness was significantly higher in pigs with AAA when compared to a normal aorta, while bursting pressure was significantly lower in the AAA group due to decrease in structural strength caused by the AAA calcification.

Kolipaka et al. performed the first in-vivo quantification of MRE-derived aortic stiffness in AAA patients and studied the correlation between stiffness and AAA diameter²⁴. In this study, 36 individuals (24 AAA patients and 12 age-matched healthy volunteers) were recruited to undergo an aortic MRE using a rapid GRE MRE sequence with 60Hz harmonic excitation. No significant correlation was found between AAA stiffness and diameter or the amount of thrombus or calcium score. AAA stiffness (mean: $13.976 \pm 4.2\text{ kPa}$) was significantly higher than in normal subjects (mean $7.16 \pm 1.9\text{ kPa}$). Figure 18 demonstrates aortic stiffness in AAA patients with different diameters indicating AAAs with small diameters have higher stiffness or vice-versa.

Recently, Dong et al. conducted a longitudinal study in 37 AAA patients to understand the relationship between the AAA stiffness variation and diameter over a period of 3 years^{114,115}. Each patient was serially scanned every 6 months to obtain MRE-derived aortic stiffness via a rapid GRE MRE sequence with 60Hz mechanical excitation. MRE results

demonstrated that aortic stiffness varied during the serial follow-ups, indicating changes in the AAA wall integrity. However, no significant correlation was observed between aortic stiffness and the AAA diameter, suggesting that the AAA diameter may not be adequate to determine the mechanical integrity of aneurysms.

6.4 Lung MRE

Lung parenchyma is a constantly pre-stressed mesh containing mainly connective tissues, such as elastin, collagen, and proteoglycans. It is appreciated that the functionality of the lung is closely associated with its gross topographically heterogeneous mechanical properties¹¹⁶. For instance, emphysema is a lung disease in which the lung loses its parenchymal tissues over time, leading to reduced lung stiffness and thus causing hyperinflation and airway collapse^{117,118}. On the other hand, in lung fibrosis, parenchyma stiffness increase is observed attributing to the elevated deposition of collagens and concomitant change of tissue architecture¹¹⁹. The widely accepted diagnostic methods for lung diseases, such as computed tomography (CT) and spirometry, can only provide a global evaluation of lungs without spatially resolved mapping of the intrinsic mechanical properties of the lung⁶⁶. This promotes the use of MRE in lung applications. However, performing lung MRE is technically challenging due to (1) low tissue density (0.2–0.3 g/cm³) and (2) very short T2* (less than 3 ms).

The feasibility of quantifying the mechanical properties of lung parenchyma using ¹H MRE in a small-animal model was studied by McGee et al.¹²⁰. In this work, a pneumatic drum-like driver with a needle tip was applied on 10 ex-vivo rats' lungs to generate 200Hz harmonic waves, which were imaged via a SE MRE sequence. The study demonstrated that the proposed approach was capable of resolving differences in shear stiffness associated with change in inflation pressure. Mariappan et al. developed in-vivo ¹H lung MRE and validated the technique in 10 healthy volunteers¹²¹. In the study, a modified SE sequence with fractional encoding, MEG splitting and employing MEG as crushers for 180° refocusing pulse was proposed to shorten the TE. Lung stiffness at different respiration states was tracked. Figure 19 displays that density corrected stiffness values demonstrating stiffness at total lung capacity (TLC) was higher than that of the residual volume (RV). Another study was performed in 10 adult pigs to study the relationship between MRE-derived lung stiffness and airway opening pressure (P_{ao})¹²². It was demonstrated that the change in shear stiffness was observed due to change in airway opening pressure. Recently, the reproducibility of lung MRE was studied using an SE-EPI MRE sequence in 15 healthy volunteers¹²³. Good reproducibility of lung MRE-derived stiffness measurements was observed in RV ($R^2 = 0.88$) and TLC ($R^2 = 0.96$).

McGee et al. assessed parenchymal stiffness in normal and edematous lung in rats using MRE¹²⁴. Significant lower stiffness was observed in the diseased lungs. Recently, in a patient study performed by Marinelli et al., lung parenchymal shear stiffness increased in patients with fibrotic interstitial lung diseases when compared to normal controls¹²⁵ (Figure 20).

6.5 MRE of Breast

Elasticity of breast tissue plays a critical role in diagnosing suspicious breast lesions. Malignant breast tumors are usually stiffer than benign tissues. Currently, palpation and x-ray mammography still remain as the primary methods for initial detection and screening of breast cancer. Although an initial clinical study suggests the potential of ultrasound elastography in differentiating cancerous masses in the breast; however, many malignant lesions are detected at a later pathological stage because of the small size of the lesion and the insignificant elasticity change when compared to surrounding healthy tissue¹²⁶.

Recent advancement in MRE has demonstrated its reproducibility of quantifying breast stiffness¹²⁷, and the possibility of early detection of malignant breast tumors using high-resolution tensor MRE¹²⁶. Hawley et al. evaluated the reproducibility of MRE-based breast stiffness estimation using a soft sternal driver at 3T MR scanner and compared the results with qualitative measures of breast density (i.e. BI-RADS scores)¹²⁷. High reproducibility was observed. Moreover, significantly higher stiffness was found in dense breasts compared to non-dense breasts. Sinkus et al. assessed the entire symmetric elasticity tensor in the breasts via evaluating the harmonic wave phases within one mechanical cycle, allowing estimation of the anisotropy of the elasticity tensor¹²⁶. It was observed that malignant tumor tissue possesses an anisotropic elasticity distribution while surrounding benign tissue exhibits isotropy. Sinkus et al. also studied the viscoelasticity of breast lesions in a recent study¹²⁸. It was found that malignant lesions exhibited a more liquid-like behavior when compared to benign breast tissues (Figure 21), indicating that understanding the solid/liquid duality using MRE has the potential in improving the specificity of contrast-enhanced MR mammography.

7. Future Work

This review has highlighted the recent developments and the importance of novel driver technology, accelerated acquisition strategies, robust inversion algorithms as well as promising pre-clinical MRE applications. The future development of MRE involves the following aspects. First, there is a need for developing high-amplitude and high-frequency shear wave drivers that can be used in imaging small regions of interest. Second, it is critical to accelerate MRE by further developing/adapting CS and SMS techniques so that MRE measurements can be obtained in a breathhold or shorter scan time which is more clinically viable. Third, developing a robust inversion algorithm that accounts for the geometry, tissue heterogeneity, anisotropy and longitudinal waves is important in generating accurate stiffness maps. Finally, most of the techniques discussed in this review are implemented in pre-clinical settings. These methods have to be demonstrated in clinical settings to make MRE a promising imaging modality for diagnosis.

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Figure 1. Cardiac-Gated SE-EPI MRE Sequence.

A spin-echo preparation is followed by rapid EPI readout. The external mechanical waves start 100 ms after receiving an ECG R-wave for the first phase offset and the trigger point will be shifted accordingly to create subsequent phase offsets. A MEG can be applied along any encoding axis to sensitize the motion along that specific direction. In this sequence, a 1–2–1 MEG is employed to avoid flow-induced spin dephasing.

Figure 2. MEG Timing for SLIM-MRE.

In SLIM-MRE, MEGs along all three motion-encoding directions are simultaneously applied with different starting times. This figure demonstrates the starting time of MEGs for 8 MRE phase offsets (a). Only one MEG cycle is shown for each phase offset and encoding direction. The real part of the complex displacement images in x-, y- and z-direction acquired with SLIM-MRE were compared to those yielded via conventional MRE (b). In (c), storage modulus (G_S) and loss modulus (G_L) maps estimated from both methods using algebraic Helmholtz inversion were displayed. This figure was reproduced with permission.

Figure 3. Schematic of DTI-MRE Sequence.

A spin-echo based DTI-MRE sequence with shaded gradient lobes for diffusion/motion sensitizing and can be applied along any of three encoding directions (a). The relationship between MRE phase offsets and DTI directions was shown in (b) for the case where 4 MRE phase offsets and 12 DTI directions were required. The gradient waveform used in the study was displayed in (c). This figure was reproduced with permission.

Figure 4. Comparison between DTI-MRE and Conventional DTI and MRE.

Results from DTI-MRE and conventional DTI and MRE were compared. Fractional anisotropy (FA) and mean diffusivity (MD) maps were compared in (a). The real part of the complex displacement images in x-, y- and z-direction acquired with DTI-MRE were compared to those yielded via conventional methods (b). Elastograms (i.e., stiffness maps) estimated from the measured displacement were demonstrated in (c). This figure was reproduced with permission.

Figure 5. Myocardial Stiffness in a Volunteer.

Stiffness maps (in kPa) of the left ventricle estimated from fully sampled ($R=1$), GRAPPA ($R=10$) and CRCM ($R=10$) MRE dataset were compared. CRCM maintained the accuracy of the recovered stiffness map while allowing high acceleration rates. This figure was reproduced with permission.

Figure 6. Comparison between GRAPPA and BEAM with Different Acceleration Rates in In-Vivo Liver Scan.

Liver stiffness maps obtained using BEAM under different acceleration rates were compared to the one estimated using current clinical protocol: GRAPPA (R=1.4) (a). Similar stiffness was observed. Bland-Altman analysis performed between BEAM (R=6) and GRAPPA (R=1.4) is shown in (b) and it confirms the tight narrow confidence interval and low mean bias. This figure was reproduced with permission.

Figure 7. Comparison between In-Vivo SMS and Sequential Liver MRE.

Measurements from a healthy subject with normal liver stiffness were demonstrated in (a). Similar magnitude images, wave images and stiffness maps were observed. Mean liver stiffness for sequential rMRE and SMS-rMRE was 1.57 ± 0.59 kPa and 1.58 ± 0.045 kPa, respectively. For all volunteers, a strong linear correlation ($R^2 = 0.9$) was observed (b). This figure was reproduced with permission.

Figure 8. Waveguide Elastography in Corticospinal Tracts.

The DTI tractography of the left and right CSTs from a volunteer was shown in (a). The unfiltered displacement along the CSTs was displayed in (b). The results after applying the spatial-spectral filter and Helmholtz decomposition on the measured data demonstrates the transverse waves (c) and the longitudinal waves (d) propagating up the CSTs. The displacement directions in (b), (c) and (d) were represented by arrows and the vector lengths indicate relative amplitudes. The dynamic range is ± 80 microns for (b) and ± 2.0 microns for (c) and (d). The color represents the stiffness values. This figure was reproduced with permission.

Figure 9. Stiffness Measurements using Optimization Inversion.

MRE measurements were performed on a physical phantom. Wave images and the corresponding stiffness maps yielded by LFE and optimization method were demonstrated (a). More consistent and less noisy stiffness estimation was observed in optimization-derived results when compared to LFE-derived stiffness maps. Degradation in stiffness accuracy was more significant in LFE results when higher Gaussian noise (i.e., 5%) was added to the wave images as demonstrated in (b) and (c). This figure was reproduced with permission.

Figure 10. Comparison between MMDI and NNI in Liver MRE.

Wave images and the corresponding stiffness maps yielded by MMDI and NNI method were demonstrated in (a). High correlation was observed between MMDI and NNI results with $R^2 = 0.974$ (b). MMDI and NNI results as a function of fibrosis stage are displayed in (c) and (d), respectively. This figure was reproduced with permission.

Figure 11. Brain MRE in Healthy Subject and AD Patient.

The magnitude images, wave images and the corresponding stiffness map were displayed. Top row and bottom show the MRE measurements from an 89-year-old PIB-cognitively normal (CN-) male subject and 93-year-old AD male patient, respectively demonstrating lower stiffness in the AD patient. This figure was reproduced with permission.

Figure 12. Thalamus White Matter Stiffness in Sagittal View using Mixed-model Inversion. Sagittal view of the healthy control (left) and the TBI patient (right) using mixed-model inversion showing diffusion ellipsoids colored by isotropic and anisotropic shear stiffness, C44, in white matter in magnified views of the thalamus region. The healthy volunteer demonstrated higher white matter stiffness. This figure was reproduced with permission.

Figure 13. Brain Tumor Stiffness in Two Patients.

The magnitude images, wave images and the corresponding stiffness maps were displayed. Top and bottom row demonstrated the brain MRE measurements from two patients with hard and soft meningioma, respectively. This figure was reproduced with permission.

Figure 14. Pre-operative Assessment of Tumor-Brain Adhesion in Vestibular Schwannoma Patient.

Brain MRI and MRE were performed on a 62-year-old female patient with vestibular schwannoma. The cerebrospinal fluid cleft was observed as high signal intensity on the bSSFP image (a) and low signal intensity on the T2-weighted FLAIR image (b). The low-signal shear line in (c) and high OSS values around the tumor surface (d) suggest the independent motion between the tumor and the adjacent tissues, which was also confirmed by subsequent surgical findings. This figure was reproduced with permission.

Figure 15. Cardiac MRE in Hypertension Porcine Model.

The magnitude images, wave images and the corresponding stiffness maps at end-systole (ES) and end-diastole (ED) were displayed for measurements at baseline, one month post-surgery and two months post-surgery. Higher stiffness was detected at ES than that of ED. Moreover, myocardial stiffness increased as the disease progressed. This figure was reproduced with permission.

Figure 16. Cardiac MRE in Myocardial Infarction (MI) Porcine Model.

The magnitude images, wave images and the corresponding stiffness maps at end-systole (ES) and end-diastole (ED) were displayed for measurements at baseline and 21 days after MI. Higher stiffness was detected at ES than that of ED. Moreover, myocardial stiffness increased as the disease progressed. This figure was reproduced with permission.

Figure 17. MRE-Derived Aortic Stiffness of Normotensive and Hypertensive Subjects.

The magnitude images (a), wave images (b-e) and the corresponding MRE-derived effective aortic stiffness (f) were displayed for a healthy control (top row) and a hypertensive patient (bottom row). The mean aortic stiffness was higher in hypertensive patients (11.4 kPa) when compared to normotensives (4.20 kPa). This figure was reproduced with permission.

Figure 18. Aortic Stiffness in AAA Patients.

Sagittal magnitude image of one of the participants with red contour delineating the aorta was displayed in (A). Snapshots of wave propagation at four points in time were shown in (B-E). Weighted stiffness map from x-, y- and z-encoding directions of the same participant was shown in (F). Sagittal magnitude images and the corresponding stiffness maps for three participants with AAA diameters of 5 cm, 4.5 cm and 3 cm and mean stiffness values of 10.3, 28.1 and 12.2 kPa, respectively, were demonstrated in (G-L). AAAs with similar diameters have considerably different mean aortic stiffness. This figure was reproduced with permission.

Figure 19. Lung MRE Data at Residual Volume and Total Lung Capacity.

Magnitude images (a, d), displacement images (b, e) and the stiffness maps (c, f) at RV and TLC were demonstrated. Longer shear waves and higher lung stiffness was observed at TLC. This figure was reproduced with permission.

Figure 20. Lung MRE in Healthy Subject and Patient with Interstitial Disease.

MRE-derived lung stiffness map of a healthy subject (top row) and a patient (bottom row) at RV and TLC were demonstrated, respectively. Higher stiffness was observed at RV and TLC in the patient with interstitial disease when compared to that of a healthy volunteer. This figure was reproduced with permission.

Figure 21. Viscoelasticity of Breast Lesion.

Real part of complex modulus, G_d (red), imaginary part of complex modulus, G_l (green), magnitude of complex modulus, $|G^*|$ (blue) and the exponent y (black) as a function of frequency for a healthy volunteer's parenchyma were demonstrated in (a). The real part (G_d) and imaginary part (G_l) of the complex modulus G^* of a breast tumor patient were shown in (b) and (c), respectively. The original variables describing a power law behavior for propagation y and attenuation α_0 were displayed in (d) and (e), respectively. Elevated stiffness and more liquid-like behavior was observed when compared to benign breast tissues. This figure was reproduced with permission.