MRI & Mechanobiology: New Science at the Intersection of Engineering and Medicine

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ABSTRACT

Many disease processes such as cancer cause profound changes in the mechanical properties of tissues. This accounts for the efficacy of palpation for detecting abnormalities and provides motivation for developing practical methods to quantitatively image tissue elasticity. Magnetic Resonance Elastography (MRE) is an emerging MRI-based technique that can quantitatively image tissue properties such as stiffness, viscosity, attenuation, and anisotropic behavior - providing access to a new range of previously unexplored tissue imaging biomarkers highly relevant in diagnostic medicine and in the emerging field of mechanobiology.

Human studies have demonstrated that it is feasible to apply MRE to quantitatively assess skeletal muscle, brain, thyroid, breast, myocardium, kidney, liver, and skin. The first established clinical application of the technology is for detection of hepatic fibrosis, which is a growing health problem and the most important precedent to primary hepatic malignancy. Growing clinical experience indicates that MRE is at least as accurate as liver biopsy for this diagnosis, while also being safer, more comfortable, and less expensive.

Preliminary studies suggest that MRE may be helpful in differentiating between benign and malignant neoplasms. New research has also shown that MRE-assessed estimates of tumor stiffness are helpful in the preoperative assessment of patients with brain tumors such as menigiomas.

Keywords: Magnetic resonance elastography, MRE, shear stiffness, shear waves, hepatic fibrosis

Introduction

For centuries, physicians have used palpation as an important diagnostic tool. The efficacy of this time-tested physical examination technique is based on the fact that many disease processes cause marked changes in the mechanical properties of tissue. Many tumors of the breast, thyroid, and prostate are first detected by touch. In vitro testing of surgical specimens has shown that the elastic modulus of breast tumors is typically much higher than normal fibroglandular tissue[1]. Other diseases cause diffuse changes in the stiffness of tissues. For instance, measurements of the shear elasticity of liver tissue in humans have shown that patients with advanced hepatic fibrosis have stiffness values that are 3-5 times higher than normal[2]. It is also known that the elastic moduli of many tissues can vary widely in response to physiologic state[1,3]. For example, the elasticity of muscle in the relaxed and contracted state can differ by more than 100-fold[3].

None of the conventional imaging technologies such as CT, MRI, and US provide the type of information elicited by palpation. These observations have provided motivation for developing practical imaging technologies for quantitatively assessing the mechanical properties of tissues.

Elastic Properties of Tissues

Various terms such as “hardness” and “compressibility” are used in clinical medicine to describe the mechanical properties of tissues elicited by palpation. In physics and engineering, elastic properties are described quantitatively as *moduli*. For instance, *Young’s modulus* of elasticity (E) describes longitudinal deformation (strain) in response to longitudinal force (stress). The *shear modulus* (μ) relates transverse strain to transverse stress. The *bulk modulus* (K) describes the change in volume of a material due to an external stress. Another physical property of isotropic Hookean solids is *Poisson’s ratio* (ν), which is the ratio of transverse contraction per unit breadth divided by longitudinal extension per unit length.

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Which of these physical parameters correspond most closely to the tissue characteristics elicited by palpation? Most soft tissues have mechanical properties that are intermediate between those of fluids and solids. As a result, the value of Poisson's ratio for soft tissues is in the range of v= 0.490 - 0.499, close to the value for liquids ($\nu = 0.500$). This leads to the result that there is a consistent relationship between the Young's and shear moduli of most soft tissues in that they differ only by a scaling factor of 3 *($E = 3\ \mu$)*. Another characteristic that soft tissues share with liquids is that they are nearly incompressible. In contrast to the many orders of magnitude over which the Young's and shear moduli are distributed, the bulk moduli of most soft tissues differ by less than 15% from that of water[4].

These concepts represent a simplification of the mechanical behavior of soft tissues, which in general are anisotropic, non-Hookean, and viscoelastic. Therefore, elastic moduli may be represented as complex quantities that vary with stress rate and with spatial orientation. Depending on the rheological model used to explain the observed stress/strain relationship as it varies with shear rate, these phenomena may provide additional independent parameters for tissue characterization[5]. As a convention, when we report the scalar coefficient that relates dynamic stress to strain at a given experimental shear rate, we generally refer to it as the observed *"shear stiffness"*, and reserve the term *"shear modulus"* for calculated values that take into account the complex value of the quantity and the effect of shear rate.

Motivation for Developing Quantitative Elastography

Tumor Detection and Characterization

The hallmark of many malignant tumors is high stiffness, which has been attributed to increased interstitial pressure, altered cytoarchitecture, and matrix stiffening due to fibrosis[6]. Our research, and that of others, has demonstrated the feasibility of using MRE to delineate breast tumors *in vivo*[7,8]. A particularly attractive potential application of MRE in this context is to use it in conjunction with dynamic conventional contrast-enhanced MRI to potentially improve the specificity of lesion classification[9].

Diagnosis of Non-Neoplastic Disease

Many other disease processes (inflammatory, fibrotic, infiltrative, etc.) may significantly affect the mechanical properties of tissues. Tissue fibrosis (of the liver, pancreas, bowel wall, etc.) is a common pathway in many diseases, which can cause markedly increased tissue stiffness and significant organ dysfunction long before any changes in gross morphology appear[10,11]. MRE offers a range of potential new parameters for tissue characterization including, most importantly, the complex-valued shear modulus, as well as shear wave attenuation, strain-dependent nonlinearity, frequency dependence, rheology, and anisotropy. These parameters may provide important new criteria for tissue characterization in the evaluation of diseases affecting many tissues and organs, from liver to brain.

Noninvasive Observation of Biomechanical Loading in Tissues

The observed shear stiffness of a tissue, such as muscle, depends not only on the intrinsic mechanical properties of the tissue but also on the static mechanical preload ("stretched cable" effect) and the stiffening effect of crossbridge formation during active muscle contraction. Thus, MRE may provide a unique way to observe the functional status and distribution of tension in tissues such as the uterine, bladder, and bowel walls when subjected to biomechanical loading[12]. This capability offers new ways to study functional disorders such as myofascial taut bands.

Tissue Matrix Mechanobiology

In the field of cell biology there has been a recent growing awareness of the importance of tissue matrix mechanics on cellular function in natural and engineered tissues. Cells are known to sense their mechanical environment through myosin-based contractility of the cytoskeleton in conjunction with adhesion molecules such as integrins and cadherins. Cells react to the dynamic and static properties of their matrix environment through mechanotransduction and cytoskeletal remodeling[13]. There is increasing interest in assessing the mechanical properties of the matrix environment, given its profound influence on the behavior of cells in diverse areas such as morphogen-mediated cell programming and differentiation in developing embryos[13-15], activation of hepatic stellate cells to initiate liver fibrosis[16-18], and cell behavior in engineered tissue constructs[19]. Research has shown that the stiffness of the ovarian matrix has a profound influence on follicular development and has implicated abnormal ovarian matrix stiffness as the underlying cause of

polycystic ovary syndrome, a condition that affects 1 in 10 women of childbearing age[20-21]. Other recent research has also shown that increased matrix stiffness perturbs epithelial morphogenesis through integrins to increase cellular contractility and rigidity and there is some evidence that this process may even drive the onset of malignant transformation in some tissues[6].

Mechanical Properties of Normal Tissues and Biomaterials

Valid estimates of the mechanical properties of tissues in vivo are needed for surgical simulation systems, biomechanical modeling of certain disease processes (e.g., normopressure hydrocephalus), design of implanted medical devices, and many other applications. Conventional laboratory mechanical testing devices have significant limitations for quantitatively assessing the mechanical properties of semi-solid materials such as tissue and some biomaterials. In addition, the lack of normal metabolic activity, vascular perfusion, mechanical preloading, and neural/humoral inputs in tissue specimens makes the validity of such measurements questionable.

Methods for Imaging Mechanical Properties

Over the last two decades, investigators have developed and tested a number of approaches for noninvasively assessing the mechanical properties of tissue. Conventional ultrasound imaging is not capable of directly evaluating the shear or Young's modulus of tissue. Instead, ultrasonography delineates echogenicity, related to the heterogeneity of acoustical impedance, which depends on bulk modulus and density[3,4].

The elastography method developed by Ophir et al. employed a device such as the ultrasound transducer itself to apply a small axial compression to tissue[22]. Images depicting local strain estimates have been shown to provide an informative qualitative depiction of the elasticity of materials in tissue-simulating phantoms and surgical tissue specimens[23]. In vivo studies of the method have demonstrated value for delineating breast cancer[24]. The sonoelasticity method described by Parker et al. employs a vibrational mechanical stress, typically in the range of 20-400 Hz[25]. Tissue is imaged with Doppler ultrasonography to observe the regional amplitude of the resulting standing wave pattern. An in vitro study of excised prostates has demonstrated that this qualitative technique delineates adenocarcinoma with higher sensitivity than conventional sonographic imaging. Another approach for elasticity imaging, described by Nightingale et al employs ultrasound radiation force as a source of quasi-static stress, and measures the resulting strain[26,27]. This technique has also been extended to provide quantitative results by generating shear waves using impulsive acoustic radiation force and measuring propagation speed[28], providing estimates of human liver stiffness. A device for quantitative "transient elastography" was developed and is in clinical use for assessing liver fibrosis[29]. The device employs an external vibrator as a source of shear waves and uses 1D ultrasonic interrogation to measure wave speed.

Magnetic Resonance Elastography (MRE)

In 1995, our research group published a preliminary report in Science, describing a method for imaging the elastic properties of tissue based on a novel MRI technique capable of directly visualizing the pattern of propagating mechanical waves within objects[30]. We showed in experiments with tissue-simulating gels that quantitative images depicting the shear modulus can be obtained. Experiments showed that the technique can delineate mechanical waves with displacement amplitudes as small as 100 nanometers or less[31]. Since that time, research by our group and others has focused on developing practical implementations of the technology of dynamic MR elastography and exploring a promising range of applications[32,33].

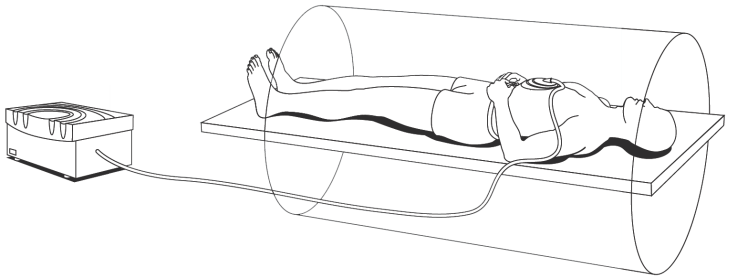
MR Elastography (MRE) can be considered as a three-step process, involving: (i) generating mechanical waves within the tissues of interest, (ii) imaging the micron-level displacements caused by propagating waves using a special MR imaging technique with oscillating motion-sensitizing gradients, and (iii) processing the wave images using an "inversion" algorithm to generate quantitative maps of mechanical properties[32,33].

Diagnosing Liver Fibrosis – The First Established Clinical Application of MRE

The most advanced current application of MRE is for diagnosing hepatic fibrosis[34-41]. Chronic liver disease is serious worldwide problem, and hepatic fibrosis is the most important consequence, which if not detected and treated, eventually leads to cirrhosis which is irreversible and associated with high mortality. Needle biopsy has been the standard method for detecting and quantifying hepatic fibrosis. Biopsy is invasive, expensive, and affected by sampling error.

Hepatic MRE can be readily implemented on a standard MRI system. In a typical implementation, a simple, drum-like "passive" acoustic driver is placed over the right anterior chest wall and coupled to a source of low frequency sound wave by a flexible tube. Vibrations at 40-90 Hz are generated in the abdomen with this device. The waves are imaged with a modified phase contrast MRI pulse sequence. Imaging time is approximately 15 seconds, using parallel acquisition techniques and is done during suspended respiration. Because the incremental imaging time is so small, MRE can readily added to standard abdominal MR imaging protocols. The MRE data are processed with a special inversion algorithm to generate a quantitative image showing the elasticity of the liver and other tissues in the upper abdomen.

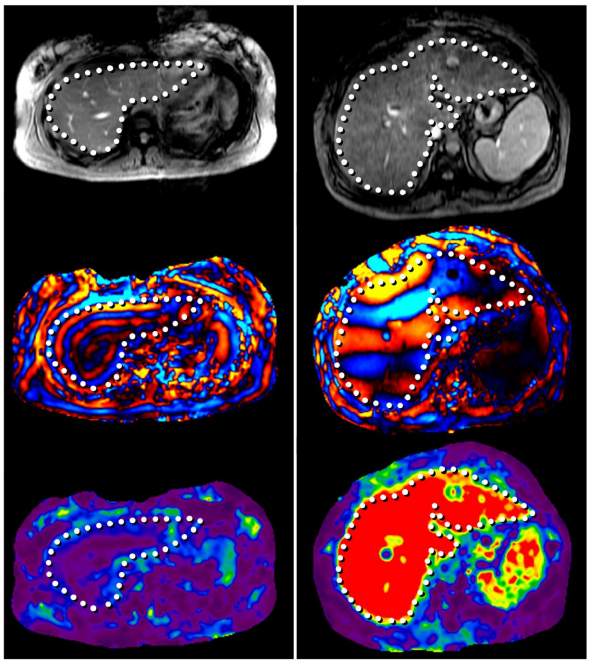
Clinical studies by multiple investigators have now established that MRE is an accurate method for diagnosing hepatic fibrosis[41] (Figure 2). MRE-measured hepatic stiffness increases systematically with fibrosis stage. MRE is intrinsically safer, less expensive, and probably more accurate than biopsy in this regard.



Emerging Applications of MRE

Human studies have demonstrated that it is feasible to apply MRE to quantitatively assess skeletal muscle, brain, thyroid, breast, myocardium, kidney, liver, and skin[32-33].

The next established clinical application of MRE is likely to be brain imaging[42,43]. Studies suggest that MRE may be helpful in differentiating between benign and malignant neoplasms. New research has also shown that MRE-assessed estimates of tumor stiffness are helpful in the preoperative assessment of patients with brain tumors such as menigiomas.



(Left column) Magnitude, wave, and stiffness images in a normal volunteer. Stiffness of liver is comparable to subcutaneous fat (~2kPa). **(Right)** In patient with biopsy-proven stage 4 fibrosis, shear wavelength is longer and elastogram shows very high liver stiffness.

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