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Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study

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ABSTRACT

Aim: The aim of this international multicenter study was to evaluate the reliability of Acoustic Radiation Force Impulse (ARFI) elastography for predicting fibrosis severity, in patients with chronic hepatitis C.
Patients and methods: We compared ARFI to liver biopsy (LB) in 914 patients (10 centers, 5 countries) with chronic hepatitis C. In each patient LB (evaluated according to the METAVIR score) and ARFI measurements were performed (median of 5–10 valid measurements, expressed in meters/second – m/s). In 400 from the 914 patients, transient elastography (TE) was also performed (median of 6–10 valid measurements, expressed in kiloPascals – kPa).
Results: Valid ARFI measurements were obtained in 911 (99.6%) of 914 cases. On LB 61 cases (6.7%) had F0, 241 (26.4%) had F1, 202 (22.1%) had F2, 187 (20.4%) had F3, and 223 (24.4%) had F4 fibrosis.

A highly significant correlation ($r = 0.654$) was found between ARFI measurements and fibrosis ($p < 0.0001$). The predictive values of ARFI for various stages of fibrosis were: $F \geq 1$ – cut-off > 1.19 m/s (AUROC = 0.779), $F \geq 2$ – cut-off > 1.33 m/s (AUROC = 0.792), $F \geq 3$ – cut-off > 1.43 m/s (AUROC = 0.829), $F = 4$ – cut-off > 1.55 m/s (AUROC = 0.842).

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The correlation with histological fibrosis was not significantly different for TE in comparison with ARFI elastography: $r = 0.728$ vs. 0.689, $p = 0.28$. TE was better than ARFI for predicting the presence of liver cirrhosis ($p = 0.01$) and fibrosis ($F \geq 1$, METAVIR) ($p = 0.01$). ARFI elastography is a reliable method for predicting fibrosis severity in chronic hepatitis C patients.

1. Introduction

Chronic hepatitis C is an important public health problem. In these patients, evaluation of liver fibrosis is essential, because prognosis and treatment decisions often depend on fibrosis severity. Liver biopsy (LB) is still considered the "gold standard" for liver fibrosis assessment, despite being an invasive method and not totally risk free [1].

LB was criticized because it evaluates only a small part of the liver, approximately 1/50,000 of the total liver volume [1]. It has been proven that liver fragments obtained in the same session, by laparoscopic biopsy, from the left and right liver lobes may have different stages of fibrosis in almost half of the cases [2].

In the last 10 years several ultrasound-based non-invasive methods for liver fibrosis assessment were developed. Transient elastography – TE (FibroScan®) is the first ultrasound-based elastographic method developed about 10 years ago, validated at first for liver fibrosis evaluation in patients with chronic hepatitis C and subsequently also in other etiologies of chronic hepatopathies [3]. In the last 2–3 years, at least 3 elastographic methods for the non-invasive assessment of liver fibrosis were developed: Real-Time Elastography – Hi-RTE [4], Supersonic Shear Wave Elastography [5], and Acoustic Radiation Force Impulse Elastography – ARFI [6,7], implying different physical principles and different technologies. As compared with TE, Hi-RTE, Supersonic Shear Wave Elastography and ARFI are real-time elastographic methods, integrated into a conventional ultrasound system, which can be also used to perform standard ultrasound evaluation and contrast-enhanced ultrasonography. Moreover, in these equipments elastometry is superimposed to conventional B-mode images, so that the parenchymal areas in which the measurements are made is exactly detailed.

The aim of this international multicenter study is to evaluate the reliability of ARFI for predicting fibrosis severity in patients with chronic hepatitis C, using LB as "gold standard". In a subgroup of patients we also evaluated ARFI for liver fibrosis assessment as compared to TE.

2. Patients and methods

2.1. Patients

Our retrospective international multicenter study included 914 patients (10 centers, 5 countries) with chronic hepatitis C (positive anti-HCV antibodies and positive PCR HCV RNA for more than 6 months). No patient had coinfection with hepatitis B virus or human immunodeficiency virus. Liver fibrosis was evaluated by means of LB, ARFI and, in a subgroup of patients, also by TE. The distribution of patients according to the centers included in the study and investigation performed are presented in Fig. 1.

Some patient data have been published in previous studies [6–12] and were pooled in the present study.

All the patients included in our study had a homogeneous liver structure (without liver masses) and they did not have ascites on abdominal ultrasound examination.

All the patients signed an inform consent before LB and ARFI measurements, and each center had an approval from the Local Ethics Committees.

2.2. ARFI elastography

The principle of ARFI elastography is that compression of the examined tissue induces a strain into the tissues. The ultrasound probe automatically produces an acoustic "push" pulse that generates shear-waves which propagate into the tissue, perpendicular to the "push" axis. The speed of the shear-waves, measured in meters/second (m/s), is displayed on the screen and the highest theoretically reachable velocity in the hardest mean would correspond approximately to 6 m/s. The propagation speed increases, in fact, with tissue stiffness, thus with fibrosis severity. Shear wave speed may be quantified, in a precise anatomical region, focused on a region of interest, with a predefined size, provided by the system. Speed measurement value and depth of the samples are also reported and the results of the elasticity are given in m/s [13].

ARFI was performed in all patients with a Siemens Acuson S2000TM ultrasound system (Siemens AG, Erlangen, Germany) with 4CI transducers. Scanning was performed with a right intercostal approach, in the right liver lobe, segment V–VIII, 1–2 cm (Hyogo, Timisoara) or 2–3 cm (other centers) under the liver capsule, with minimal scanning pressure applied by the operator, while the patients were asked to stop normal breathing for a moment, in order to minimize breathing motion. The operator selects the depth at which the liver elasticity is evaluated by placing a "measuring box" (10 mm long, 5 mm wide) in the desired area (Fig. 2). The maximum depth at which ARFI measurements can be performed is 8 cm. A total of 5 (Saga), 6 (Bologna, Verona) or 10 valid measurements (the other centers included in this study) were performed in every patient and a median value in m/s was calculated. If the measurement was not reliable "X–X–X" was displayed of the screen.

The operators who performed ARFI measurements were blinded to all patients' clinical, serological and histological data.

2.3. Transient elastography

Liver stiffness (LS) was measured by means of TE using a FibroScan® device (Echosens, Paris, France) in 400 patients. In each patient we performed 10 TE measurements, the median value was calculated and the results were expressed in kilopascals (kPa). ARFI and TE measurements were performed in the same session. We considered reliable only LS measurements with a success rate (SR = ratio of the number of successful acquisitions over the total number of acquisitions) $\geq$ 60% and an interquartile range (IQR = the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) < 30%.

2.4. Liver biopsy

LB was considered in this study as the "gold-standard" for liver fibrosis evaluation. LB was performed using different methods