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Diagnostic value of real-time elastography in the assessment of hepatic fibrosis in patients with liver iron overload

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ABSTRACT

Objective: The objective of our prospective monocentric work was to determine the diagnostic value of real-time elastography (RTE) in the assessment of liver fibrosis in patients with iron overload, using transient elastography (TE) as reference standard.
Methods: Sixty-seven consecutive patients with MRI detectable iron overload (T2* < 6.3 ms) were enrolled. TE and RTE were performed on the same day as MRI. Elastograms were acquired by an experienced operator and analyzed by calculating the elastic ratio between perihepatic soft tissues and liver parenchyma. An elliptical ROI of 1 cm^2 (Z_1) was positioned in the liver parenchyma and a smaller elliptical ROI of 2 mm^2 (Z_2) was positioned in a homogeneously soft (red) region of the diaphragm, which was considered as internal control to calculate the elastic ratio Z_2/Z_1.
Results: Seven patients were excluded because of invalid TE or RTE examinations. The remaining 60 patients were 57% males and 43% females (mean age: 42 [21–76] years), including 37 homozygous-β-thalassemics, 13 patients with β-thalassemia intermedia, 6 with primary hemochromatosis, and 4 with myelodysplastic syndrome. Increasing elastic ratios were significantly correlated with increasing TE values ($r = 0.645$, 95% CI 0.468–0.772, $P < 0.0001$). The mean elastic ratios for each METAVIR group were as follows: F0/1 = 1.9 ± 0.4; F2 = 2.2 ± 0.4; F3 = 2.9 ± 0.5; F4 = 3.2 ± 0.4. The diagnostic accuracy of RTE for $F \geq 2$ evaluated by AUC-ROC analysis was 0.798 (95% CI 0.674–0.890). The diagnostic accuracy of RTE for $F \geq 3$ was 0.909 (95% CI 0.806–0.968). At a cut-off ≥ 2.75, RTE showed a sensitivity of 70% (95% CI 45.7–88.1) and a specificity of 97.5% (95% CI 86.8–99.9).
Conclusions: In patients with MRI-detectable liver iron-overload RTE allows to discriminate between F0/1–F2 and F3–F4 with a reasonable diagnostic accuracy.

1. Introduction

In patients with liver iron overload related to primary (genetic) or secondary hemochromatosis [1,2], the risk for developing fibrosis and cirrhosis has been associated to the liver iron content (liver iron concentration [LIC]), the duration of iron exposure by the liver, and the presence of co-factors of hepatotoxicity, such as viruses and alcohol [3,4]. Liver biopsy is still considered the gold-standard method for evaluating the stage of hepatic fibrosis and to measure LIC in patients with hemochromatosis [5]. However, this invasive technique has many procedure-related complications, as well as wide variations in the results [6]. Sampling error studies have shown that a single biopsy may miss cirrhosis in 10–30% of patients and incorrectly classify fibrosis by at least one stage in 20–30% [7]. Currently, magnetic resonance imaging (MRI) with T2*-weighted sequences is considered a reliable method for detecting iron deposits in the liver, showing high correlation to the values found in specimens from biopsy, which are expressed as milligrams of iron per gram of dried tissue (mg Fe/g dry weight) [8]. Beside LIC quantification, a correct estimation of liver fibrosis has important implications regarding patient's management, prognosis assessment and long term follow-up. In recent years, non-invasive methods were developed in order to replace liver biopsy. Non-invasive methods (Fibrotest, aspartate transaminase-to-platelet ratio index) using biological

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parameters such as bilirubin, haptoglobin, platelet count cannot be applied to hematological diseases requiring blood transfusion [9]. Ultrasound-based elastographic methods include transient elastography (TE), acoustic radiation force impulse (ARFI) elastography, shear wave elastography (SWE), and real-time elastography (RTE) [10]. While TE has already been validated in patients with liver iron overload (i.e. primary hemochromatosis [11], multi-transfused adult β-thalassemia major and thalassemia intermedia patients [12], sickle cell disease and myelodysplastic syndrome [13]), no study has investigated the diagnostic performance of RTE in staging liver fibrosis in such patients. The main objective of the present work was to determine the diagnostic value of RTE in assessing hepatic fibrosis stage according to the METAVIR classification [13] in a heterogeneous cohort of patients with liver iron overload using TE as reference standard.

2. Methods

2.1. Patient inclusion

This was a prospective monocentric study and patient's enrollment was performed at the Unit of Microcitemia and Hereditary Anaemias of our Institution, where subjects with different diseases leading to liver iron overload are routinely evaluated with MRI. From January 1st, 2011, through December 31st, 2012, all consecutive patients with MRI T2* detectable hepatic iron (liver T2* value $\leq$ 6.3 ms) were enrolled into the study. TE and RTE were performed on the same day as MRI. The study protocol was approved by the institutional review board. Written informed consent was obtained from all patients before the MRI study. Exclusion criteria were general contraindications to 1.5 T MRI [14], decompensated liver cirrhosis with ascites (which can influence both TE and RTE results [10]), and the presence of an inhomogeneous patchy pattern of iron deposition detected by MRI. This latter criterion was introduced to avoid sampling bias when performing TE, since it is likely that a patchy iron deposition may lead to inhomogeneous fibrosis throughout the liver parenchyma [8]. Serum ferritin levels were determined using a standard laboratory method performed within 1 month from the imaging examinations (normal adult blood levels are 12–300 ng/mL for males and 10–150 ng/mL for females [5]). Eligible patients were also screened for the presence of hepatitis C virus (HCV) antibodies and hepatitis B surface antigen (HBsAg) in serum.

2.2. Magnetic resonance imaging

MRI is considered a reliable method for detecting iron deposits in the liver [15], and gradient-echo sequences are used to quantify the proton-transverse relaxation through transverse relaxation time (T2*) measurements. The reciprocal of T2*, known as transverse relaxation rate (R2*), increases in the presence of iron and is proportional to LIC over the clinically relevant range [16]. Breath-hold R2*-MRI measurements were performed using an eight-element cardiac/torso coil in a 1.5T Signa HDx scanner (General Electric Medical Systems, Milwaukee, WI, USA) scanning the whole liver of the patients. To obtain quantitative R2* maps, a multigradient echo sequence with the following parameters was used: eight echoes and minimum echo spacing, echo times (TE) 1.1–6.7 ms, repetition time (TR) 200 ms, flip angle 20°, matrix 128 × 96 pixels, bandwidth 125 kHz, number of excitations 1, slice thickness 10 mm, and spacing 0 mm. The duration of each sequence was 20–30 s. Measurements of R2* were performed using a publicly available software (C-Iron, Camelot Biomedical Systems, Genoa, Italy; website: http://c-iron.camelotbio.com) and the signal decay was fitted to every pixel in the image to an exponential plus a constant function. A region of interest (ROI) comprising the whole liver and excluding blood vessels and biliary ducts was drawn from a transverse midhepatic slice. Hepatic iron overload was defined by MRI T2* values less than 6.3 ms, corresponding to a liver iron concentration in dry tissue (LIC dry weight) of 4.2 mg/g. Hepatic iron overload was categorized as mild (6.3–2.7 ms), moderate (2.6–1.4 ms) or severe (<1.4 ms) [17].

2.3. Transient elastography

The physician performing all TE examinations was a hematologist (MB) with more than 5 years of experience in this technique. TE is a corroborate method for the assessment of liver fibrosis in patients with hemochromatosis [11–13], since it has been shown that iron overload does not influence the diagnostic accuracy of this technique [18]. TE was performed with FibroScan (Echosens, Paris, France), a medical device based on elastometry. In this device an ultrasound probe, mounted on the axis of a vibrator, transmits low-frequency vibrations from the right intercostal space, creating an elastic shear wave that propagates into the liver. A pulse-echo ultrasound acquisition is then used to detect the wave propagation velocity, which is proportional to tissue stiffness; faster wave progression occurs through stiffer material. Liver stiffness measurement is then performed and measured in kiloPascals (kPa) (values between 2.5 kPa and 75 kPa are expected) [19]. Acquisitions that do not have a correct vibration shape or a correct follow-up of the vibration propagation are automatically rejected by the software. Measurements of liver stiffness were performed on the right lobe of the liver through intercostal spaces in correspondence to the mid-axillary line, while patients are lying in the supine position with the right arm in maximal abduction. Only patients with 10 correct measurements with an interquartile range (IQR) of less than 30% of the median liver stiffness value were included [20]. TE values were expressed in kilopascals (kPa); further they were converted in the corresponding semi-quantitative fibrosis score of METAVIR, a widely diffused histopathological staging system for liver fibrosis. It is based on a semi-quantitative 5-point scale from 0 to 4: F0, the absence of parenchymal fibrosis; F1, enlarged fibrotic portal tract; F2, periportal or initial portal-portal septa but intact architecture; F3, architectural distortion but no obvious cirrhosis; and F4, cirrhosis. The conversion of TE values into the corresponding METAVIR stage was made by means of validated cut-off values (i.e. F0/F1 vs F2–F4 = 8.8 kPa; F0/F1–F2 vs F3–F4 = 9.6 kPa; F0/F1–F3 vs F4 = 14.6 kPa), which were obtained in a previous study by Ziol et al. using biopsy as reference standard [21].

2.4. Real-time sonoelastography

A radiologist (FP) with more than 5 years of experience in conventional ultrasound examinations and 1 year of experience in RTE, blinded to TE results, consecutively performed all RTE examinations. RTE measures mechanically probe-induced deformation (strain) of structures examined in the B-mode ultrasound image, generating color-coded maps of the strain distribution (i.e. elastograms), which reflect tissue elasticity [22,23]. The RTE module displays two images simultaneously: the conventional B-mode image and the color-coded elastography region of interest (ROI), overlaid on the B-mode image (Fig. 1).

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. In the Esaote elastographic module (Elaxto) numerical values of pixels are from 0 to 100 (100 stepwise grading) according to color mapping from blue (0) to red (100). It is possible to generate a histogram of pixel distribution derived from the color image by 100 stepwise grading. The examinations were performed on the right lobe of the liver through the intercostal spaces