Chapter 4
Characterizing Liver Stiffness with Acoustic Radiation Force

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Introduction

Methods to characterize the elastic properties of the liver typically have two means of introducing mechanical perturbations into liver to then monitor the liver's response and estimate its stiffness: (1) external vibration—such as transient elastography and MR elastography—and (2) an internally applied acoustic radiation force. For more details see also other chapters of the book section II "Techniques to measure liver stiffness." While external sources of vibration can be well-controlled at fixed frequencies with external vibrators and couple relatively strong waves into the body, these waves must couple from the skin surface, through superficial tissues (i.e., skin, subcutaneous fat, muscle), into the liver. These propagating external waves can be distorted through interactions with these tissues surrounding the liver, and in some circumstances, such as abdominal ascites, cannot couple through fluids into the liver. Given some of the challenges that external vibration sources can face when characterizing the liver, there was parallel development in the 1990s and early 2000s to develop acoustic radiation force methods that would generate sources of mechanical perturbation in the focal zone of an ultrasonic excitation inside the target tissue of interest and not relying on coupling external mechanical energy into the patient. These acoustic radiation force methods have been developed and deployed on standard diagnostic ultrasound scanners as software features, allowing clinicians to evaluate the liver without any additional hardware.

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What Is Acoustic Radiation Force?

Acoustic radiation force is a phenomenon that was first described in the acoustics literature by Nyborg in 1965 in the context of acoustic streaming [1] and further by Apfel and Chu in 1985 [2]. Acoustic radiation force is generated in the direction of propagation of an acoustic wave in a lossy (attenuating) medium, where the loss of momentum of the propagating wave results in an impulse transfer to the tissue. The direction and magnitude of acoustic radiation force ($\vec{F}$) can be represented as:

$$\vec{F} = \frac{2a\bar{I}}{c},$$

where a is the acoustic attenuation of the tissue, $\bar{I}$ is the acoustic intensity vector, and c is the sound speed of the tissue [1, 3, 4].

The application of acoustic radiation force to tissue results in a transient displacement of the tissue, where the magnitude of that displacement is related to the magnitude of the acoustic radiation force applied to the tissue, and the stiffness of the tissue. Stiffer tissues resist deformation than more compliant tissues and, therefore, experience less induced displacement. The transient, impulsive application of acoustic radiation force also leads to the generation of shear waves that emanate out from the region of acoustic radiation force application, and the speed of these shear waves can also be related to the stiffness of the tissue they are propagating in [5–7]. While acoustic radiation force is associated with all ultrasonic insonification of tissue (e.g., B-mode and Doppler imaging), the ultrasonic pulses for acoustic radiation force-based elasticity imaging must be intense and/or long enough to generate tissue displacements that can be estimated ultrasonically (on the order of microns) [8]. Commercial implementations of acoustic radiation force imaging methods that are described in this chapter have traditionally adhered to U.S. Food and Drug Administration diagnostic ultrasound output limits [9, 10], but new research efforts are exploring the benefits of using elevated acoustic output for more robust imaging performance, especially in the difficult to image demographic, such as those with high Body Mass Indices [11].

Acoustic Radiation Force Impulse (ARFI) Imaging

ARFI imaging refers to images of tissue displacement (or metrics related to tissue displacement, such a time-to-peak displacement or maximum displacement) that result from the application of impulsive acoustic radiation force excitations [3, 12]. The "impulsive" nature of the excitation refers to an insonification time that is less than the mechanical response time of tissue, which is related to the tissue's stiffness, with stiffer tissues reacting faster [12]. For liver tissue, this typical impulsive excitation lasts for less than 1 ms [12].

A single A-line of an ARFI image typically involves the following sequence:

1. A single, B-mode-like tracking pulse to determine the RF data associated with the tissue pre-ARFI-induced deformation;
2. A impulsive ARFI excitation either at a single focal depth, or over a range of focal depths to extend the effective depth-of-field of the excitation energy [13];
3. A series of B-mode-like tracking pulses at a relatively high pulse repetition frequency (typically 5–10 kHz) to track the tissue displacement and recovery from the ARFI excitation using correlation, phase-shift, or more complex displacement estimation methods [8, 14–19].

To form a 2D ARFI image, the A-line sequence is repeated at laterally offset positions from one another to form an image. Displacement estimation can be affected by motion (and other) artifacts, include those related to respiratory and cardiac motion. While clinical imaging protocols may recommend techniques like suspended breathing to minimize these effects [20, 21], most scanner post-processing includes motion filtering, through means of temporal profile shape-fitting [22], or frequency-domain filtering. While ARFI images can utilize elasticity as a mechanism of contrast not present in B-mode images, ARFI images are not typically used to estimate absolute stiffness of tissues (i.e., relating displacement amplitude to elastic modulus) since the magnitude of the acoustic radiation force is a function of acoustic attenuation [23], which is not easily estimated for different imaging targets/tissues. Additionally, the acoustic radiation force magnitude is not constant as a function of depth, and instead varies as a function of focal depth, requiring some depth-dependent normalization scheme to be applied to compensate for these force gradients [3].

Shear Wave Elasticity Imaging (SWEI)

SWEI was first described in the literature by Saravazyan et al. [24] as novel approach to generating shear wave with acoustic radiation force and measuring the resultant shear wave propagation and shear wave speed to ultimately reconstruct an elastic modulus. Unlike ARFI images that can generate images of relative tissue stiffness differences, SWEI allows for absolute metrics of stiffness to be estimated in tissue. The typical assumptions surrounding the reconstruction of an elastic modulus (E, Young's modulus, or μ, shear modulus) from shear wave speed (c_T) include the tissue being linear, isotropic, incompressible, and having a density of water ($\rho = 1.0$ g/cm^3), such that the following relationships can hold [25]:

$$E = 3\mu = 3\rho c_T^2.$$

The incompressibility assumption allows the Young's modulus to be simply related to the shear modulus by a factor of 3. For more details see also book Part II "Techniques to measure liver stiffness." It should be noted that the relationship

between elastic moduli and shear wave speed is quadratic, and therefore, when statistical analyses are performed on data acquired on systems that report different metrics, retrospective conversion of reported thresholds for diagnostic purposes should not be attempted with simple linear scaling. Instead, thresholds for significance and confidence intervals should be recalculated as they may change with this nonlinear relationship. Like ARFI imaging, the acoustic radiation force excitations used for SWEI can involve single or multiple focal zones, depending the depth-of-field being characterized by the shear wave propagation. Rapid firing of multiple focal zone excitations such that a virtual extended shear wave front is launched is referred to as a "supersonic" shear excitation, which was popularized by SuperSonic Shear Wave™ Elastography [26].

One challenge with SWEI can be the distance over which shear wave propagate with displacements that can be reliably tracked. Greater distances can be achieved with stronger radiation force excitations [27, 28], more advanced displacement estimation approaches [29, 30], or creative implementations of interspersed acoustic radiation force excitation, tracking, and directional filtering to tease apart the complexities of intersecting propagating wave fields [31, 32].

Unlike MR elastography, which can measure displacement components in three dimensions and reconstruct a resultant (complex) shear modulus from these data using the Helmholtz equation [33], ultrasonic shear wave methods have a much higher resolution for displacement estimation in the single direction orthogonal to the transducer face, and have instead utilized time-of-flight methods to estimate shear wave speed [26, 34–39]. These shear wave speed estimation methods applied over 2D regions of interest (ROI) can be used to generate two types of quantitative images:

1. *Point Shear Wave Elastography (pSWE)* utilizes all the propagation data in the 2D ROI to estimate a consensus shear wave speed in that region [3, 21]. Typically, a singleton shear wave speed metric is reported per measurement, and clinical studies have supported using a median value across 12 repeated measurements to report as a representative measurement for diagnostic purposes [20, 21]. Quality metrics can be reported along with the shear wave speed to increase diagnostic confidence.
2. *2D-shear wave Elastography (2D-SWE)* breaks the ROI into smaller shear wave reconstruction kernels to generate 2D images of shear wave speed to characterize local variabilities in elasticity [21, 40].

As the confounding factors—viscosity, nonlinearity, anisotropy, structural boundaries—surrounding accurate reconstruction of an elastic modulus from shear wave speed became more well understood, many derivatives of SWEI have settled on directly reporting shear wave speed instead of making additional assumptions to report an elastic modulus. Thus, additional details about the conditions under which an elastic modulus has been estimated must be provided (e.g., the frequency of excitation used in transient elastography or MR elastography) [41, 42]. Given the complexities and nuances surrounding the different commercial implementations of

Table 4.1 Frequency content of different shear wave elastography methods

Method	Frequency content of shear wave
Transient elastography (TE)	50–60 Hz
Point shear wave elastography (pSWE)	100–500 Hz
2D shear wave elastography (2D-SWE)	100–500 Hz
MR elastography (MRE)	60 Hz

SWEI for liver characterization, guidelines have been established for its recommended clinical usage by the World Federation of Ultrasound in Medicine and Biology [20] and the Society of Radiologists in Ultrasound [21].

Viscosity Tissue viscosity is a material property that makes the shear wave speed dependent on the frequency content of the shear wave, and is a confounding factor when assuming that liver tissue is purely elastic (shear wave speed is independent of the shear wave frequency content) [43]. It is known that different elasticity imaging methods can generate shear waves of differing frequency content [21] (see also Table 4.1). The frequency differences can lead to different reconstructed group shear wave speeds in viscoelastic media [44], which can be a source of discrepancy when comparing measurements with different elasticity imaging modalities [41]. Additionally, the processing methods used by each manufacturer—specifically the use of displacement versus velocity data—can also influence the estimated speeds in the presence of viscosity. Velocity data are effectively high pass filtered displacement profiles, and this higher frequency bias can lead to an increase in the estimated shear wave speed.

Some investigators have sought to characterize the viscosity of liver tissue as a measurement of hepatic steatosis or inflammation [45–47], but no conclusive conclusions have been drawn to date.

In addition to the elastography guidelines and consensus documents that have been published, the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) establishes an Ultrasonic Shear Wave Speed (US SWS) working group in 2012 to study the factors that influence the consistent reconstruction of the shear wave speed metric across different manufacturer systems [41, 48, 49]. This working group is composed of international researchers, manufacturers, and regulatory members, and a profile guiding best practices for manufacturers to achieve consistent measurements across different systems is available for consultation.

Another resource generated through the RSNA QIBA US SWS effort has been the generation and public release of digital phantom data generated through finite element method models of shear wave propagation in elastic and viscoelastic materials for shear wave reconstruction development validation [50]. Additionally, standardized sequences for generating and processing shear waves using the Verasonics ultrasound research platform have also been released for public use [51].

Table 4.2 Publicly released digital phantom data and standardized sequences for generating and processing shear waves

Webpage
https://github.com/RSNA-QIBA-US-SWS/QIBA-Digital Phantoms
https://doi.org/10.7924/r4sj1f98c
https://github.com/RSNA-QIBA-US-SWS/Verasonics PhantomSequences

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One confounding factor discovered by the QIBA group in calibrated elastic and viscoelastic phantom studies has been the presence of a negative bias in shear wave speed as a function of increasing focal depth when using curvilinear arrays. The relative magnitude of these biases has been <4% for focal depths ranging from 3 to 7 cm (https://github.com/RSNA-QIBA-US-SWS/).

Another resource generated through the RSNA QIBA US SWS effort has been the generation and public release of digital phantom data generated through finite element method models of shear wave propagation in elastic and viscoelastic materials for shear wave reconstruction development validation [50]. Additionally, standardized sequences for generating and processing shear waves using the Verasonics ultrasound research platform have also been released for public use [51]. The weblinks to this information is provided in Table 4.2.

Conclusions

Acoustic radiation force elasticity imaging methods have become a viable clinical option to noninvasively evaluate liver stiffness. Unlike external vibration-base methods, acoustic radiation force excitations can be focused directly in the tissue of interest, while also providing real-time, ultrasonic B-mode imaging guidance and clinical evaluation. Acoustic radiation force methods are also available to screen for and characterize liver masses. Efforts to standardize and provide more consistent measurements between different manufacturer systems is being addressed by consensus documents and guideline documents, and the RSNA QIBA Ultrasonic Shear Wave Speed group is taking important steps toward characterizing the performance of these systems in calibrated elastic and viscoelastic media.

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