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Liver Elastography: Basic Principles, Evaluation Technique, and Confounding Factors

Felix Bende and Tudor Moga

Abstract

Ultrasound-based elastography techniques have received considerable attention in the last years for the noninvasive assessment of tissue mechanical properties. These techniques have the advantage of detecting tissue elasticity changes occurring in various pathological conditions and are able to provide qualitative and quantitative information that serves diagnostic and prognostic purposes. For liver applications and especially for the noninvasive assessment of liver fibrosis, ultrasound-based elastography has shown promising results. Several ultrasound elastography techniques using different excitation methods have been developed. In general, these techniques are classified into strain elastography, which is a semi-quantitative method that uses internal or external compression for tissue stimulation, and shear wave elastography, which measures the ultrasound-generated shear wave speed at different locations in the tissue. All liver elastography techniques have a standardized examination technique, with the patient in a supine position, while the measurements are performed through the right liver lobe. There are also some confounding factors that need to be taken into account when performing liver elastography such as a higher level of aminotransferases, infiltrative liver disease, liver congestion, cholestasis. This chapter briefly introduces the basic principles of liver elastography and discusses some important clinical aspects of elastography, such as the examination technique and the limitations.

Keywords: liver ultrasound elastography, shear wave elastography, transient elastography, acoustic radiation force impulse, strain elastography, liver fibrosis

1. Introduction

Chronic liver disease is a major health problem worldwide. This situation is generated by a wide range of chronic liver injuries such as chronic viral hepatitis, chronic alcohol abuse, non-alcoholic fatty liver disease, autoimmune hepatitis, primary biliary cirrhosis, and other less frequent causes. Regardless of the liver disease etiology, a common pathway of fibrosis is set up, which progresses and leads to liver cirrhosis that may be complicated by portal hypertension, liver failure, and hepatocellular carcinoma.

The evaluation of patients with chronic liver disease must be as simple as possible, cost efficient, and easily repeatable. While the liver biopsy is still considered the gold

standard for liver fibrosis evaluation, due to its shortcomings (invasiveness, potential complications, inter-/intra-observer variability, sampling error) [1–3] scientific and practical interest has focused on the development of noninvasive techniques for the diagnosis of liver fibrosis.

Elastography can be used to assess liver fibrosis noninvasively. It measures the tissue behavior when mechanical stress is applied, either using ultrasound (ultrasound-based elastography) or magnetic resonance (magnetic resonance elastography).

Ultrasound elastography is perhaps the most important breakthrough in the evolution of ultrasound in the last 20 years. The basic idea behind liver elastography is that the elasticity of the tissue examined offers information on liver health. A stiffer liver tissue usually indicates the presence of chronic liver disease.

Mainly, most liver ultrasound elastography techniques are based on the principle of measuring the speed of the shear wave that propagates through the liver which is influenced by the stiffness of the tissue. The speed of the shear wave is proportional to the tissue stiffness. Basically, the stiffer the liver, the faster the shear wave will propagate through the liver.

The value of ultrasound-based elastography for staging chronic liver disease has been established by numerous studies [4–7]. Moreover, its value for evaluating and predicting chronic liver disease complications (portal hypertension, hepatocellular carcinoma) has been also proven in different studies [8–10].

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and the World Federation of Societies for Ultrasound in Medicine and Biology (WFUMB) have issued guidelines and recommendations on the clinical use of ultrasound-based elastography and describe in detail their basic principles [11–13].

This chapter focuses on the basic principles of elastography, which is an important aspect for every clinician or practitioner who is performing or learning liver elastography. Moreover, clinical features such as the examination techniques of different liver elastography methods and the factors that influence the liver elastography results are described and discussed.

2. Basic principles

Elastography assesses tissue elasticity, which is the tendency of tissue to resist deformation with an applied force or to resume its original form after removal of the force. Elastography can be considered a type of remote palpation that allows the measurement and display of the biomechanical properties in a tissue that acts against the shear deformation. Shear deformation is generated by applying a force either to a single location or broadly across the body surface. A force can be applied by vibrating the body surface that produces a natural internal physiological motion or using the ultrasound transducer to create focused acoustic radiation force at controlled depths [13, 14].

All ultrasound-based elastography methods use ultrasound to measure the tissue shear deformations resulting from an applied force. The type of force applied can be quasi-static or dynamic. Quasi-static forces do not allow the acquiring of images that are quantitative for tissue properties. Dynamic forces allow the quantification of the tissue properties. They include impulses that can be produced mechanically at the body surface or by acoustic radiation force impulse at controlled depths.

According to the EFSUMB guidelines [11], elastography techniques can be classified according to how the displacement data are shown. Three options are available as follows:

- a. Display of displacement without further processing. This type of displacement is used in acoustic radiation force impulse (ARFI) imaging, which allows a quantitative measurement (units of μm), and the image displayed is scaled between bright (soft tissue) and dark (hard tissue). This technique is not used for liver elastography measurements.
- b. Display of tissue strain or strain rate, which is calculated from the spatial gradient of displacement or velocity. This type of displacement works according to Hooke's law, which states that $E = \sigma/\epsilon$, where stress is the applied force per unit area and strain is the change in length of the tissue divided by its original length. If the stress (not known in strain module) is assumed to be the same for all image locations, an image of strain can be thought of as an inverse relative to Young's modulus map. Strain is a quantitative measurement (%) and image brightness is typically scaled between bright (soft) and dark (hard).
- c. Display of shear wave speed, which is calculated by measuring the arrival time of a shear wave at different locations in the tissue. This is possible only when the force is applied dynamically. Shear wave speed may be displayed in units of m/s. Alternatively, it may be converted to either Young's modulus E or shear modulus G , which are expressed in units of kilopascal (kPa). These elastography techniques are called shear wave elastography (SWE) and include transient elastography (TE), point shear wave elastography (pSWE), and multidimensional shear wave elastography (2D-SWE and 3D-SWE).

For liver applications, elastography methods that display the shear wave speed are the most commonly used in practice, followed by strain and displacement imaging (for liver lesions), which are less frequently used. The elastography methods integrated into clinical practice for the liver are described in **Table 1**.

2.1 Strain elastography

Strain elastography is the most widely implemented elastography method on commercial systems; however, it is the least used technique for liver applications. The force used in strain elastography is either produced with the ultrasound probe or due to the internal physiological motion. The axial displacement images are calculated using radiofrequency echo correlation tracking or Doppler processing, which converts the axial displacement images into strain images [14, 15]. Excitation with manual pressure measures elasticity in superficial tissues. A disadvantage of this excitation method is that manual stress is not efficiently transmitted to deeper tissues. Excitation from natural physiologic motion, such as cardiac pulsation and respiration, is another mechanism of generating tissue stress. Deep organs, such as the liver or the kidney, can be assessed with this method [14, 15].

Strain/displacement techniques	Strain elastography
Shear wave elastography techniques	Transient elastography Point shear wave elastography Multidimensional shear wave elastography (2D-SWE and 3D-SWE)

Table 1.
Elastography methods used for the liver.

Strain elastography is a semi-quantitative method for tissue elastic property analysis, which has not demonstrated high accuracy for liver applications.

2.2 Shear wave elastography (SWE)

2.2.1 Transient elastography (TE)

TE has been designed only for liver elasticity measurement. It uses an automated piston, which is also a disk-shaped ultrasound transducer, that applies a low-frequency (50 Hz) mechanical push to the body surface with controlled applied force [16]. A transient shear wave is created that propagates into the tissue. The shear wave propagation velocity is proportional to tissue stiffness, which increases with fibrosis [17]. TE measures tissue stiffness over a 1 cm diameter and 4 cm length region of tissue, which is 100 times larger than those evaluated with liver biopsy. The transient shear wave deformation is propagated at a constant speed, for 4 cm, and measured by a straight line automatically displayed in a displacement M-mode shown in the result (Figure 1) [11]. If the pulse is not transmitted and recorded successfully, the software does not provide a reading. Transient elastography is marketed under the trade name FibroScan®. Stiffness values are presented in kPa. Controlled attenuation parameter (CAP) is a technology that quantifies liver steatosis by measuring the energy loss as the sound wave passes through the medium. Total attenuation at 3.5 MHz is expressed in dB/m, and steatosis is estimated using the same radiofrequency data as elastography, in the same location that stiffness is measured [18]. A schematic representation of the basic principle of TE is presented in Figure 2.

Figure 1. Transient elastography (TE) and controlled attenuation parameter (CAP) with the Fibroscan® device. Sample display showing the echo M-scan on the left, single-line amplitude A-scan in the middle, and the displacement M-mode after a vibration-controlled impulse push on the surface on the right. Numeric values for CAP are displayed on the left side (db/m) and for TE on the right side (kPa).

Figure 2.
Schematic representation of the principle of transient elastography. A mechanically induced impulse at the tissue surface with an A-mode transducer produces an axial shear wave pulse. The measured shear wave speed is proportional to the fibrosis.

2.2.2 Point shear wave elastography (pSWE)

Applying an ARFI at a controlled depth within a tissue generates a shear wave that propagates away from the pushing beam's axis and focal point (**Figure 3**). Its average speed of propagation from the focal point positioned on one lateral

Figure 3.
Schematic representation of the principle of point shear wave elastography (pSWE). An ultrasound-induced focused radiation force impulse is produced at a controlled depth generating a lateral shear wave in a region of interest (ROI). The measured shear wave speed represents tissue stiffness.

Figure 4. Point shear wave elastography (pSWE) implemented on virtual touch quantification (VTQ) from Siemens (4a), ElastPQ from Philips (4b), and S-Shearwave from Samsung (4c). A region of interest (ROI) is placed 1–2 cm below the liver capsule for liver stiffness assessment.

boundary of a measurement region of interest (ROI) to another on the opposite lateral boundary of the ROI may be measured by detecting its time of arrival at that point, relative to that of the ARFI [14]. Ultrasound imaging is used to guide placement of the ROI; however, no elasticity images are produced (**Figure 4**). First introduced by Siemens, pSWE is available on different commercial systems from different vendors (e.g., Philips, Samsung, Hitachi, Esaote). The results can be expressed either in m/s or in kPa.

Figure 5. Schematic representation of the principle of 2D shear wave elastography (2D-SWE). Multiple ultrasound-induced ARFI lines create transverse shear waves that produce quantitative images of their speed.

Figure 6. 2D shear wave elastography (2D-SWE) implemented by SuperSonic imagine (6a) and General Electric (6b). The elastogram, which is superimposed on the B-mode image, is placed 1–2 cm below the liver capsule. A circular ROI is placed inside the elastogram for tissue stiffness measurements. A color-coded scaled quality map (6b left image) can be available for guiding the measurement placement. The result is expressed in kPa and m/s.

2.2.3 Two-dimensional shear wave elastography (2D-SWE)

In this technique, acoustic radiation force impulse is used to create tissue displacement at multiple points (**Figure 5**). By placing the ARFI focus at multiple sequential locations and, at each, detecting the shear wave speed and arrival time, quantitative images of the shear wave speed can be produced [13, 14]. A large quantitative color-coded elasticity map (elastogram) is presented, which can be overlaid on the B-mode image or displayed separately, side by side (**Figure 6**). In addition to the visual impression of the elastogram against a color scale, a quantitative measurement can be obtained by placing smaller ROIs (measurement boxes) inside the elastogram. The result of one measurement is displayed usually as the mean and standard deviation either in m/s as shear wave propagation speed or in Young's modulus in kPa (**Figure 6**).

This technique is available on multiple ultrasound systems including SuperSonic Imagine, GE Healthcare, Canon, Philips, Siemens, Mindray.

3. Evaluation technique

All elastography methods follow an evaluation technique that enables a good approach toward the liver parenchyma. The patients will be positioned in a supine position with their right arm in maximal abduction in order to widen the inter-costal spaces thus offering a better view of the right liver lobe. The measurements from the left liver lobe are not recommended due to higher values and significant variability. A minimum training is required that one may perform liver stiffness measurements, and the acquisition itself will take usually less than 5 minutes. Patients should be in fasting condition (for at least 3 hours) and rest for a minimum of 10 minutes prior to the evaluation. When scanning for the ultrasound section, large vessels and artifacts should be avoided in both A-mode (TE) and B-mode image (pSWE and 2D-SWE) as well as deep inspiratory movements [12, 19, 20]. A dedicated ultrasound gel is used as an interface between the probe and the patient's skin.

3.1 Transient elastography (TE)

For the TE technique, the transducer is placed between the 9th and 11th right intercostal spaces in order to penetrate at least 4 cm thickness of liver parenchyma. The device offers an A-mode image that will assist the examiner to choose the best section into the liver. TE probe will transmit a mechanical impulse to the liver through a special piston (cylinder-shaped) that will apply a controlled force and thus will generate an elastic shear wave. The probe is able to detect the velocity of the shear wave propagation into the liver reflecting the liver stiffness. Measurements are expressed in kilopascals with a range between 1.5 and 75 kPa. If the system detects errors in the acquisition process, it will automatically discard the measurement. At the end of the examination, the median of 10 measurements is displayed as well with the quality parameters (IQR, SR) [12, 19, 20]. For more accurate evaluations, manufacturers provided M, XL, and S probes that are recommended in order to overcome the confounding factor of obesity and thoracic circumference variations [20]. Studies demonstrated that at least 100 measurements are needed for training for one to achieve reliable results and 500 for expert level [21, 22]. It is also a reproducible method with an excellent intra- and interobserver agreement [23].

3.2 Point shear wave elastography (pSWE)

pSWE is a different method integrated into an ultrasound machine that evaluates liver fibrosis by noninvasive means. The acoustic “push” of the probe will generate shear waves that will be transferred to liver parenchyma. Being an ultrasound-assisted method, ultrasound experience plays an important role in performing reliably the technique; even so, the reproducibility of the method is excellent [20, 24]. Using this technique, ascites is not a barrier for liver stiffness measurement. The probe, as in TE, should be placed in the right intercostal spaces in order to depict full liver tissue, without large vessels or other structures. Following, ROI should be set at depths between 1 and 6 cm beneath the liver capsule, ideally at 1–2 cm or 2–3 cm [25]. Special attention should be given to breathing oscillations and to cardiac cycles, patients should hold their breath for a few seconds during the acquisition, and the operator should choose a fair distance from the heart when selecting the ultrasound section and the ROI. However, no elastogram is provided by pSWE. Ten valid measurements are recommended and the result (the median of the measurements) is shown in m/s or kPa. Quality parameters such as IQR/M and standard deviation (SD) are used to optimize the performance of the method [11, 26].

3.3 2D shear wave elastography (2D-SWE)

As in the other methods, 2D-SWE uses a section through the right live lobe free of large vessels and other structures that need a steady image in order to make the acquisition. Patients should hold their breath for 4 to 5 seconds or even longer so that the high frame rate should record the tissue displacement of the shear wave propagation into the color-coded box. Tissue displacement by the shear waves is displayed by a color-coded map; thus, the technique offers both quantitative and qualitative assessments of the tissue stiffness. The colored box should be positioned at least 1–2 cm below the liver capsule but not deeper than 7 cm into the liver parenchyma [27]. The ROI will express the results as the mean value and standard deviation in kPa or in m/s. The biggest advantage that this method is offering is the fact that it evaluates a larger area of the

liver parenchyma (up to 10 cm²). Usually, stiffer tissue will be depicted in red and softer tissue in blue. The operator should obtain as many elastogram loops to which in post-processing will select the ROI for LSM acquisition on the most homogeneous elastogram [26]. A minimum ultrasound training (>300) is necessary to be able to achieve good elastograms [28]. Recommended quality criteria are the IQR/M and measurement depth < 5.6 cm as quality technical [11, 29]. The median of at least three measurements should be used when performing LSM, but the examiner can choose between 3 and 15 measurements [30–32]. Even though it is a reproducible method [33], the inter- and intra-observer agreement in patients might be slightly inferior to pSWE [34, 35].

3.4 Real-time strain elastography (SE)

SE, offered by the Hitachi system (HI-RTE) [36], uses a regular ultrasound transducer that has embedded the SE module in it. It needs a good echoic window for the SE system to work properly; thus, a good ultrasound section is mandatory. The probe will generate echo signals under mild tissue compression and by this will produce a real-time elasticity image by overlapping a colored map on the B-mode image [37, 38]. It has all the advantages of the B-mode imaging and the examination approach will be as for the rest of the techniques with the patient in dorsal decubitus with the right arm in maximal abduction and a short breath hold when the acquisition is made, ascites and high BMI not being a contraindication for this method. However, the method is mainly used as a qualitative evaluation. Results will be displayed as blue for stiffer tissue and in red for soft tissue. Several methods have been developed in order to quantitatively assess tissue stiffness such as Elastic Ratio, Elastic Index, Elasticity Score, and Liver Fibrosis Index but without a proven consistency. The examiner must have ultrasound skills and special training is necessary for ROI setting and probe adjustment for homogeneous compression/relaxation index [20, 38]. Even though experience plays a role in SE, studies [39, 40] demonstrated that SE has a good and very good intra- and inter-observer variability and is a reproducible method.

4. Confounding factors

When measuring liver stiffness with ultrasound-based elastography, we have to acknowledge some factors that can influence the results. Some of the factors are related to a physiological state, and some are linked to pathology. Hepatic inflammation with a threshold of ASAT and/or ALAT >5 times the normal value, hepatic congestion, cholestasis, acute hepatitis, and infiltrative liver disease are known to increase liver stiffness [20]. It is also known that food intake and physical activity can falsely increase LSM; thus, a minimum of 2 hours fasting and resting for 10 minutes before the examination are recommended [20, 41, 42]. Confounding factors of the SWE according to their method are depicted in **Figure 7**.

For TE, BMI seemed to be the main factor influencing the results [43]; hence, a new dedicated XL probe (2.5 MHz) was produced for overweight and obese patients (BMI > 28 Kg/m²) with good clinical results [44, 45].

Besides BMI, TE results can be influenced by increased transaminase, cholestasis, hepatic congestion, infiltrative liver disease, food intake, and heavy alcohol consumption. Several limitations of TE that are worth mentioning are the contraindication of LSM in patients with ascites and the lack of B-mode imaging [26, 46].

Figure 7.
Associated confounding factors in ultrasound-based liver elastography.

The *pSWE* technique uses a B-mode image to select a proper liver section where the acquisition will be made, therefore making it more dependent on ultrasound image selection ergo the operator [24]. Selection of ROI deepness and values obtained in the right vs. left lobe [47, 48] were the aspects that could influence the results. Increased BMI, moderate/severe steatosis, elevated transaminase, congestive liver, and cholestasis are influencing LSM as well as food intake. The examination should be done in fasting condition or at least after 3–4 hours from the last meal [49–51].

The *2D SWE technique* is an operator-dependent method, with experience playing a role in obtaining reliable results [28]. Even though the method overcomes some of the previous limitations, it might have impaired results in patients with severe ascites, bad echoic window, obesity (BMI >30), inability to hold their breath, increased wall thickness (≥ 25 mm), steatosis, waist circumference (≥ 102 cm), and recent food intake [20, 52–55].

The *real-time strain elastography method* is an operator-dependent method, the clear echoic window being a prerequisite for a proper acquisition. Experience would be the front confounder. The method is not very common in daily practice due to its inconsistency [12, 20, 38, 56].

Ultrasound-based liver elastography confounding factors are described in **Figure 7**.

5. Conclusions

Ultrasound elastography comprises a set of techniques that noninvasively measure tissue stiffness. In this chapter, we have provided a brief introduction into the physical concepts of liver elastography and discussed several aspects important for clinical practice. In conclusion, elastography techniques that measure the shear wave speed are the most appropriate for liver applications. The liver elastography examination technique is standardized and co-founding factors need to be taken into consideration before performing liver stiffness measurements.

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