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Virtual Palpation: The Role of MR Elastography in Quantifying and Spatially Resolving Tissue Stiffness as a Biomarker of Disease

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INTRODUCTION

Over the past several decades, dramatic advances in the diagnosis and treatment of a broad spectrum of diseases and conditions have been made in no small part thanks to the development and advancement of sophisticated technologies, including rapid gene sequencing, active implanted devices, and diagnostic imaging technologies, including but not limited to MR, CT, ultrasound, PET, and single-photon emission computed tomography. However, one of the most ubiquitous, cost-effective, and widely used diagnostic tools is and continues to be physical touch (ie, palpation). The utility of palpation is due to the sensitivity of human touch to extremely small differences in stiffness and the fact that many diseases, both benign and malignant, alter the intrinsic mechanical properties (ie, stiffness) of tissue.

IMAGING THE ELASTIC PROPERTIES OF TISSUE

There are several imaging modalities that allow the quantification and spatial resolution of tissue stiffness. This field, generally referred to as elastographic imaging or more simply elastography, is most commonly performed using either ultrasound [1] or MRI [2] and involves the spatial encoding of propagating shear waves generated by either mechanical excitation using an external driver (actuator) or intrinsically, as in the case of ultrasound elastography using acoustic radiation force imaging. Shear wave–induced displacements imaged with either modality are then mathematically processed to provide spatial maps of stiffness.

MR ELASTOGRAPHY

Quantification of tissue stiffness using MR is achieved using a methodology known as MR elastography (MRE). In MRE, shear waves are most commonly generated by means of an external driver system. The driver system consists of an active-passive driver combination in which the active driver is an audio speaker and amplifier synchronized to the MR pulse sequence. The passive driver consists of a rigid housing and flexible membrane that provides contact between the driver and patients' skin surface. The active-passive driver combination is connected by means of a semirigid plastic tube from the MR scanner equipment room into the scan room. Shear waves are generated in vivo by mode conversion of longitudinal waves emanating from the passive driver's flexible membrane, and imaging of these waves is achieved using a phase-contrast MR pulse sequence. Because MRE is sensitive to encoded motion instead of the MR signal, MRE is somewhat independent of field strength and has been used routinely at both 1.5 and 3.0 T. The final step in the process of MRE involves the processing of the shear-wave induced displacement data encoded into the phase-contrast image. This processing step, also known as inversion [3], results in the generation of a spatial map of tissue stiffness.

In many publications, and as used in this report, MR elastographic values are stated in terms of shear stiffness instead of shear modulus. The reason for this is that early MR elastographic inversion algorithms made several assumptions that greatly simplified the mathematical processing (inversion) of shear wave–induced displacement data. One such assumption was that tissue was locally purely elastic. In doing so, the inversion algorithms calculated an "effective" instead of a true shear modulus, and as a result, the term *stiffness* instead of *modulus* was adopted to note this distinction. In reality, biologic and biologic-like materials exhibit complex mechanical properties that

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are more accurately described as being viscoelastic. That is, they exhibit both elastic and viscous (loss) components in various degrees depending upon the tissue and disease type and stage. Recently, advanced MR elastographic processing techniques have been developed to more precisely describe the mechanical properties of tissue, including viscoelasticity. This has allowed a more accurate estimation of the true mechanical properties of tissues and organs and has resulted in the generation of new MRE-derived biomarkers. Changes in both the absolute and relative values of both elastic and viscous components could have significant implications in both the type and stage of disease but also the response to therapies.

MRE IN RESEARCH AND CLINICAL PRACTICE

Today, multiple research groups are investigating the use of MRE as both a diagnostic and a prognostic tool in multiple diseases and organs [4]. However, the most advanced application is in the diagnosis of liver fibrosis [4]. This is in part because MRE addresses an urgent public health issue—the worldwide prevalence of chronic liver disease and cirrhosis—by providing a noninvasive and accurate method for the diagnosis and staging of liver fibrosis. Within the United States alone, the Centers for Disease Control and Prevention estimated that in 2015, the number of adults diagnosed with liver disease was 3.0 million, or 1.6% of the total population, whereas in 2014, the number of related deaths was 38,170, or 12 deaths per 100,000 of the population.

Within my own institution, liver MRE has largely replaced biopsy for the assessment of liver fibrosis. The reasons for this are several. First, unlike biopsy, liver MRE is completely noninvasive, provides a survey of the entire organ, and replaces the subjective histologic scoring system with a quantitative assessment of liver stiffness in units of kilopascals. The ability to spatially resolve shear stiffness also addresses another major limitation of biopsy, which is the under- or overestimation of fibrosis due to the heterogeneous nature of the disease and the small sample size of the biopsy core compared with the entire organ.

Second, unlike biopsy, there is no additional risk to the patient other than that associated with performing a diagnostic MRI examination. Liver biopsy, although a relatively safe procedure, is not without complications, the most common of which is biopsy-related hemorrhage.

Third, there are no additional costs associated with performing MRE as part of a standard liver MR examination. In contrast, biopsy is a separate surgical procedure in addition to the diagnostic MR examination if ordered as such.

Finally, MRE provides a direct correlation between the underlying biology of liver disease and cirrhosis by quantifying the fibrotic burden within the organ. Healthy liver is one of the softest organs in the body, with a mean shear stiffness of approximately 2 kPa. However, with disease, the liver is known to become increasingly stiffer. MRE provides a more precise and accurate staging of liver disease and provides the opportunity to assess not only the stage of fibrosis but also the ability to quantitatively assess response to antifibroprolific drug therapies, allowing appropriate interventions to be monitored before the onset of end-stage liver disease (ie, cirrhosis). MRE has been shown to provide a very high sensitivity and specificity when diagnosing stage 3 and greater liver fibrosis.

LIMITATIONS OF MRE

Although MRE is experiencing rapid growth in terms of applications and clinical use, it is not without its limitations. In comparison with ultrasound elastography, MRE is less portable and requires access to an appropriately equipped MR scanner. In addition, current active-passive driver systems are limited to shear-wave frequencies of up to several hundred hertz. This limits the resolving power (ie, spatial resolution) of MRE, which is proportional to the wavelength of the propagating shear wave. Another limitation is that in biologic tissue, shear-wave attenuation increases with increasing frequency, which has the potential to limit the resolvability of deep-seated and small lesions. However, ongoing research efforts including advanced mathematical modeling, 3-D MR elastographic pulse sequences, and new driver technologies are currently being directed to address these limitations.

DEVELOPING APPLICATIONS IN MRE

Recent research efforts are demonstrating that stiffness is not only a sensitive biomarker of both benign and malignant disease but also a sensitive biomarker of response to therapy, including radiation and chemotherapy [5]. Furthermore, although the effect of stiffness at the cellular level has been studied for more than a decade, MRE is providing a new tool to elucidate the macroscopic effects of disease and the response to therapy. Recent

technical advances in MR elastographic pulse sequence design, shear-wave driver technology, and reconstruction methods are increasing the spatial sensitivity of MRE and proving additional biomarkers for further study.

CONCLUSIONS

Because of the strong correlation between the mechanical properties of tissue and disease, MRE is proving to be a highly sensitive method of disease detection and staging. It is likely that the use and application of MRE will continue to grow and expand as both clinicians and researchers discover the utility and potential of this new technology.

REFERENCES

1. Jeong WK, Lim HK, Lee H-K, Jo JM, Kim Y. Principles and clinical application of ultrasound elastography for diffuse liver disease. Ultrasonography 2014;33:149-60.
2. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, Ehman RL. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995;269:1854-7.
3. Manduca A, Oliphant TE, Dresner MA, et al. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. Med Image Anal 2001;5:237-54.
4. Venkatesh SK, Ehman RL. Magnetic resonance elastography. New York: Springer; 2014.
5. Pepin KM, Ehman RL, McGee KP. Magnetic resonance elastography (MRE) in cancer: technique, analysis, and applications. Prog Nucl Magn Reson Spectrosc 2015;90-91:32-48.

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