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Factors that influence the correlation of Acoustic Radiation Force Impulse (ARFI) elastography with liver fibrosis

Simona Bota, Ioan Sporea, Roxana Şirli, Alina Popescu, Mirela Dănilă, Mădălina Şendroiu

Department of Gastroenterology and Hepatology, University of Medicine and Pharmacy, Timişoara, Romania

Abstract

Aim: To establish the influence of different factors on the correlation between liver stiffness (LS) measurements by ARFI and liver fibrosis, evaluated by liver biopsy (LB). We assessed the following factors: the success rate (SR) and interquartile range (IQR) interval, the place where ARFI was performed, liver steatosis, the quality of the specimen obtained by LB. **Methods:** We studied 471 patients: 82 with LB, 82 healthy volunteers and 307 with cirrhosis. We performed 10 valid ARFI measurements, a median value was calculated, expressed in meters/second. **Results:** Valid measurements were not obtained in 11 patients. There was a direct, strong, correlation (r=0.694) between ARFI and fibrosis (p<0.0001). There were no statistically significant differences between the mean ARFI values obtained in segments V vs. VIII (p=0.89). Considering the IQR and SR, the correlation of ARFI with fibrosis was: for IQR<30% and SR≥60%: r=0.722 and for IQR>30% and/or SR≤60%: r=0.268 (p=0.0001). The quality of the liver specimen (2-3 cm long vs. >3 cm) did not influence the correlation of ARFI with fibrosis. **Conclusions:** To obtain the best correlation between ARFI and fibrosis, IQR must be <30% and SR≥60%. These technical parameters must be introduced to improve the ARFI value for LS evaluation.

Keywords: Acoustic Radiation Force Impulse elastography, interquartile range interval, success rate, liver fibrosis

Rezumat

Scop: Stabilirea influenței diferiților factori asupra corelației elasticității hepatice (EH) determinate prin ARFI cu fibroza hepatică, evaluată prin punctia biopsie hepatică (PBH). Am evaluat următorii factori: rata de succes (SR) şi intervalul interquartilic (IQR), locul unde s-au determinat valorile ARFI, steatoza hepatică, calitatea specimenului obținut la PBH. **Metode:** Am evaluat 471 pacienți: 82 cu PBH, 82 voluntari sănătoşi şi 307 cu ciroza. Am efectuat 10 măsurători ARFI valide fiind calculată o valoare exprimată în metri/secundă. **Rezultate:** La 11 pacienți nu am obținut măsurători valide. S-a obținut o corelație directă, puternică (r=0.694) între ARFI şi fibroză (p<0.0001). Nu au existat diferențe semnificative statistic între valorile medii ale ARFI obtinute în segmental V vs. VIII (p=0.89). În funcție de IQR şi SR corelația ARFI cu fibroza a fost: pentru IQR<30% şi SR≥60%: r=0.722 şi pentru IQR>30% şi/sau SR≤60%: r=0.268 (p=0.0001). Calitatea specimenului obținut la PBH (2-3 cm lungime vs. > 3 cm) nu a influențat corelația ARFI cu fibroza. **Concluzii:** Pentru a obține cea mai bună corelație între măsuratorile ARFI şi fibroză, IQR trebuie sa fie <30% şi SR≥60%. Aceşti parametrii tehnici trebuie introdusi pentru a îmbunătăți valoarea ARFI în evaluarea EH.

Cuvinte cheie: elastografia impulsională, ARFI (Acoustic Radiation Force Impulse), interval interquartilic, rata de succes, fibroza hepatică

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Address for correspondence: Simona Bota
2, Intrarea Martir Angela Sava str,
300742, Timişoara, Romania
Tel: +40-721-656147
Fax: +40-256-488003
E-mail: bota_simona1982@yahoo.com

Introduction

Acoustic Radiation Force Impulse (ARFI) elastography is a new method used for liver fibrosis assessment [1-5], offered by Siemens and integrated into an ACUSON S2000 ultrasound system.

The principle of ARFI elastography is that compression of the examined tissue induces a smaller strain in hard tissues than in soft ones. The ultrasound probe auto-

matically produces an acoustic "push" pulse that generates shear-waves which propagate into the tissue. Their speed, measured in meters/second (m/s), is displayed on the screen. The propagation speed increases with fibrosis severity. Using image-based localization and a proprietary implementation of ARFI technology, 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. Measurement value and depth are also reported and the results of the elasticity are in m/s [6-8].

Unlike Transient Elastography (TE), the device manufacturer did not recommend the use of quality technical parameters, such as the success rate (SR), defined as the ratio of successful acquisitions over the total number of acquisitions or interquartile range (IQR) interval, defined as the difference between the 75th and the 25th percentile, essentially the range of middle 50% of the data). Also in TE, some studies proved the influence of aminotransferases level on the liver stiffness (LS) measurements [9-10].

The **aim** of this study was to assess the influence of different factors (IQR, SR, the place where ARFI was performed -liver segment V vs. VIII, liver steatosis and the quality of liver biopsy specimen) on the correlation between liver stiffness (LS) measurements by ARFI and the severity of histological fibrosis, according to the Metavir score.

Patients and methods

Our study included 471 patients (203 women and 268 men) hospitalized in our Clinic, mean age 53.5±15.03 years: 82 healthy volunteers, without known liver pathology (considered to have no fibrosis), 82 patients with chronic HBV or HCV chronic hepatitis, with liver biopsy (LB) and 307 patients with clinical, ultrasonographic, endoscopic and/or laparoscopic signs of cirrhosis. The study was approved by the local Ethics Committee and all the patients signed the informed consent.

Body mass index (BMI) was calculated in all the subjects according, to the following formula: BMI= weight (kg)/[height(m)]^2.

The healthy volunteers were medical students, nurses and medical doctors (fellows and specialists) from our hospital, without a history of liver disease (acute or chronic). We did not perform additional tests in this subgroup (such as biological tests, viral markers). In all the healthy volunteers, we performed an abdominal ultrasound examination. None of the subjects had steatosis or liver masses.

From the 82 patients with LB, 50 had chronic HCV hepatitis and 32 had chronic HBV hepatitis. In all these patients we performed an abdominal ultrasound examination. All the patients included in our study had a homogeneous liver structure and no ascites. From the 307 patients diagnosed with liver cirrhosis by clinical, ultrasonographic, endoscopic and/or laparoscopic criteria, 185 patients (60.2%) had esophageal varices, 70 (22.8%) had hepatocellular carcinoma and 134 patients (43.6%) had ascites.

ARFI elastography

ARFI was performed in all the patients in left lateral decubitus, with the right arm in maximum abduction. Scanning was performed between the ribs in the right liver lobe, 1 cm under the capsule, with minimal scanning pressure applied by the operator, while the patients were asked to stop breathing for a moment, in order to minimize breathing motion (fig 1). We performed 10 valid measurements in every patient, and a median value was calculated, the result being measured in m/s. Similar to TE, we considered as good quality technical parameters an IQR<30% and a SR≥60%.

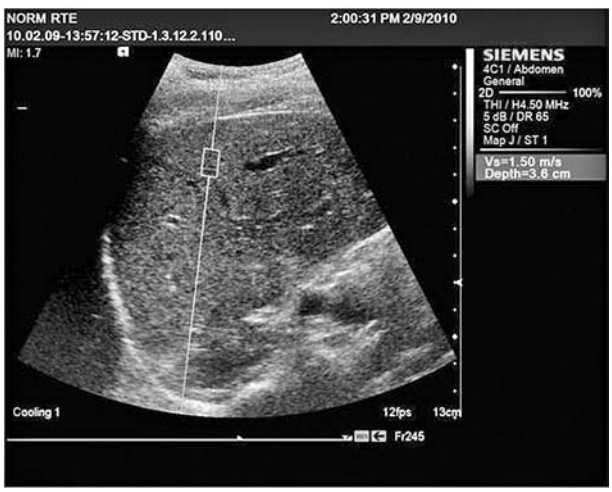

Fig 1. ARFI determination

Liver Biopsy

LB was performed echo-assisted, using Menghini type modified needles, 1.4 and 1.6 mm in diameter. All liver specimens were longer than 2 cm (a quality parameter that we use in our daily practice in our department). The length of the fragment of biopsy was evaluated by the physician who performed it. The LBs were assessed according to the Metavir score, by a senior pathologist. Fibrosis was staged on a 0–4 scale: F0 - no fibrosis; F1 - portal fibrosis without septa; F2 - portal fibrosis and few septa extending into lobules; F3 - numerous septa extending to adjacent portal tracts or terminal hepatic venules and F4 – cirrhosis**.**

Regarding steatosis evaluation, we used the Hepburn classification, according to which the patients were grouped into 5 categories, based on the percentage of steatosis on biopsy: 0–2%, 2–10%, 10–30%, 30–60%, and >60%.

Statistical analysis

The data we obtained from our patients were collected in a Microsoft Excel file, the statistical analysis being performed using the MedCalc program. ARFI measurements were numeric variables, so the mean and standard variation were calculated. For statistical analysis we used the Spearman rank correlation coefficient (r) - for the correlation between LS by means of ARFI and fibrosis depending on the various parameters, and the t test - to compare mean ARFI values for different categories of patients. To compare correlations, Fisher's Z test was used. For intra- and interobserver reproducibility we used the inter-rater agreement coefficient (kappa).

Results

Patients

The characteristics of the subjects included in the study are presented in table I.

Table I. Subjects characteristics

Parameter	
Mean age (years)	53.5±15.03
Gender	– women: 203 (43.1%) – men: 268 (56.9%)
Mean body mass index (BMI)(kg/m²)	26.1±4.8
Mean length of LB specimen (cm)	3.26±0.91
Mean number of portal tracts	25.6±11.5
Fibrosis (according to the Metavir score)	– F0: 83 (17.6%) subjects (82 healthy volunteers, considered F0 Metavir and 1 patient with F0 in LB) – F1: 6 (1.3%) – F2: 33 (7%) – F3: 27 (5.7%) – F4: 322 (68.4%) (15 patients with LB and 307 with clinical, ultrasonographic, endoscopic and/or laparoscopic signs of cirrhosis)
Steatosis on LB (according to the Hepburn classification)	– I: 49 patients (59.7%) – II: 15 patients (18.3%) – III: 6 patients (7.3%) – IV: 10 patients (12.2%) – V: 2 patients (2.5%)

In 11 patients we did not obtain10 valid ARFI measurements (2.3%); therefore valid measurements were obtained in 97.7% of evaluated cases.

Correlation with fibrosis

In the study group, there was a direct, strong correlation (r=0.694) between ARFI measurements and the severity of fibrosis (p<0.0001).

In the 82 patients with LB there was a direct, strong correlation (r=0.507) between ARFI measurements and the severity of histological fibrosis (p<0.0001) and also between ARFI measurements and histological activity (r=0.435, p<0.0001). We did not find a correlation between ARFI measurements and steatosis (r=0.03, p=0.72).

In patients with chronic HCV hepatitis the correlation of ARFI measurements with the histological fibrosis (r=0.603, p<0.001) was stronger than in the case of patients with chronic HBV hepatitis (r=0.389, p=0.02), but not statistically significant so (z=1.876, p=0.06).

IQR and SR

In 45 (9.7%) of 460 patients with valid ARFI measurements, the technical parameters were unsatisfactory (SR<60% and/or IQR≥30%), thus, finally only in 90% of the evaluated cases, good quality technical parameters were obtained.

In patients in whom the quality parameters for ARFI measurements were fulfilled (IQR<30% and SR≥60% - 415 patients), there was a very strong correlation with fibrosis (r=0.722, p<0.0001), while in patients with unsatisfactory technical parameters (SR<60% and/or IQR≥30%) there was no statistically significant correlation between LS measurements by means of ARFI and the histological fibrosis (r=0.268, p=0.07)(p=0.0001).

The mean BMI in patients with good technical parameters of ARFI measurements (IQR<30% and SR≥60%) was statistically significant lower than in patients with IQR≥30% and/or SR<60% (25.6±4.63 kg/m² vs. 30.5±4.65 kg/m², p<0.001), which means that obesity, as in transient elastography is a parameter with a negative influence of ARFI evaluation.

Place of ARFI measurements

In 83 patients (22 healthy volunteers considered F0 Metavir, 3 patients with F1 in LB, 7 patients with F2 in LB, 2 patients with F3 in LB and 49 patients with cirrhosis: 2 on LB and 47 with clinical, ultrasonographic, endoscopic and/or laparoscopic signs of cirrhosis) we performed ARFI comparative measurements in segments V and VIII of the liver.

There were no statistically significant differences between the mean LS values obtained in segments V vs. VIII (2.06±0.1 vs.2.08±0.98 m/s, p=0.89). Also the correlations between ARFI measurements and fibrosis was

similar in segments V vs. VIII (r=0.836, p<0.0001 vs. r=0.784, p<0.0001) (z=0.961, p=0.33).

Liver biopsy specimen quality

In our study, all LB specimens were longer than 2 cm. We divided the LB specimens into: shorter than 3cm (2-3 cm - 37 patients) and longer than 3 cm (45 patients).

In all the patients from the study group with LB (50 with chronic HCV hepatitis and 32 with chronic HBV hepatitis), we found no statistically significant differences between the correlations of ARFI measurements with the histological fibrosis according to the length of the liver specimen: longer than 3 cm, as compared to those in which the liver specimen was 2-3 cm long (r=0.456, p=0.01 vs. r=0.480, p=0.00; z=-0.133, p=0.89).

Considering the etiology, in patients with chronic HCV chronic hepatitis the correlation of ARFI measurements with the histological fibrosis was also similar in patients in which the LB specimen was longer than 3 cm (26 patients, r=0.582, p=0.002) as compared to those in which the liver specimen was 2-3 cm long (24 patients, r=0.564, p=0.002) (z=0.088, p=0.92).

Liver steatosis

In our patients with LB, ARFI values were not correlated with steatosis (r=0.03, p=0.72). ARFI measurements were correlated with histological fibrosis in patients with no or mild steatosis (Hepburn I, II and III on LB) (r=0.535 p<0.0001), while in patients with moderate and severe steatosis (Hepburn IV and V) there was no correlation (r=0.223, p=0.48) (table II).

ARFI reproducibility

We studied the interobserver reproducibility of ARFI in 45 patients and in 23 patients the intraobserver reproducibility.

Regarding the intraobserver reproducibility of ARFI, repeated measurements were strongly correlated (Spearman coefficient r=0.890, confidence interval – CI: 0.592 to 0.915, p<0.0001) and the inter-rater agreement coefficient k was 0.567 (CI: 0.394 to 0.740).

Regarding the interobserver reproducibility, repeated measurements were also statistically significant correlated (r=0.622, CI: 0.402 to 0.774, p<0.0001), with an inter-rater agreement coefficient k=0.445 (CI: 0.291 to 0.600).

In our study the correlation between repeated intraobserver ARFI measurements and fibrosis was statistically significant stronger than that of interobserver ARFI measurements and fibrosis: r=890 vs. r=0.622 (z=2.553, p=0.01).

Table II. Influence of liver steatosis (according to the Hepburn classification) on the correlation of ARFI measurements with the histological fibrosis.

Steatosis	Number of patients	Patients with IQR≥30% and/or SR<60%	Spearman r correlation coefficient between ARFI and fibrosis
Hepburn I+II+III (<30%)	70	7 (10%)	r=0.535, p<0.0001
Hepburn IV+V (≥30%)	12	4 (33.3%)	r=0.223, p=0.48

Discussions

Considering the fact that fibrosis is heterogeneously distributed into the liver, LB has been criticized in the past, because it evaluates only 1/50,000 of the total volume of the liver, due to the small volume of the tissue sample [11].

By means of percutaneous LB, tissue samples 1-4 cm in length are obtained (preferably at least 1.5 cm), whatever the kind of needle used [12]. Also, it was demonstrated that the smaller the liver sample is, the higher is the chance to sub evaluate the severity of the liver disease [12,13]. Using a mathematical model, the team of Bedossa [14] estimated that the chance of misdiagnosis in a fragment 2.5 cm in length, can reach 25% and that the optimal size of a LB sample is 4 cm (difficult enough to obtain in daily practice).

In the latter years non-invasive methods for liver fibrosis assessment in chronic HCV hepatitis were developed, such as the serological test (most notably FibroTest-ActiTest)[15-16] or elastographic methods: Transient Elastography [17-19], real time-elastography [20-21], Acoustic Radiation Force Impulse Elastography [1-5]. Transient Elastography is a recognised method for the evaluation of liver stiffness, the RT-E and ARFI are still being evaluated for use in clinical practice.

In TE, according to the manufacturer's recommendations, reliable measurements are considered only those with an IQR<30% and a SR≥60%, while for ARFI elastography such recommendations were not made.

In our present paper we studied the influence of quality technical parameters (IQR and SR) on the correlation of LS measurements by means of ARFI and histological liver fibrosis (according to the Metavir scoring system). We found out that in patients in whom the quality parameters for ARFI measurements were fulfilled (IQR<30% and SR≥60%) there was a strong correlation with fibrosis (r=0.722, p<0.0001), while measurements with unsatisfactory technical parameters did not correlate to the histological fibrosis (r=0.268, p=0.07). Our data show

that the introduction of quality technical parameters (IQR<30% and SR≥60%) for ARFI Elastography, similar to TE, would be beneficial for improving the correlation of ARFI measurements with the histological fibrosis.

Also we found out that higher BMI is associated with a higher chance of obtaining measurements with unsatisfactory technical parameters similar to TE, in which the failure measurements rate increases with the BMI [22,23].

Regarding the place of ARFI measurements, the manufacturer of the device did not make any recommendation. In a previous study published by our group [3] we demonstrated a significant, direct correlation between ARFI elastography (mean value of 5 measurements made 1-2 cm and 2-3 cm under the liver capsule, respectively) and the severity of liver fibrosis (Spearman r=0.675 and r=0.714 respectively), while the subcapsular measured values of LS showed a poorer correlation with fibrosis (rho=0.429).

In a study that evaluated 57 patients by means of by ARFI, Goertz et al [4] showed that the best ARFI assessments, with the lowest rate of invalid measurements, were carried out by an intercostal approach to segments VII/VIII of the liver.

In a study by Boursier et al [24], ARFI measurements were performed in the two liver lobes by two operators: an expert and a novice. Intersite ARFI agreement between the two liver lobes was fair (intra-class correlation coefficient=0.60). In our study, in the 83 patients where we performed ARFI measurement in segments V and VIII, we did not found statistically significant differences between the mean LS values obtained in the 2 liver lobes (2.06±0.1 vs.2.08±0.98 m/s, p=0.89). Also, the correlation between ARFI and fibrosis was similar in segments V vs. VIII (r=0.836 vs. r=0.784) (p=0.33). Our data show that we can perform ARFI measurements in either segment V or VIII, depending on the ultrasound window of the patient. Probably, we can use in place of ARFI evaluation, the intercostal space where we usually perform percutaneous ultraguided liver biopsy.

Regarding the influence of steatosis on the LS measurements by means of ARFI, Guzman Aroca et al [25] used this method for quantification of liver steatosis in chickens. They used 2 different diets: a standard diet (SD group) and a hyperlipidemic diet (HD group). The lowest ARFI values (≤1.3 m/s) corresponded to the chickens in the SD group, whereas ARFI values in the HD group chickens ranged between 1.6 and 2.2 m/s. A substantial correlation was observed between ARFI values with the histological semi quantitative analysis of steatosis (r=0.85, p<0.001).

In the study of Lupşor et al [2], 112 patients with chronic hepatitis C were evaluated. All patients underwent LB (fibrosis stage assessed according to the Metavir scoring system), ARFI and TE evaluation. In this study, ARFI was correlated with liver fibrosis (r=0.717, p<0.0001) and necroinflammatory activity (r=0.328, p=0.014), but not with steatosis (r=0.122, p=0.321).

In a recent paper published by Iijima et al [26], 293 patients with chronic hepatopathies were evaluated by ARFI and LB: 42 hepatitis B, 156 hepatitis C, 6 hepatitis B+C, 49 hepatitis non-B non-C. In this study a decrease in the ARFI values with an increase in fatty degeneration was observed and also an increase of ARFI values in cases of hepatitis with severe inflammation.

In our patients with LB, ARFI values were not correlated with steatosis (r=0.03, p=0.72). ARFI measurements were correlated with histological fibrosis in patients with no or mild steatosis (Hepburn I, II and III on LB) (r=0.535 p<0.0001), while in patients with moderate and severe steatosis (Hepburn IV and V) there was no correlation (r=0.223, p=0.48). In the group of patients with moderate and severe steatosis we had also a higher number of patients with IQR≥30% and/or SR<60% vs. the patients with mild or absent steatosis: 33.3% vs. 10%. Probably this is one of the explanations of the poor correlation of ARFI values with liver fibrosis in this group of patients.

We also studied the influence of the quality of liver specimens obtained by LB on the correlation of ARFI measurements to liver fibrosis. In our study, all specimens obtained by LB were longer than 2 cm and included more than 11 portal tracts. In these conditions, we did not find statistically significant differences between the correlations of ARFI measurements with liver fibrosis in cases in which the liver specimen was 2-3 cm long vs. in patients in which the LB specimen was longer than 3 cm (r=0.480 vs. r=0.456, p=0.89). The same results were obtained when only the cases with chronic HCV hepatitis were considered: r=0.564 vs. 0.682, p=0.92. Probably the quality of the liver specimen obtained in LB did not influence the correlation of ARFI and fibrosis, since all the specimens were very good (longer than 2 cm) and probably future studies must look for the inferior limit of the liver specimen, which is good enough for liver fibrosis evaluation.

Conclusion

Our data suggest that the place of ARFI measurement in the right hepatic lobe (segment V or VIII) do not influence the values of LS measured by ARFI. To obtain the best correlation between ARFI and histological fibrosis, IQR must be <30% and SR≥60%. These technical pa-

rameters must be introduced in clinical practice to improve the ARFI value for liver stiffness evaluation.

Conflict of interest: none

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