Research Article

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Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography

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Background & Aims: Quantitative shear wave elastography was shown to be an effective tool for the non-invasive diagnosis and staging of chronic liver diseases. The liver shear modulus, estimated from the propagation velocity of shear waves, is correlated to the degree of fibrosis and can therefore be used for the non-invasive staging of fibrosis.

Methods: We performed a clinical prospective study in a total of 120 patients with various chronic liver diseases to compare the accuracy of supersonic shear imaging (SSI), a technique based on acoustic radiation and ultrafast ultrasound imaging, to 1D transient elastography (FibroScan) for the staging and grading of fibrosis as assessed by liver biopsy. Since shear wave propagation spectroscopy can also provide additional mechanical information on soft tissues, such as viscosity, we also investigated those new mechanical parameters as possible predictors of fibrosis, steatosis, and disease activity.

Results: SSI was successfully performed in 98.3% of patients and it was shown to be as accurate as FibroScan for the staging of fibrosis both for the whole population (N = 120) and for the subgroup with viral hepatitis (n = 70) (AUC = 0.85 [0.77–0.96] and 0.89 [0.81–0.97] for significant fibrosis, AUC = 0.90 [0.83–0.97] and 0.87 [0.75–0.98] for cirrhosis, with respect to SSI [n = 68/70] and FibroScan [n = 66/68]). Viscosity could also be used to stage the degree of fibrosis (AUC = 0.76 [0.64–0.87] for significant fibrosis and AUC = 0.87 [0.74–0.99] for cirrhosis), for the subgroup of patients with viral hepatitis (n = 67/70) but was a poor predictor of disease activity and steatosis levels.

Conclusions: Supersonic shear imaging is a robust technique for the staging of liver fibrosis. Liver viscosity was found to be correlated with fibrosis but not to steatosis or disease activity.
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Keywords: Elastography; Shear wave; Liver stiffness; Fibrosis; Steatosis; Liver biopsies; Non-invasive markers of fibrosis; Shear wave spectroscopy.

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Abbreviations: SSI, supersonic shear wave imaging; LB, liver biopsy; BT, blood tests; FT, FibroTest; APRI, aspartate transaminase to platelet ratio; FS, Fibroscan; SWS, shear wave spectroscopy; BMI, body mass index; ROC, receiving operator curve; AUC, area under the curve; IQR, inter quartile range; kPa, kilo pascal; Pa.s, pascal-second.

Introduction

The progression of liver fibrosis is associated with persistent necro-inflammation and can lead to increased mortality and morbidity, mainly due to cirrhosis [1]. That is why the assessment of liver fibrosis is important in patients with chronic liver disease [2] and potential fibrosis progression must be monitored to adjust and determine treatment strategies.

The gold standard for the staging of liver fibrosis is still considered to be liver biopsy (LB), which can also provide important diagnostic information on necro-inflammation (disease activity) and levels of steatosis. The main limitations of liver biopsy (cost, pain, increased morbidity and mortality, sampling error or patient refusal) [2] have been partially overcome by non-invasive tests of fibrosis. They include non-invasive biochemical tests such as the FibroTest® (FT), FibroMeter®, HepaScore, aspartate transaminase to platelet ratio (APRI), FIB4, or Forns score but also physical tests such as FibroScan (FS, Echosens, Paris, France) [3]. FS provides an estimation of liver stiffness by sending a low frequency narrow band shear wave (50 Hz) and tracking its propagation inside the liver. Several studies have reported that the combination of serum markers and liver stiffness measurements (LSM) with FS were accurate for the staging of liver fibrosis [4]. French health authorities have validated and reimburse the use of non-invasive tests such FibroTest®, FibroMeter®, HepaScore or FS for the evaluation of fibrosis in HCV-infected patients. However non-invasive tests also have certain limitations: blood tests (BT) can be influenced by extrahepatic diseases including haemolysis [2], Gilbert's syndrome or chronic inflammation.

FS is gaining in popularity and has been compared with real-time strain elastography and Apri in 131 HCV-infected patients with regard to the histologic stages of fibrosis. The results showed

that transient elastography had a good diagnostic performance in assessing severe fibrosis and cirrhosis, better than strain elastography [5]. FS has also limitations (low volume of parenchyma explored, absence of ultrasound imaging to guide measurements and measurement variability). Applicability is its main limitation in clinical practice with unreliable results in around 20% of cases, mainly due to patients' obesity and limited operator experience [6].

Shear wave elasticity (SWE) imaging [7,8] has now been recognized as a useful technique for the diagnosis and characterization of liver tissue. Recently, several ultrasound techniques of elasticity imaging have been developed and investigated for the staging of fibrosis, such as supersonic shear imaging (SSI) [9], which provides a two-dimensional (2D) real-time, quantitative map of the elasticity of the liver, as well as acoustic radiation force impulse (ARFI) [10], which gives a single point stiffness value. In both cases, like FS, liver stiffness is estimated from shear wave velocity but with the advantage of having B mode guidance to help position the probe and region of interest and an internal generation of the shear wave (via an acoustic radiation force) rather than an external mechanical one.

SSI has already been evaluated in several organs, such as the liver, spleen or breast [11–13]. We have recently reported that SSI could reliably determine the degree of fibrosis compared to blood tests and was more accurate than FS [11]. However, in this study, liver biopsies were not available in all 122 patients with hepatitis C virus (HCV) chronic infection. Similarly, in 121 HCV-infected patients real-time SWE imaging has been reported to be more accurate than FS in differentiating F0–1 from F2–4 fibrosis (AUROCs of 0.92 for SWE *vs.* 0.84 for FS) [14]. We have also reported that shear wave dispersion curves in the liver using Shear Wave Spectroscopy (SWS) could estimate viscosity based on a rheological model [15].

Besides the staging of fibrosis the non-invasive assessment of disease activity and level of steatosis are also of great clinical interest. Some tests have been developed, such as the Actitest® [16] and SteatoTest® [17] (based on BT) (BioPredictive, Paris, France) or the Controlled Attenuation Parameter (CAP®, Fibroscan, Echosens, Paris, France), which relies on ultrasound attenuation changes in the steatotic liver [18] to assess steatosis. Although, their diagnostic values have not been fully confirmed, they show promising results [20,21].

In this prospective study, we compared the results of SSI in 120 patients with chronic liver disease with FS and several blood tests (APRI, FIB4, Forns, and FT) in an intention-to-diagnose analysis for the staging of fibrosis and with SWS and viscosity for the staging of disease activity and steatosis, using liver biopsy as the reference method.

Materials and methods

Patients

From February 2011 to November 2012, a total of one hundred twenty patients, who were about to undergo liver biopsy for the evaluation of chronic liver disease at Cochin Hospital, Paris, France, were enrolled in the study in a consecutive series. The indication for liver biopsy (LB) was either due to discordant results between FS and blood tests (BT), or because aetiology of the liver disease was unknown. All patients signed an informed consent form. This prospective clinical study was approved by the local ethics committee and national authorities (CPP IdF N° 12487).

Liver biopsy and staging of liver fibrosis, activity, and steatosis

All included patients underwent either percutaneous LB (N = 118) or transvenous LB (N = 2) due to coagulation disorders by a senior physician at Cochin Hospital. A senior pathologist ([B. Terris] unaware of the results of SSI and FS) assessed the scores for fibrosis and disease activity according to the METAVIR scoring system, as well as the percentage of steatosis (graded by the Brunt score [19]: S0 = 0%, S1 = 1–33%, S2 = 34–66%, and S3 = 67–100% of hepatocytes with fatty accumulation). Fibrosis was staged on a 0–4 scale as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and a few septa; F3, numerous septa without cirrhosis; F4, cirrhosis. Disease activity was graded as follows: A0, none; A1, mild; A2, moderate; A3, severe. The length of each LB specimen (in millimetres) and the number of fragments were recorded.

Liver stiffness measurements by FibroScan (FS)

FS measurements were performed on the same day or a few days before biopsy by a single qualified operator with 7 years training on 114 patients (N = 6 not available) who were not necessarily fasting (no recommendation available at the time of the study). The validity criteria was a success rate $\geqslant$60% and an interquartile range $\leqslant$30% of the median value. The FS measurements did not meet those manufacturer recommendations for 6 patients out of 114, yielding an applicability of 94.7%.

Liver stiffness measurements by supersonic shear imaging (SSI)

SSI was used to image liver stiffness with the Aixplorer ultrasound imaging system (Aixplorer, Supersonic Imagine, Aix-en-Provence, France) with an abdominal curved probe (SC6-1) just before performing LB (Fig. 1). Ten acquisitions were obtained for each intercostal space, using the shear wave elastography imaging mode (SWE™) of the Aixplorer scanner in the 'penetration' setting. A "QBox™" region of interest (mean diameter 30 mm) was positioned inside the elasticity image (mean centre depth 40 mm) after each acquisition to obtain a mean stiffness value. In the absence of guidelines in the literature, the liver stiffness measurement by SSI was defined in this study as the median of ten successive stiffness values using the QBox, similarly to the definition of liver stiffness measurement obtained by FS.

In order to evaluate the role of the probe position, three successive intercostal positions A, B, C were acquired corresponding to the 6th, 7th, and 8th intercostal spaces following the median underarm line at the projection of the right lobe of the liver.

To evaluate the inter-observer variability of SSI, a second operator performed the same ten measurements for each of the three intercostal spaces in the first 88 patients (73%), including 54 patients in the viral hepatitis subgroup (79%).

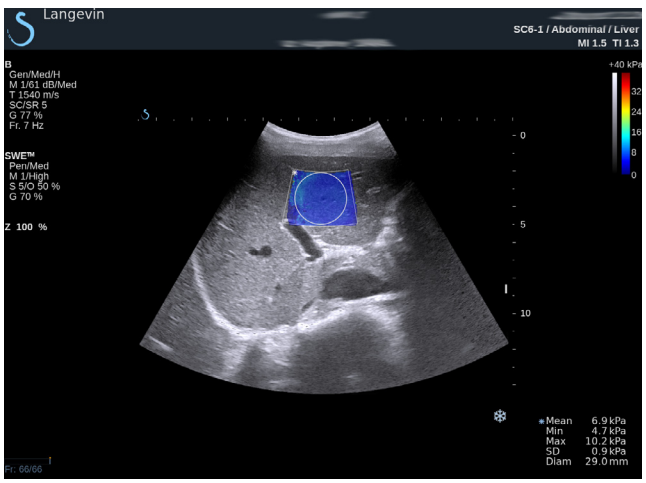

Fig. 1. Real-time stiffness map of the liver in kPa as displayed on the Aixplorer. The white circle denotes the positioning of the ROI used for the measurement. All shear wave propagation data were also saved for offline processing with the shear wave spectroscopy technique. (This figure appears in colour on the web.)

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