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Appendix E1

Principles of Elastography

To measure elasticity and other mechanical properties, a stress must be applied and the resulting tissue deformation measured. The incident stress can be applied by the operator or via physiologic motion, in the case of static and quasistatic US elastography, but more generally the stress is applied via shear-wave propagation, delivered as a transient impulse or as a continuous, dynamic excitation. Shear waves travel slowly in tissue (1–10 m/sec), with particle motion perpendicular to the direction of propagation and shear-wave speed related to the shear modulus. In contrast, longitudinal waves travel rapidly in tissue (approximately 1540 m/sec), with particle motion parallel to the direction of propagation and longitudinal wave speed related to the bulk modulus. Various methods of mechanical property quantification via transient and dynamic elastography have been developed using both US- and MR imaging–based techniques. In the literature, elastography is often described as measuring the "stiffness" of tissue, but more formally elastography measures the shear modulus (*G*, or the resistance to a shear stress) or Young modulus (*E*, often referred to as the elastic modulus in the literature, or the resistance to longitudinal stress), both with units of kilopascals. Under simplifying assumptions of incompressibility, *E* and *G* are approximately proportional: $E \cong 3G$. *G* is often considered as the complex shear modulus, $G^* = G' + iG''$, which describes response of a viscoelastic material. In the MR elastography literature, the most popular parameter reported is the so-called shear stiffness, which is the magnitude of the complex shear modulus, |G*|.

US-based elastography methods estimate stiffness by tracking and measuring the speed of shear waves propagating through the liver and generally report the value as *E*. In contrast to US elastography systems, MR elastography quantifies mechanical properties through mathematical inversion of the imaged displacement "wave field." Commercial implementations report the shear stiffness, which is the magnitude of the complex shear modulus, $|G^*|$. The main quantitative elastographic techniques will be discussed in further detail below.

US Elastography Methods

US elastography methods can be categorized by means of tissue deformation and subsequent measurement of the tissue strain. In static and quasistatic elastography, the deformation is applied manually by the operator or is produced through physiologic motion, such as heartbeat. Though promising results have been published in Japanese cohorts (327–329), these methods are qualitative rather than quantitative owing to the unknown nature of the applied stress and are not discussed.

Transient elastography (TE) was the first commercially implemented quantitative elastography technique. In TE, an impulse is applied to the skin surface and the propagation of the generated shear wave is tracked. Acoustic force radiation impulse (ARFI) elastography generates shear waves in the tissue of interest by focused US compression waves. The focused compression generates shear waves through mode conversion and tracking lines measure the time of arrival of the shear wave front. Several commercial systems utilize variations of this

technique to quantify tissue stiffness. The available quantitative US elastography methods are discussed in detail below.

Transient Elastography

The FibroScan system uses an amplitude modulation (A)-mode image for organ and measurement site localization. TE measures the velocity of a low-frequency (50 Hz) shear wave propagating through the liver. The strain induced in the liver is assessed on a time/depth curve, with the slope of the wave front defined as the wave speed under the assumption that the liver is a nonviscous, isotropic soft elastic medium (330). TE is performed in a patient lying supine, with the right arm elevated to facilitate access to the right liver lobe. The tip of the probe is placed against the intercostal skin with coupling gel in the ninth to 11th intercostal space, at the level where a liver biopsy would be performed. The TE probe is not integrated into a US imaging system and so direct visualization to aid region of interest (ROI) placement is not possible. A time-motion image is generated from which a liver portion at least 6 cm deep and free of large vascular structures is identified. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface using the standard M probe (operating frequency 3.5 MHz) and between 35 and 75 mm using the more recently introduced XL probe (2.5 MHz), which is aimed at improving the rate of reliable measurements in overweight subjects. The software includes a quality control routine to determine whether each measurement is successful or not. When a shot is unsuccessful, the machine does not return a value, and the entire procedure is considered to have failed when 10 shots produce no successes. As suggested by the manufacturer, 10 successful acquisitions should be performed in each patient. The median of these measurements is displayed and used for interpretation. Only results obtained with a success rate of at least 60% and an interquartile range (IQR) of 30% or less of the median value should be considered reliable (331,332). However, other research suggests an even lower IQR should be used, especially in non-Asian patients with advanced fibrosis, but these criteria have not been independently validated (333). The results, expressed in terms of Young modulus (in kilopascals) range from 1.5 to 75 kPa, with normal values at about 5 kPa and below (334).

Advantages of TE include a short procedure time (< 5 min), immediate results, and point-of-care capability at the bedside or in an outpatient clinic. It is not a difficult procedure to learn and can be performed by a nurse after minimal training (about 100 examinations). Nevertheless, TE results should always be interpreted by an experienced clinician and should be made with full knowledge of patient demographics, disease etiology, and essential laboratory parameters.

ARFI Elastographic Techniques

In point share-wave elastography (pSWE), the local compressional displacement produced by the ARFI push pulses in turn generates transient shear waves, which propagate perpendicular to the focused ultrasound beam's axis. US tracking beams are emitted laterally to the focus of the push pulse, which measure the arrival time of the induced shear wave front at predetermined locations, allowing an average shear-wave speed within an ROI (typically 10×5 mm^2 in commercial pSWE) to be determined (335). In pSWE, the ROI is overlaid on the US image to aid placement; however, no elasticity maps are produced. The recommended ROI depth is 4–5 cm from the transducer surface (336) though this depends on the transducer used (337). Depending on the manufacturer and scanner model, measurements may be reported as shear-wave speed (in meters

per second) or Young modulus (in kilopascals). Unsuccessful measurements are flagged automatically by the scanner with self-explanatory, vendor-dependent codes. It has been suggested that to ensure accurate measurement of tissue stiffness using pSWE, the success rate (ratio of successful measurements to total attempted measurements) should exceed 60% and the IQR of all measurements should be less than 30% of the median value (338). Acquisition of 10 separate measurements is suggested, the median of which is the reported value.

In two-dimensional (2D) SWE, multiple points of shear-wave generation are produced by rapidly sweeping the focus of the ARFI push pulses along the acoustic axis, at a speed greater than the speed of shear-wave propagation in tissue (339). Thus, tissue displacement occurs at all points along the acoustic axis almost simultaneously. The shear waves from the acoustic foci constructively interfere forming a Mach cone, which travels away from the acoustic axis. An ultra-high frame rate imaging sequence then captures the shear-wave propagation in real time. The acoustic axis is swept across the tissue generating a larger field of view than that of pSWE. As in pSWE, the ROI for 2D SWE measurement can be freely positioned under B-mode US vision away from interfering structures such as vessels, the gallbladder, and focal lesions, with optimal depth at 4–5 cm from the transducer. Unlike pSWE, the ROI size can be modified by the operator. Color elasticity maps are overlaid on the US image displaying units of wave speed (in meters per second) or Young modulus (in kilopascals). Similar reliability thresholds should be adhered to for 2D SWE as for pSWE, that is, IQR of 30% or less of median value and success rate greater than 60%. No consensus has been agreed on with regard to the number of measurements required to ensure a valid result. The Society of Radiologists in Ultrasound consensus document recommends 10 measurements (336) though there is some evidence that as few as three may suffice (340). As compared with TE, pSWE and 2D SWE have the advantage of being integrated in commercial US systems enabling the additional performance of elastography with the same probes as those performing a traditional abdominal US scan.

MR Elastography

Unlike US-based elastography, which determine mechanical properties in a small region of the liver, MR elastography provides full cross-sectional measurement of stiffness by imaging the propagation of externally induced shear waves through the tissue of interest. Several methods for generating the requisite shear waves have been developed such as piezoelectric ceramics (341), electromechanical actuators (342), and pneumatically powered actuators (343). The most common method of wave generation is achieved by placing a passive driver over the liver, along the midclavicular line, lateral to the xiphoid process. The passive driver is then secured with an elastic strap. The tissue displacements caused by the propagating waves are encoded into the MR phase signal by the addition of motion-encoding gradients (MEGs) to the pulse sequence. Sinusoidal (344,345) and trapezoidal MEGs (346–348) have been used to encode the tissue displacement into the phase signal, though trapezoidal MEGs provide superior motion sensitivity (349). In 2D MR elastography, the tissue displacements in only one direction are acquired. Generally, the MEG frequency is the same as that of the induced shear waves; however, fractional encoding schemes have also been proposed (350–354), which reduce the echo time of the sequence though at the expense of motion-encoding sensitivity. Liver MR elastography examinations are typically performed at 60 Hz vibration frequency; however, multifrequency acquisitions have also been explored (350,355–359), which aim to provide additional information based on the response of tissue to different frequencies. These techniques are not common in the clinic due to the requirement for offline processing to model the tissue response

and extended acquisition times. Multifrequency MR elastography is discussed in the new technical developments section.

The initialization of the pulse sequence imaging gradients and onset of vibration are carefully synchronized between the MR system and the source of external vibration. A delay is introduced between vibration and imaging to capture the wave propagation at a certain time point. Four to eight time points are usually acquired by shifting the delay, or phase offset, systematically and when viewed consecutively form a cine video of the wave propagation, which can then be used to determine the complex harmonic displacement field after temporal Fourier transform. Several common pulse sequences have been modified to enable MR elastographic imaging such as gradient-recalled-echo (GRE) (360), spin-echo (SE) (361), SE echo-planar imaging (EPI) (358), and balanced steady-state free precession (352). Once the wave propagation has been captured in the MR phase image, an inversion algorithm generates colorized parametric maps of stiffness, known as elastograms. Similar to US elastographic methods, assumptions must be taken regarding the imaged tissue such as local homogeneity, isotropy, and incompressibility to process the data in a clinically feasible time. Currently available commercial MR elastography packages include 2D GRE and SE EPI sequences, a 2D reconstruction algorithm (362), and a pneumatic actuator (Resoundant, Rochester, Minn). In the commercial implementation, a confidence map is produced, which is overlaid on the elastogram and provides an estimate of the reliability of the stiffness measurement in every voxel. The confidence map is calculated by determining the goodness of fit (R^2) between the tissue displacement data and the equations of motion modeling the wave displacement (362). Areas with R^2 less than 0.95 are demarcated with a grid, indicating measurement unreliability. Care should be taken when analyzing MR elastographic measurements as even areas inside the confidence map may be affected by wave interference or regions of high tissue displacement near the actuator.

The use of SE EPI sequences instead of GRE reduces imaging time and makes the technique more reliable in the case of iron deposition. Liver stiffness measurement with 2D SE EPI and GRE sequences has been found to be equivalent, with larger areas of reliable measurement in the liver produced with 2D SE EPI (363).

The availability of MR elastography is not limited to commercial packages; however, research into alternative reconstruction algorithms (341,364–368), vibration sources (369,370), and imaging approaches (350,371–373) is ongoing. MR elastography can be performed before or after administration of intravenous gadolinium contrast agents, which does not significantly affect the measurement (374,375).

Three-dimensional MR Elastography

Though 2D MR elastography is a volumetric technique, in that multiple 2D sections can be acquired over a volume to provide substantial organ coverage, the wave propagation through the imaged volume is only encoded into the MR phase signal in the through-plane direction and the corresponding inversion algorithm only considers planar wave propagation, that is, each section is processed individually. The assumption of through-plane wave propagation required for 2D MR elastography (376) can be violated in complex organs such as the kidneys, as well as near tissue boundaries and features, such as large blood vessels. When the incident waves are no longer planar, the encoded wavelength can be artificially increased leading to falsely elevated stiffness measurements (377). To address this limitation, three-dimensional MR elastography, in which all three directions of motion are encoded into the MR phase signal by switching the

orientation of the MEGs, has been proposed. Acquiring the additional directions of motion requires a tripling of imaging time compared with the single direction acquired for 2D MR elastography; however, three-dimensional implementations generally utilize SE EPI sequences, which can acquire the full wave displacement field in the same time as a 2D GRE acquisition (approximately 1 minute). The use of the SE EPI sequence also allows full liver coverage in approximately 30 sections compared with the four-section standard acquisition with 2D MR elastography. Three-dimensional MR elastography is discussed further in the new technical developments section in the main document.

MR Elastography Parameters

The shear stiffness $\left|G^*\right| = \sqrt{G'^2 + G''^2}$ is the parameter reported on clinical MR systems (378). Additional mechanical tissue parameters can be extracted from MR elastography data and have been investigated in the literature, most of which are derived from *G**. Examples include the real storage modulus (*G'*) and imaginary loss modulus (*G''*) through the relation *G* = G'+iG'',* as well as arithmetical expressions of *G*' and *G''* to describe relative contributions of viscosity to tissue behavior, such as the damping ratio $\left(\xi = G''/2G'\right)$ and phase angle $\left(\varphi = \frac{2}{\pi} arctan\left(G''/G'\right)\right)$ (378–380). Other parameters such as wave number (*k*) recovery, volumetric strain (341,366), and parameters describing frequency dependency of any of the above parameters are under investigation. The most clinically beneficial parameters, alone or in combination, have yet to be established. Until then, clear statements regarding the parameters reported should be included by researchers to aid interpretation.

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