

Development of Ultrasonic Elastography in the Lesion Diagnosis

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Palpation and Tissue Stiffness

Palpation is a method of feeling patient's body to examine the size, consistency, texture, location, and stiffness of an organ with the fingers or hands in response to the applied pressure during a physical examination. It is still essential in the physical detection of tumors now as thousands years ago despite low sensitivity for deep objects and less spatial resolution. In isotropic tissues, Young's modulus (E) describes the amount of longitudinal deformation that occurs in a given material in response to an applied longitudinal force while the shear modulus (μ) relates transverse strain to transverse stress. The elastic moduli of biological soft tissues depend on both their composition (i.e., fiber, fat and collagen) and structural organization. There is a good correlation between the pathological or physiological process and changes in tissue stiffness. Many cancers have 3-5 times in stiffness as the normal tissue. In comparison, the difference of the acoustic impedance depicted by B-mode sonography between them is quite small. Therefore, discrimination of tumor or cancer, which feels much harder than the surrounding tissue, in the standard B-mode sonography is challenging.

Elastography

The potential value of characterizing mechanical properties *in vivo* has led extensive studies of imaging tissue elasticity. A stress is applied to the tissue, and the resulting strain distribution is observed or measured using a conventional imaging technique. Magnetic Resonance Elastography (MRE) can directly visualize and quantitatively measure propagating acoustic strain waves subjected to harmonic mechanical excitation [1,2]. A phase-contrast Magnetic Resonance Imaging (MRI) technique is used to spatially map the shear wave displacement patterns (sensitivity of 100 nm) at frequencies of 10-1000 Hz and to calculate the local quantitative values of shear modulus. MRE does not require estimation of the regional static stress distribution, and is little more sensitive to physiologic motion than a conventional gradient echo sequence. However, the purchase and maintenance of MRI are expensive, and patient with metal implant should be excluded. Though a MRI exam is not painful, patients must tolerate the potential claustrophobia (fear of small spaces).

Therefore, ultrasonic method is used more popularly in the practice. The mode of stress application can be static/quasi-static [3-5], dynamic (a low frequency vibration: <1 kHz) [6,7], or transient [8-10]. Remote and transient perturbation to the tissue can be produced by acoustic radiation force using high-intensity focused ultrasound pulse, by the low frequency vibration in the interference of two high intensity ultrasonic beams with different driving frequency (i.e., vibroacoustography), or the generation of shear waves by acoustic radiation force at multiple locations. Sonograms of pre- and post-perturbation or mechanical stimuli are correlated to determine the local displacement or strain. The spatial correlation, phase-shift tracking, and the Combined Autocorrelation Method (CAM) have been introduced for measuring tissue displacement [11]. The spatial correlation method uses a two-dimensional pattern-matching algorithm so that its processing time is lengthy. The phase-shift tracking method is based on an autocorrelation method for rapid and precise determination of longitudinal tissue motion. Because of aliasing errors, it works poorly for large displacement

and cannot compensate for the lateral motion. CAM provides a higher frame rate while maintaining satisfactory image quality by using phase-domain processing without aliasing at the optimal strain range of 0.5-2.0% with compensation for lateral slip up to 4 mm.

Commercialization and Clinical Application

Ultrasonic elastography has been commercialized for clinical use, such as acoustic radiation force impulse (ARFI) imaging by Siemens, eSie Touch™ elasticity imaging by Siemens, Elastography on GE's LOGIQ E9 device, Strain-Based Elastography on the iU22 device of Philips, ShearWave Elastography (SWE™) on Aixplorer by SuperSonic Imagine, Hitachi Real-Time Tissue Elastography (HI-RTE) and Real-Time Elastography by Toshiba.

In the last decade, great effort has been made to the clinical evaluation. Elastography is found useful for characterizing breast lesions in general and allows differentiation between malignant (4.2 ± 0.9 for ductal carcinoma in situ (DCIS), invasive ductal carcinoma of non scirrhous type and invasive ductal carcinoma of scirrhous type in elasticity score) and benign (2.1 ± 1.0 for Intraductal Papilloma, Fibro adenomas and Aberrations of Normal Development And Involution (ANDI) without fibro adenoma) lesions. The width of cancers was greater on elasticity images than on B-mode images. The sensitivity, specificity and accuracy for Elastography was 86.5%, 89.8% and 88.3%, respectively at the cutoff point between 3 and 4 while the corresponding values for conventional sonography was 71.2%, 96.6% and 84.7%, respectively, at a best cutoff value between 4 and 5. Although the sensitivity of elastography is higher, its specificity and accuracy were not inferior or equivalent to those of sonography [11]. In the prostate application, most of the normal prostatic parenchyma showed uniform color when vibrated, except for the fibro muscular stroma and the peri-urethral tissues that showed no and reduced color, respectively. Elastography correctly identified cancer in 3 of the 100 patients whose diagnosis was not possible because the tumor lay outside the region sampled by conventional segmental biopsies [12]. This justifies the addition of elastography imaging with biopsy of abnormal areas detected as its real clinical value. Liver elasticity measurements in 106 patients with chronic hepatitis C were reproducible, operator-independent and well correlated to fibrosis grade (METAVIR, partial correlation coefficient=0.71) [13]. Furthermore, elastography was also used for intravascular atherosclerotic plaque characterization [14]. 24 diseased postmortem coronary arteries were investigated with

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intravascular elastography at 54 cross sections. The sensitivity was 88%, and the specificity was 89% to detecting vulnerable plaques.

Altogether, ultrasonic elastography is a noninvasive, painless, rapid and objective method to quantify lesion. As a result, the number of biopsies or other invasive diagnostic procedures will be reduced for fewer complication rates and increased patient tolerance.

Future Work

Although elastography is a new and promising sonography-based noninvasive method for the assessment of benign and malignant lesions, more investigation are needed in both technical improvement and the cancer screening in the terms of sensitivity, specificity, accuracy, positive predictive value, false-positive rate and false-negative rate. Many approaches have been developed to improve the performance of elastography, i.e., Signal-To-Noise Ratio (SNRe), Contrast-To-Noise Ratio (CNRe) and strain contrast. Those include the fields of displacement determination, spatial and angular compounding and combination with ultrasonic tomography and so on. As the other imaging modalities, elastography has some artifacts (i.e., mechanical, acoustic and signal processing artifacts). Strains in the tissue depend not only on the stiffness distribution of the biological structure but also on both internal and external boundary conditions, which present the true variations in strain. Understanding the mechanism of artifacts and developing methods of reduction is of importance for reliable and accurate reconstruction of elastogram. An ideal freehand elastography system will have a large dynamic range of strain for stable and reproducible measurements that does not depend on the speed and extent of compression but the minimal influence of probe movement on the skin's surface in the lateral direction (creep or slip) especially *in vivo*. It is unknown whether the applied pressure is inappropriate for elastography operation. If a pressure gauge on the transducer is available, the optimal real-time image can be obtained for elasticity. Use of elastography for the characterization of small lesion is necessary, and few studies have been carried out for lesions in the size smaller than 5 mm. In addition, the precise elasticity quantization is quite hard because of the requirement of estimating local stress distribution, which in turn depends on the spatial composition of the object and knowledge of the applied stress. Although the Inverse Problem (IP) approach is used extensively in electromagnetic, optics and geophysics, most of them are ill-posed in the sense of Hadamard due to many reasons (i.e., non-linearity, noise in the data, and lack of complete data set). In summary, it is believed that elastography may obtain more acceptances in tumor detection, diseased tissue characterization, and the evaluation of rehabilitation in the near future.

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