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CLINICAL APPLICATIONS OF ELASTOGRAPHY: AN OVERVIEW

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ABSTRACT

Elastography is a non-invasive medical imaging technique that detects tumors based on their stiffness (elasticity) compared to normal tissue. The most common type of elastography uses ultrasonic imaging to compare the shapes of the tissue under examination before and after it is compressed slightly. Cancerous tumors tend to be many times stiffer than normal tissue, which "gives" under compression. An image in which different degrees of stiffness show as different shades of light and dark is called an elastogram. Many tumors, including breast tumors, show up better in an elastogram than in conventional ultrasonic images. Elastography has been studied in the laboratory since the mid-1990s. It is now being considered as a possible substitute for a breast biopsy, which is an invasive surgical procedure that removes a sample of tissue for pathological examination. The aim of present article is to provide in depth knowledge about clinical applications of elastography technique in current medical scenario.

KEYWORDS

Elastography, Sonoelastography, Real-Time Tissue Elastography, Elasticity Imaging, MRE, Fibroscan and Transient Elastography.

INTRODUCTON

Elastography is an ultrasonic imaging technique that displays the elasticity of soft tissues. It has been found useful in demonstrating abnormalities of both muscle and breast tissue. Magnetic resonance elastography (MRE) is a medical imaging technique that images propagating mechanical waves using MRI. It non-invasively measures the stiffness of biological tissues. Pathological tissues are often harder than the surrounding normal tissue. This has also been utilized in ablative treatments done with Focused Ultrasound where the treated necrosed tissue can be distinguished with MRE even in real time. Magnetic resonance elastography was first introduced by Muthupillai et al. in 1995[1].

Relative stiffness imaging is of great interest since the pathological state of soft tissues is often correlated with changes in their stiffnesses. Palpation, which is a standard medical practice, relies on qualitative estimation of the low frequency (LF) stiffness of tissue. But despite the difference in stiffnesses a pathological lesion may not be detectable by palpation if it is located deep in the body or if it is too small. Moreover the echogenicity and the stiffness of tissues are generally uncorrelated and the lesion may not be ultrasonically detectable. Different elastographic techniques have been developed in order to image tissue stiffness. These techniques differ by the kind of perturbation which is applied to the medium and by the imaging system used to estimate displacements within the medium.

Breast cancer is one of the major threats to public health all over the world. Currently, X-

ray mammography is the primary method for early detection and characterization of breast tumors[2]. While more efficient in detecting malignancies as age increases or the breast becomes fatty; mammography fails to detect small cancers in dense breasts. Further, mammography may not be specific in terms of tumor benignity and malignancy[3–5].

To solve these problems associated with mammography, a number of technologies have been explored. Detection and characterization of breast tumors can be enhanced by recognizing the difference of elastic modulus (stiffness) among normal soft tissues and malignant and benign tumors. Elastic properties of breast tissues may become an indicator of histological diagnosis[6]. An imaging technology called elastography was developed as an approach to imaging tissue elastic modulus in a quantitative manner for detection of breast tumors in 1990s. The general basis of elastography is to induce motion within tissues under investigation by either external or internal mechanical stimulation. Conventional medical imaging modalities are then used to measure the spatial deformation, from which the mechanical properties can subsequently be reconstructed. Most simulations are either ultrasound or magnetic resonance (MR) image based that take the dynamic or quasistatic interior displacement field, completely or partially, as input for identification of the elasticity properties[7–11]. Current elastography reconstruction framework is based on the assumption of linear elasticity theory. It is shown, however, that the deformations of most biological soft tissues are not linearly elastic. Consideration of nonlinear models is essential for elastography in clinical applications.

CLINICAL APPLICATIONS OF ELASTOGRAPHY

Clinical Application of Transient Elastography (Fibroscan) In Liver Diseases

In patients with chronic liver diseases, determination of the severity of liver fibrosis is important for prognostic reasons, and for identifying patients who will benefit from treatment. For those patients already receiving treatment, assessment of liver fibrosis can determine their response to treatment. In addition, hepatocellular carcinoma and variceal screening can also be implemented for patients identified with underlying cirrhosis. At present, liver biopsy remains the current gold standard for assessing liver fibrosis, even though the diagnostic accuracy is limited by the specimen size and fragmentation, sampling error, and inter-observer variability. The accuracy of liver biopsy can be reduced to 80% because of these limitations[12].

Furthermore, liver biopsy is an invasive procedure which can be associated with significant morbidity and rarely mortality, rendering it less acceptable by patients[13].

In the past few years, however, transient elastography (FibroscanR, Echosens, France) has been increasingly used as a non-invasive tool for the assessment of liver fibrosis by measuring liver stiffness. The probe consists of an ultrasound transducer which is located at the end of a vibrating piston (Figure 1).

Figure 1.*The Probe of the Fibroscan*

The piston produces a vibration of low amplitude and frequency, which generates a shear wave that passes through the skin and liver tissue. The ultrasound then detects the propagation of the shear wave through the liver (at a depth from 25 to 65 mm below the skin surface) by measuring its velocity. The shear wave velocity is directly related to the tissue stiffness, with a higher velocity equating to higher tissue stiffness, corresponding to increasing severity of fibrosis. The advantages of transient elastography are that the results are immediately available, and the procedure is painless, rapid (~3 minutes per patient), and easy to perform.The test is performed with the patient lying in the supine position, with the probe placed at the intercostal space overlying the liver (Figure 2).

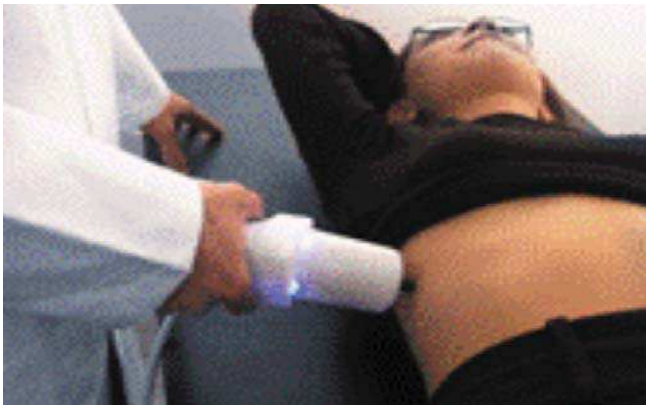

Figure 2: Positioning of Patient for Fibroscan

Ten validated measurements are required, with the median value taken as the final result, which is expressed in units of kilopascals (kPa). Transient elastography has been shown to be highly reproducible with minimal inter- and intra-observer variability[14]. The range of possible liver stiffness values obtained with transient elastography is from 2.5 to 75.0 kPa, with the normal liver stiffness value for healthy individuals being around 5.5 kPa.4 The age of the subject does not affect liver stiffness, and males tend to have a slightly higher liver stiffness value compared to females[15].

Although transient elastography is an easy and rapid procedure, strict adherence to quality criteria should still be followed to ensure the reliability of the results obtained. The interquartile range of all the readings should not exceed 30% of the final result (the median value), and the success rate of the scans should be greater than 60%. The results should always be interpreted by a qualified clinician according to the clinical context, taking into account the patient demographics, disease aetiology, and laboratory parameters. If the liver stiffness value appears to be discordant with the clinical scenario, then consider repeating a scan or proceed to a liver biopsy. The earliest validating studies of transient elastography have been performed on patients with chronic hepatitis C[16, 17]. Many other studies have been performed since then on other liver diseases including chronic hepatitis B, hepatitis C/human immunodeficiency virus co-infection, non-alcoholic steatohepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and recurrent hepatitis C after liver transplantation[18-21].

MAGNETIC RESONANCE ELASTOGRAPHY

Introduction

Malignancies and other pathological processes are often characterized by marked changes in tissue mechanical properties. This accounts for the efficacy of palpation as a clinical tool for detecting cancer in accessible regions of the body. Indeed, many tumors of the thyroid, breast, and prostate are still first detected by this centuries-old diagnostic technique. Unfortunately, small or inaccessible lesions cannot be detected by touch, and conventional diagnostic imaging methods do not provide information that is in any way analogous. In engineering terms, palpation assesses the tendency of tissue to resist deformation, a

physical property called elastic modulus. The elastic moduli of various human tissues are known to vary over a wide range. Most of the physical properties depicted by conventional medical imaging modalities are distributed over a much smaller range. For instance, the x-ray attenuation coefficients of various soft tissues assessed in CT imaging vary by only by a factor of about 2. In contrast, the elastic moduli of soft tissues vary by factors of as much as 10,000. In addition, the elastic modulus of tumors may differ from surrounding tissues by a factor of 20. While the potential for detecting and characterizing abnormal tissue provided the original motivation for seeking practical methodologies for imaging the elastic properties of tissues, additional impetus has come from the 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[22, 23]. There is increasing interest in assessing the mechanical properties of the matrix environment, given its profound influence on the behaviour of cells in diverse areas such as morphogen-mediated cell programming and differentiation in developing embryos, growth of tumors, activation of hepatic stellate cells to initiatie of liver fibrosis, regulation of ovarian follicular function, and cell behaviour in engineered tissue constructs. Magnetic resonance elastography (MRE) has emerged over the last decade as a practical and powerful technique for quantitatively assessing the mechanical properties of organs, tissues, cells, and biomaterials. This presentation provides an overview of the basic methodology and a survey of results obtained by investigators who have been working in the field.

APPLICATIONS OF MAGNETIC RESONANCE ELASTOGRAPHY:

MRE has been implemented by multiple investigators on large and small bore MR imagers, at field strengths from 0.5 – 7.0 T. The technique has been applied successfully to generate quantitative images of mechanical properties of biomaterials, engineered tissue constructs, tissue specimens, as well as tissues and organs in vivo, from mice to humans. The MRE technique can image acoustic shear waves with displacement amplitudes of less than 100 nanometers in tissues[24]. MRE-derived measurements of the shear modulus of tissue-simulating gel specimens correlated well with independent mechanical testing results. Investigators have shown that MRE can be used to quantitatively assess the matrix mechanical properties of engineered constructs and to non-invasively follow the behavior and development of cells within engineered tissues. Studies of organ and tissue specimens have provided quantitative elastograms depicting the shear modulus of kidney, liver, muscle, breast, eye, aortic wall, and adipose tissue. Measurements have demonstrated that the viscoelastic properties of some tissues are isotropic, while other tissues such muscle is highly anisotropic. Studies of human pathologic specimens have demonstrated the feasibility of delineating breast and prostate tumors with the technique[25-27]. In human studies, MRE has been applied by multiple investigators to quantitatively depict the mechanical properties of brain, skeletal muscle, breast, thyroid, heart, lung, liver, spleen, pancreas, and other tissues. MRE studies of the brain in human volunteers have provided quantitative images of brain elasticity, demonstrating for instance, that white matter has a higher shear modulus than gray matter. In applications to brain imaging, human studies have demonstrated that it is feasible to apply MRE to quantitatively image the mechanical properties of gray and white matter, providing a new tool for tissue characterization, diagnosis, and mechanical modeling in brain pathologies such as hydrocephalus. A variation of the technique, using impulse mechanical waveforms, allows dynamic visualization of micron level strains as mechanical transients propagate through the brain, providing a direct way to study the biomechanics of traumatic brain injury. In recent years, investigators have begun to report applications of MRE to study abnormal tissues in humans, including brain tumors and skeletal muscle in myopathy. Studies of volunteers and patients have

demonstrated the feasibility of imaging normal breast anatomy with MRE and delineating breast cancer[28-34]. These results provide motivation for exploring the capacity of MRE to detect and characterize breast tumors, particularly in premenopausal women. However, the first well-established clinical application of MRE is to evaluate liver disease. 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. Currently, needle biopsy is the accepted method for detecting and quantifying hepatic fibrosis[35-37]. This procedure is invasive, expensive, and is affected by sampling error. Clinical studies by multiple investigators have recently established that MRE is an accurate method for diagnosing hepatic fibrosis. In this application, the liver is illuminated with shear waves, typically in the range of 40-90 Hz. MRE-derived hepatic stiffness increases systematically with fibrosis stage. In a recent published study, encompassing 50 patients with biopsy-proven liver disease and 35 normal volunteers, ROC analysis showed that, with a shear stiffness cut-off value of 2.93 kPa, the predicted sensitivity and specificity for detecting liver fibrosis is 98% and 99%, respectively. ROC analysis also provided evidence that MR elastography can discriminate between patients with moderate and severe fibrosis (grades 2–4) and those with mild fibrosis (sensitivity, 86%; specificity, 85%). Importantly, hepatic stiffness is not systematically influenced by the presence of steatosis. Recent research has also suggested that MRE has promise for characterizing focal liver lesions. Benign focal liver masses, including cavernous hemangioma, hepatic adenoma, and focal nodular hyperplasia have typical stiffness values in the 3 kPa range, slightly stiffer than normal liver parenchyma. Malignant focal masses of the liver, including hepatocellular carcinoma, metastases, and cholangiocarcinoma are much stiffer than normal liver tissue. In a series of 48 liver masses (36 malignant and 12 benign), a threshold of 5 kPa correctly differentiated 100% of malignant from benign masses[38-39].

CARDIAC ELASTOGRAPHY

Early detection of cardiovascular diseases has been a very active research area in the medical imaging field. Assessment of the local and global mechanical functions is one of the major goals for accurate diagnosis. In its non-invasive applications, elastography has been typically used to determine local tissue strain through the use of an externally applied compression. Future prospects include the assessment of the role of elastography in the detection of ischemia as well as infarction. Detection of cardiac dysfunction through assessment of the mechanical properties of the heart muscle has been the long-term goal in diagnostic cardiology. Ischemia and infarction can successfully be determined through characterization of the regional cardiac function. Despite the fact that Magnetic Resonance Imaging (MRI) has been shown capable of generating high quality images of the cardiac defamation with methods such as cardiac tagging and HARP MRI, in echocardiography, techniques formapping the mechanical response of the cardiac muscle are still in their infancy. However, echocardiography remains the main dominant imaging modality in diagnostic cardiology due to its real-time feedback, high temporal resolution and a multitude of complementary methods that can be used for a complete and accurate diagnosis. The two main areas of investigation are motion estimation techniques and tissue characterization methods. Motion estimation methods include Doppler Myocardial Imaging (DMI) and Strain Rate Imaging (SRI), which use Doppler techniques to obtain regional velocity estimates and velocity gradients of the myocardium, respectively. The field of tissue characterization, a complement to the motion estimation techniques, measures acoustic parameters, such as attenuation, speed of sound and Integrated Backscatter (IB) to determine such myocardial attributes as thickening and thinning (cyclic variation), and anisotropy. Despite it being their main goal and unlike their MRI counterparts, ail of the aforementioned methods, measure parameters that are only indirectly dependent on the mechanical attributes of the cardiac muscle. For example, SRI calculates the strain rate curve through the velocity gradient while the method of

speed of sound estimation provides indirect measures of the regional Young's modulus. Elastography is a technique that estimates local tissue strain through cross correlation of RF segments before and afier a small (external or internal) deformation. Based on the principle of palpation, elastography was initially designed for the detection of stiffer masses (i.e., tumors) inside normal tissue and shown to have successful results in muscle, prostate and breast in vitro and in vivo applications. Recently, however, elastography has been shown to have an important impact on several other applications, such as normal tissue strain and poroelasticity imaging[40, 41]. Since assessment of the myocardial mechanical parameters has proven to be a crucial step in the detection of cardiac abnormalities, elastography could also have a significant impact in this field. In this preliminary study, we concentrated on a normal volunteer case to mainly determine the feasibility of elastography on cardiac muscle and subsequently design the optimal ultrasound system parameters for cardiac elastographic measurements. The examples of left-ventricular muscle considered were the posterior wall and intraventricular septum, a muscular wall, which separates the left ventricle from the right ventricle.

CONCLUSION

Over the past few years, significant progress has been made in the use of transient elastography in clinical practice. Despite the absence of consensus guidelines regarding the use of liver stiffness measurements in clinical practice, transient elastography is already widely used in many places. This widespread use is probably the consequence of patients and clinicians not wanting or advocating liver biopsies respectively. Transient elastography has been shown to be an excellent diagnostic tool if strict quality criteria are applied, ensuring the reliability of the results. Finally, the main focus now should be on the development of validated guidelines on the use of transient elastography, and to incorporate this new technology into current treatment guidelines. MR Elastography is emerging as a practical and versatile quantitative tool for mapping the viscoelastic properties of tissue in vivo. The technique allows measurement of shear modulus, shear viscosity, and the anisotropy of these properties, as new tissue characterization parameters. Studies of MRE as a clinical diagnostic method, have shown that it can be used to non-invasively "palpate" regions of the body that are beyond the reach of the physician's hand. Multiple studies have now established that MRE is a reliable method for diagnosing hepatic fibrosis and that it is intrinsically safer, less expensive, and probably more accurate than biopsy in this regard. In addition, MRE seems to offer unique opportunities to explore tissue matrix mechanics and to address unique questions in cellular mechanobiology, as well new experimental options in fields of acoustics and materials science.

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