Real-time elastography: a comparison of qualitative and semi-quantitative methods for analysis of the elastograms

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Learning objectives

The prognosis of patients with chronic liver diseases is related to the progression of hepatic fibrosis and the increased risk of complications such as portal hypertension, liver failure or hepatocarcinogenesis [1]. Liver biopsy is still considered the gold standard for the assessment of liver fibrosis, but this method is not suitable for frequent monitoring because of its invasiveness [2]. In addition, the accuracy of liver biopsy is limited by significant intra- and inter-observer variability when two or more pathologists analyze the same sample [3].

An estimate of liver fibrosis can be achieved with different noninvasive approaches, including blood markers with their derived indices (FibroTest, Forns score, aspartate transaminase-to-platelet ratio index [APRI]), magnetic resonance (MR), and ultrasound (US) techniques [4]. Blood markers and derived indices have not been validated in all conditions [5]. MR-elastography is a promising imaging technique but limited by high costs and low availability. US-based techniques include transient elastography (TE), acoustic-radiation force-impulse (ARFI) elastography, shear-wave elastography (SWE) and real-time elastography (RTE) [6]. Most of the ultrasound-based modalities (i.e. TE, ARFI, SWE) provide a quantitative estimate of liver stiffness, while RTE offers a color-coded representation of the relative elasticity of tissues included in the B-mode image. Using this latter modality, secondary analysis of real-time elastograms is required for obtaining semi-quantitative information.

The objectives of this work are:

- give an overview of the currently available US-based techniques for the assessment of liver fibrosis
- describe in detail the methods for analysis of real-time elastograms.
Background

RTE is an imaging technique that directly reveals the physical property of tissues using conventional US probes [7]. Unlike other US-based elastography techniques (TE, ARFI and SWE elastography), that provide a quantitative measure of liver stiffness, RTE measures probe-induced deformation (strain) of the structures examined in the B-mode ultrasound image, generating color-coded maps of the strain distribution (i.e., elastograms), which reflect tissue elasticity [8,9].

Therefore, RTE demonstrates the relative difference in tissue stiffness by assessing changes in local strain in response to an external stress. Because the elastogram is not a quantitative map of tissue stiffness but only a qualitative representation of the relative elasticity of anatomical structures included in the B-mode image, different methods of elastogram analysis have been developed in order to retrieve a semiquantitative estimate of parenchymal fibrosis from RTE examination of the liver.
Findings and procedure details

Generation of the elastogram

When performing RTE to assess liver fibrosis, B-mode imaging is first used to visualize a portion of the liver parenchyma free of large vessels, which can affect the strain response [10]. Then, the elastography module is activated by the operator, who has to apply slight compressions to the patient's cutis with the US probe, allowing the system to generate the elastogram. RTE module can assess liver stiffness by calculating the displacement of tissues along the axial direction of the US beam. The system generates a color map where hard tissue areas are marked with blue, intermediate tissue areas with green, and soft tissue areas with red. The strain response of tissues is color-coded according to its magnitude and translucently superimposed on the conventional two-dimensional US image (Figure 1).

When performing liver RTE, the right lobe is usually examined through the intercostal spaces. The abdominal wall layers visualized include the skin, subcutaneous fat tissue, intercostal muscles, diaphragm, Glisson capsule and liver parenchyma. Some Authors proposed to position the elastography ROI at least 10 mm below the liver capsule, excluding the most superficial portion of the liver parenchyma, because it was considered constantly harder than the deeper parenchyma [11, 12] (Figure 2).

Even the inclusion of large intrahepatic vessels (>3 mm) in the elastogram ROI has to be avoided, because the presence of these soft structures induces clear artifacts in the elastograms, influencing the strain distribution and the quality of information [13] (Figure 3).

The large majority of Authors [14] excluded patients with ascites from their studies, considering that RTE works only with close contact to the liver surface; in patients with ascites, the portion of liver parenchyma included in the elastography ROI is constantly depicted as homogeneously hard, irrespective of its real elasticity [13] (Figure 4).

Methods of elastogram interpretation and analysis

Qualitative method

Qualitative assessment of the color-coded map is the most immediate method of analysis of the elastograms. The pattern of strain induced by operator's compressions becomes patchy as fibrosis progresses [15] (Figure 5).

Semi-quantitative methods
**Histogram of pixel distribution**

Tissue main elasticity (TME) calculation is one of the simplest methods to obtain semi-quantitative information from elastograms.

Each pixel of the image has a specific numeric value to represent tissue elasticity. For quantification, all pixel data in the colored image are transformed into a hue histogram. Lower TME values are related to an increased liver stiffness.

**Elastic Ratio**

The elastic ratio is the ratio of strain distribution in two selected ROIs [2]. A larger elliptical or rectangular ROI is positioned in the liver parenchyma, while a smaller ROI of few square millimeters is positioned in a homogeneously soft anatomical structure, which is considered as internal control. Using this method, a higher elastic ratio reflects a lower elasticity of hepatic parenchyma, and, therefore, a higher stage of liver fibrosis (Figure 6).

**Fibrosis Index**

The fibrosis index (also called elastic index) represents an evolution of the TME calculation; this peculiar method of elastogram analysis is available with the Hitachi RTE module. There are two main elastic indexes: the Japanese elastic index [15] and the German elastic index [14]. As the same for TME, the calculation of the Japanese elastic index starts from the analysis of the histogram. The mean value with standard deviation of pixels within a selected ROI in the liver parenchyma is calculated along with several other parameters derived from the elastogram analysis [1,6,12,15-17].

In the German elasticity score, numerical values of pixels were determined from 0 to 10 according to color mapping from blue/hard (1) to red/soft (0), followed by the calculation of mean, median, minimum, maximum, frequency of pixel values above 0.75 of a single measurement, and descriptive statistics of all measurements. The elasticity score was then calculated by a formula, which was developed by stepwise multivariate logistic regression analysis.

A comparison between the German Elasticity Score and the Japanese Elasticity Score shows that the letter one provides a better correlation with histopathological assessment of liver fibrosis according to Desmet/Scheuer stage and Chevallier score in patients with chronic liver disease [7].

**Comparison of methods**

The qualitative method of elastogram analysis is intuitive, but it has been little used throughout literature [12].
Some Authors, performing a dynamic analysis of the individual histograms of each frame from an RTE movie, showed that RTE may be useful for the prediction of fibrosis, especially in the case of fibrosis #2 (METAVIR stages), where the accuracy reaches 92% [11,13].

The elastic ratio method has shown a good correlation with the liver fibrosis stage determined by histopathological examination of biopsy samples [3,6,11,12,15-17].

Xie et al., using substantial fibrosis (#S2 according to the Scheuer fibrosis stage) as the diagnostic criteria, found that the elastic strain ratio determined by RTE was more accurate than other conventional blood parameters [18].

Studies employing the fibrosis index achieved good results and showed that RTE has an excellent diagnostic accuracy for the diagnosis of liver cirrhosis and even better correlation with histopathology than TE, but only moderate diagnostic accuracy for discriminating mild (F0-1) from significant fibrosis (F2-4) [7,12].
**Fig. 1:** Liver RTE examination in a 28-year-old healthy volunteer without liver fibrosis (transient elastography value= 4.1 kPa, corresponding to F0-1 fibrosis stage according to the METAVIR classification). Elastography module simultaneously shows two images: a conventional B-mode ultrasound image (A) and the color-coded elastogram superimposed on the morphological ultrasound image. The elastography ROI was positioned to include the inner portion of the perihepatic soft tissues, avoiding intra parenchymal large vascular structures. The diaphragm (arrows in A) appears as a homogeneously soft (red) structure when compared to the liver parenchyma, which shows a diffuse, relatively homogeneous, light-green soft pattern in this healthy volunteer. Images were obtained by the RTE module of the ultrasound system MyLab Twice (Esaote, Genoa, Italy) equipped with a multi frequency linear probe (3-11 Mhz, 3-cm array). Elastic ratio calculation was performed in offline modality using a dedicated software program (MyLab Desk; Esaote, Genoa, Italy).

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Fig. 2: Different methods of RTE ROI positioning in a 28-year-old healthy volunteer without liver fibrosis. The elastography ROI was placed including the diaphragm and the perihepatic soft tissues (A), in order to clearly compare and distinguish the strain between the liver and these structures. The diaphragm (asterisk in A) appears as a homogeneously soft (red) structure, while the most superficial portion of the liver parenchyma (arrowheads in A), adjacent to the Glisson’s capsule, appears harder than the deeper parenchyma. In B, the elastography ROI was positioned 10 mm below the liver capsule, excluding large vascular structures.

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Fig. 3: Artefacts in the liver RTE examination of a 32-year old man with chronic viral hepatitis C. This patient had F0 score (i.e. absence of fibrosis) at histological analysis of liver biopsy, according to the METAVIR system, and a normal value of liver stiffness at transient elastography (4.09 kPa). The B-mode ultrasound image (A) shows a parenchymal vessel >3 mm inside the elastography ROI (arrows in A and B). The inclusion of a relatively large, homogeneously soft (red), vascular structure inside the ROI affects the entire color-coded map, where the surrounding liver parenchyma artifactually appears hard (blue).

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Fig. 4: 65-year old man with decompensated alcoholic liver cirrhosis and ascites. In patients with ascites the elastography ROI should be positioned excluding the perihepatic fluid (asterisk in A), which is constantly depicted as a homogeneously soft (red) element. Consequently, the adjacent liver parenchyma is represented as homogeneously hard, irrespectively of its real stiffness. Excluding the ascites from the elastography ROI, the liver cirrhosis assumes a more heterogeneous, mottled appearance characterized by a blue background with green and light-green spots (B).

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**Fig. 5:** Qualitative assessment of RTE examinations of three patients with different degrees of liver fibrosis. The first patient (A) is a 42-year-old man with chronic viral hepatitis C (F1 METAVIR stage at histological analysis of liver biopsy; transient elastography value= 4.8 kPa). The color-coded elastogram shows a diffuse soft pattern, characterized by a relatively homogeneous light-green image. The second patient (B) is a 53-year-old man with chronic viral hepatitis B (F3 METAVIR stage at histological analysis of liver biopsy; transient elastography value= 10.2 kPa). The color-coded elastogram shows an intermediate pattern, characterized by a mottled, dotted image with blue spots on a light-green background. The last patient (C) is a 64-year-old man with chronic viral hepatitis C (F4 METAVIR stage at histological analysis of liver biopsy; transient elastography value= 15.1 kPa). RTE demonstrates the hard pattern, defined as a patchy effect of green, light-green, and blue.

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**Fig. 6:** Calculation of the elastic ratio in a 35-year-old healthy volunteer, using a small intrahepatic vein as internal control. The first RTE image (A) shows a small hepatic vein (2 mm) within the color-coded elastogram, which is depicted as a homogeneously soft structure. In the second RTE image (B), a large elliptical ROI of 65 mm² (Z1) was positioned in the liver parenchyma, excluding the hepatic vein, and a smaller elliptical ROI of 0.9 mm² (Z2) was positioned inside the lumen of the venous vessel, which was considered as internal control. The elastography software generates the histogram of pixel distribution inside the selected ROIs (C), providing two numerical values (74 for Z1 and 93 for Z2, expressed in arbitrary units) for calculating the elastic ratio Z2/Z1. In this case, the elastic ratio was 1.26, a normal value according to the cut-off values previously reported by Koizumi et al.

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Conclusion

RTE technology is rapidly evolving, and a precise knowledge of the different techniques of elastogram analysis may be useful for better understanding how to interpret its results. Technological advances are needed to improve computer-assisted secondary analysis of real-time elastograms for a better differentiation between stages of liver fibrosis, thus reducing biases due to inter- and intra-observer variability.


