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Acoustic Radiation Force Impulse (ARFI) – a new modality for the evaluation of liver fibrosis

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Abstract

Aim: to assess the accuracy of transient elastography (TE) and Acoustic Radiation Force Impulse (ARFI) for liver fibrosis assessment, as compared to percutaneous liver biopsy (LB) in patients with chronic hepatitis. **Patients and methods:** Our study included 71 patients (P) (54 with HCV and 17 with HBV chronic hepatitis) in which we compared TE and ARFI to the LB (evaluated according to the Metavir scoring system). **Results:** On LB, from the 71P, 6P (8.4%) had F1, 25P (35.2%) had F2, 24P (33.8%) had F3 and 16P (22.5%) had F4. A direct, strong, linear correlation (Spearman r=0.707) was found between TE measurements and fibrosis (p<0.0001) and a weaker one, between ARFI and fibrosis (rho=0.469; p<0.0001). TE measurements were also correlated with ARFI measurements r=0.532, p<0.0001. By comparing the AUROC curves, TE and ARFI had similar predictive values for the presence of significant fibrosis (F≥2 Metavir): AUROC ARFI=0.649, AUROC TE=0.731 (p=0.476); and cirrhosis (F=4 Metavir): AUROC ARFI=0.868, AUROC TE= 0.936 (p=0.294)**Conclusion:** LS measurements assessed by means of TE correlate better than those assessed by means of ARFI to the histological fibrosis in patients with HBV and HCV chronic hepatitis. Both methods have excellent predictive values for the presence of cirrhosis.

Keywords: Liver stiffness, Transient Elastography, ARFI (Acoustic Radiation Force Impulse)

Rezumat

Scop: să evaluăm acurateţea elastografiei impulsionale (TE) şi a metodei Acoustic Radiation Force Impulse (ARFI) pentru aprecierea fibrozei hepatice comparativ cu biopsia hepatică percutană (LB) la pacienţi cu hepatopatii cronice. **Pacienţi şi metode:** studiul nostru a cuprins 71 pacienţi (P) (54 cu hepatopatii cronice HCV şi 17 cu HBV) la care am comparat TE şi ARFI cu LB (evaluată prin scorul Metavir). **Rezultate:** în cazul LB, dintre cei 71P, 6P (8.4%) au avut F1, 25P (35.2%) au avut F2, 24P (33.8%) au avut F3 şi 16P (22.5%) au avut F4. O corelaţie directă lineară puternică (Spearman r=0.707) a fost găsită între valorile TE şi fibroză (p<0.0001) şi o corelaţie mai slabă între ARFI şi fibroză (rho=0.469; p<0.0001). Valorile TE s-au corelat de asemenea cu valorile ARFI r=0.532, p<0.0001. Prin compararea curbelor AUROC, TE şi ARFI au avut valori predictive similare pentru prezenţa fibrozei semnificative (F≥2 Metavir): AUROC ARFI=0.649, AUROC TE=0.731 (p=0.476); şi pentru prezenţa cirozei (F=4 Metavir): AUROC ARFI=0.868, AUROC TE= 0.936 (p=0.294) **Concluzii:** elasticitatea hepatică determinată prin TE se corelează mai bine cu fibroza histologică la pacienţii cu hepatopatii cronice HCV şi HBV, comparativ cu valorile obţinute prin ARFI. Ambele metode au valori predicitive excelente pentru prezenţa cirozei.

Cuvinte cheie: Duritatea hepatică, elastografia impulsională, ARFI (Acoustic Radiation Force Impulse)

Introduction

The prognosis of chronic hepatopathies is based on the severity of fibrosis. Thus the evaluation of liver fibrosis is essential in these patients. In Romania and worldwide, the number of patients with chronic liver diseases is increasing, due to viral hepatitis, as well as due to alcoholic and non alcoholic steatohepatitis (ASH and NASH).

Liver biopsy (LB) is still considered the „gold standard" for hepatological evaluation [1], but in the latter years the recently developed ***non-invasive methods*** have attempted to replace this invasive procedure. The reason for this is that LB is usually a stressful medical procedure

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for many patients and often not enough histological material is obtained. On the other hand, the advantages of noninvasive ultrasound based methods for the evaluation of liver stiffness (LS) are: they are well tolerated by the patients, a quick answer concerning the severity of the disease is available in a few minutes, sometimes the software used is integrated in ultrasound machines existing in the hospital (RT-E Hitachi and ARFI Siemens), so that the price of the evaluation is not very high.

Ultrasound waves play an important role in the development of non-invasive methods for the evaluation of fibrosis. Starting with transient elastography (TE) and finishing with ShearWave Elastography, the newest technique for the evaluation of fibrosis, all these methods have tried to replace the LB, or at least to reduce the number of LB's performed in the world.

Today there are several non-invasive methods for the evaluation of liver fibrosis using ultrasound waves such as: TE (FibroScan) [2,3,4]; SonoElastography (Real-Time Tissue Elastography) (Hi RT-E) [5-9], Acoustic Radiation Force Impulse (ARFI) (on Siemens Acuson S2000) [10-13] and ShearWave Elastography (on the Aixplorer® system).

The aim of our study was to assess the accuracy of two elastographic methods, transient elastography (TE) and ARFI, for liver fibrosis assessment, as compared to percutaneous liver biopsy (LB) in patients with chronic hepatitis.

Patients and Methods

Our study comprised 71 patients, 54 with HCV and 17 with HBV chronic hepatitis in which we compared TE and ARFI to the liver biopsy (LB) (evaluated according to the Metavir scoring system, considered to be the „gold standard")

In each patient we performed LS measurement by means of TE (FibroScan®, EchoSens) and ARFI (by using a Siemens Acuson S2000™ ultrasound system) and liver biopsy in the same session.

Transient Elastography

TE was performed in all patients with a FibroScan® device (Echosens® – Paris, France) by experienced physicians (more than 1000 examinations) (fig 1). In each patient, 10 valid measurements were performed, after which a median value of the LS was obtained, measured in kPa. Only patients in which 10 LS measurements were obtained with a success rate of at least 60%, with an IQR<30%, were included in our study.

ARFI (Acoustic Radiation Force Impulse)

ARFI was performed in all the patients with a Siemens Acuson S2000™ ultrasound system. The probe automatically generates a pressure wave that propagates into the liver. Its speed, measured in m/s, is displayed on the screen. The propagation speed increases with fibrosis. The operator selects the depth at which the liver elasticity is evaluated, by placing a „measuring box" (10 mm long and 5 mm wide) in the desired place (fig 2). The patients were examined in a supine position with the right arm in maximum abduction. Scanning was performed between the ribs in the right liver lobe (for instance in the 8th segment) (in order to avoid cardiac motion), with minimal scanning pressure applied by the operator, while the patients were asked to stop breathing for a moment, in order to minimize the breathing motion. The „measuring box" was placed 1 cm below the surface of the liver.

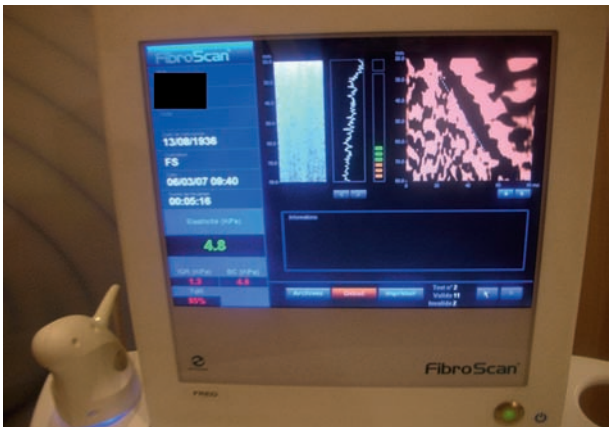

Fig 1. TE measurement in a normal patient (value 4.8 kPa).

We performed 10 valid measurements in every patient, and a median value was calculated, the result being measured in m/s.

Liver Biopsy

LB was performed in all 71 patients echoassisted, by using Menghini type modified needles, 1.4 and 1.6 mm

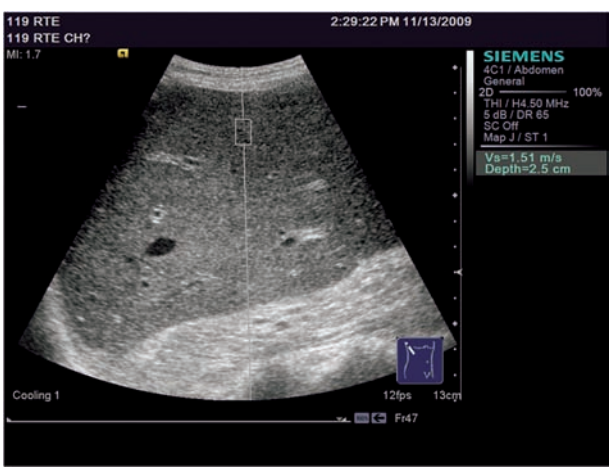

Fig 2. ARFI measurement (placement of the „measuring box").

in diameter. Only LB fragments at least 2 cm in size were considered adequate for pathological interpretation. 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**.**

Statistical Analysis

The data we obtained from our patients were collected in a Microsoft Excel file, the statistical analysis being performed using GraphPad Prism and MedCalc programs. All the predictors for the stage of fibrosis (TE and RT-E measurements) were numeric variables, so the mean and standard deviation were calculated.

Associations between assay results and fibrosis stage according to the Metavir scoring system (range: 0–4, ordinal scale) were described using the Spearman rank correlation coefficient (rho).

The diagnostic performances of the non-invasive tests were assessed by using receiver operating characteristics (ROC) curves. ROC curves were thus built for the detection of significant fibrosis (F≥2 Metavir) and cirrhosis. Optimal cut-off values were chosen to maximize the sum of Se and Sp. Sensitivities and specificities were calculated according to standard methods. Exact CIs of 95% were calculated for each predictive test and used for comparing AUROC curves.

Results

a) Patients

Our study comprised 71 patients (30 women, 41 men, mean age 50.7±12.9 years): 54 subjects (76%) with HCV chronic hepatitis and 17 patients (24%) with HBV chronic hepatitis.

b) Liver biopsy evaluation

From the 71 patients, 6 (8.4%) had mild fibrosis (F1), 25 (35.2%) had significant fibrosis (F2), 24 (33.8%) had severe fibrosis (F3), and 16 (22.5%) had cirrhosis (F4), according to the Metavir scoring system.

c) *Stiffness measurements*

The LS measurements ranged from 3.5 to 73.5 kPa. ARFI measurements ranged from 0.90 to 3.59 m/s. In two (2.8%) patients, we were not able to obtain valid measurements by ARFI.

A direct, strong, linear correlation (Spearman r=0.707) was found between TE measurements and fibrosis ($p<0.0001$) and a weaker one between ARFI and fibrosis (rho=0.469; $p<0.0001$). TE measurements were also correlated with ARFI measurements r=0.532, $p<0.0001$.

Table I. Mean value of liver elasticity assessed by means of TE and ARFI.

FIBROSIS	Nr. of cases	ARFI (m/s)	Nr. of cases	TE (kPa)
0	-	-	-	-
1	6	1.70±1.14	6	6.43±1.7
2	25	1.56±0.64	24	6.54±2.28
3	24	1.78±0.77	23	9.26±2.6
4	16	2.70±0.52	16	23.79±15.79

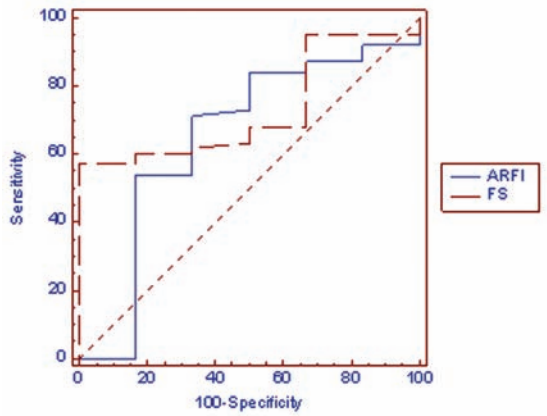

Fig 3. Comparative predictive values of LS measurements by means of TE and ARFI for the prediction of significant fibrosis (F≥2 Metavir).

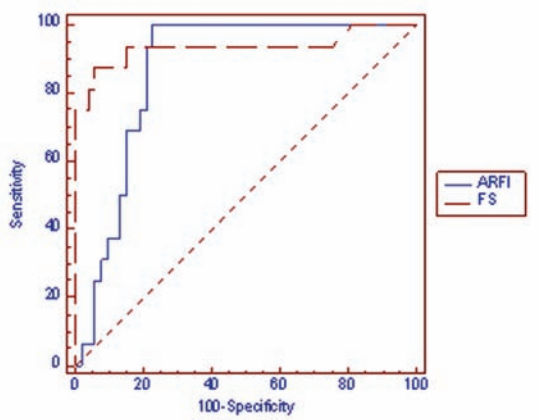

Fig 4. Comparative predictive values of LS measurements by means of TE and ARFI for the prediction of cirrhosis (F=4 Metavir).

The mean values of liver elasticity assessed by means of TE and ARFI are presented in table I.

By comparing the AUROC curves, TE and ARFI had similar predictive values for the presence of significant fibrosis (F≥2 Metavir): AUROC ARFI=0.649, AUROC TE=0.731 ($p=0.476$) (fig 3, table II)

Table II. Comparative predictive values of LS measurements by means of TE and ARFI for the prediction of significant fibrosis (F≥2 Metavir)

Test Result Variable(s)	Cut-off	Sensitivity	Specificity	Area	Std. Error	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
ARFI	1.33 m/s	71%	66%	0.649	0.107	0.525	0.760
TE	7.6 kPa	60%	83%	0.731	0.0919	0.611	0.831

Also, both methods had similar performance in predicting cirrhosis (F=4 Metavir): AUROC ARFI=0.868, AUROC TE= 0.936 (p=0.294) (table III; fig 4)

Discussions

Transient elastography (FibroScan) and Acoustic Radiation Force Impulse (ARFI) (on Siemens Acuson S2000) are non-invasive methods for the evaluation of liver fibrosis using ultrasound waves.

Transient elastography (FibroScan). By using an ultrasound transducer probe mounted on the axis of a vibrator, the transmission of low-frequency vibrations from the right intercostal space creates an elastic shear wave that propagates into the liver. A pulse-echo ultrasound acquisition is then used to detect the velocity of wave propagation. This velocity is proportional to the tissue stiffness, with faster wave progression occurring through stiffer material. Measurement of liver stiffness is then performed and the result is measured in kilopascals (kPa) [3].

TE assessment of LS was validated as a method of evaluation in chronic hepatitis C. There are also some articles that have proved the value of this method in other chronic hepatopathies (such as HBV chronic infection, haemochromatosis, primary biliary cirrhosis or non-alcoholic steato-hepatitis) [14-19].

Two meta-analyses [3,15] showed that this method is very good for the diagnosis of cirrhosis and advanced fibrosis.

We used this method in our department for two and half years and we made more than 5000 TE evaluations. Now we use this method especially in patients in whom we have the clinical suspicion of liver cirrhosis, but also in patients with chronic hepatitis in order to estimate the severity of the disease [14]. Our study, like other international studies demonstrated that this method is a good tool for the evaluation of viral chronic B and C hepatopathies [3,14,15].

At the same time, we can obtain valid measurements by means of TE in approximately. 94-95% of the patients [20], but is it enough if we consider that the LSMs are reliable only if the success rate is at least 60%, and the IQR<30%, valid and correct evaluation is obtained only in 84% of patients [21] Probably not, and maybe a real time elastography evaluation of the LS is necessary.

Real Time Elastography is a method that evaluates tissue elasticity, integrated in an ultrasound machine and is technically different from TE [8]. The Hitachi system (EUB-8500 and EUB-900), the first one that appeared on the market, uses a conventional ultrasound probe, echo signals before and under slight compression being compared and analyzed [22].

Elastography from Siemens uses a different technology. Virtual Touch™ tissue imaging application implements **Acoustic Radiation Force Impulse (ARFI) technology** for the evaluation of deep tissues, not accessible to superficial compression elastography techniques. Using image-based localization and a proprietary implementation of Acoustic Radiation Force Impulse (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, the results of the elasticity are in m/s.

ARFI imaging involves targeting an anatomic region to be interrogated for elastic properties using a region of-interest cursor, while performing real-time B-mode imaging. Tissue in the region of interest is mechanically excited by using short-duration (262 μsec) acoustic pulses with a fixed transmit frequency of 2.67 MHz to generate localized tissue displacements. The displacements result in shear-wave propagation away from the region of excitation tracked by using US correlation-based methods. The shear-wave propagation velocity is proportional to the square root of tissue elasticity.

Thus, the advantage of ARFI technology is the fact that measurements can be performed with software integrated into a conventional ultrasound machine. Thus the elastography examination can follow in the same session with the same machine the screening ultrasound examination. This is different for TE in which only elastography can be performed (FibroScan is a machine costing approximately 80,000 Euros).

So, if these non-invasive methods are desirable, how good are they?

Studies that compare LB to the non-invasive methods of evaluation in chronic liver disease are made in order

to assess if they are fit to replace this invasive method in the future [23].

In our study, the optimized cut-off values of LS for liver cirrhosis (F=4 Metavir), 13.2 kPa for TE (AUROC=0.936, with 81% Se, 96% Sp, 85% PPV and 93% NPV) and 1.8m/s for ARFI (AUROC=0.868, with 100% Se, 77% Sp, 58% PPV and 100% NPV).

For predicting significant fibrosis (F≥2 Metavir), TE with a cut-off 7.6 kPa was slightly better (AUROC 0.731 with 60% Se, 83% Sp, 97% PPV and 16% NPV) than ARFI (cut-off 1.27m/s (AUROC 0.649, with 71% Se, 66% Sp, 95% PPV and 18% NPV).

In a study performed by Friedrich-Rust [10], in which ARFI was compared to LB and blood markers in 86 patients with chronic hepatitis (B or C), the Spearman correlation coefficients between the histological fibrosis stage and ARFI, TE, FibroTest and APRI scores, indicated significant correlations: 0.71, 0.73, 0.66 and 0.45 respectively ($p<0.001$).

In another study performed by Lupsor and co-workers [13], 112 consecutive patients with chronic hepatitis C were evaluated through histology (Metavir score), ARFI and TE. 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 this study there was a significant increase of ARFI values in parallel with the increase in fibrosis stage: 1.079±0.150 m/s (F0-F1), 1.504±0.895 m/s (F2), 1.520±0.575 m/s (F3), 2.552±0.782 m/s (F4) ($p<0.0001$), but there was a certain degree of overlap between the consecutive stages F1-F2 ($p=0.072$) and F2-F3 ($p=0.965$). In this study the cut-off values (m/s) predictive for each fibrosis stage were: 1.19 (F≥1), 1.34 (F≥2), 1.61 (F≥3) and 2.00 (F4). Concerning the comparison between ARFI and TE, this study found that the AUROCs were: 0.709 vs. 0.902, $p=0.006$ (F≥1), 0.851 vs. 0.941, $p=0.022$ (F≥2), 0.869 vs. 0.926, $p=0.153$ (F≥3) and 0.911 vs. 0.945, $p=0.331$ (F4).

These two studies [10,13], together with the study that we presented in this paper showed that ARFI measurements are statistically significantly correlated to histological fibrosis. In addition the best performances of this method are in the prediction of severe fibrosis and cirrhosis and therefore ARFI is not better than TE for the evaluation of liver stiffness.

Anyway, the use of ARFI measurements could be an advantage, being a „real-time" evaluation of liver stiffness; it can also be used in patients in which valid measurements of LS by TE could not be obtained, for instance in patients with ascites, due to the fact that the place of ARFI measurement can be chosen under direct US guidance. Also, ARFI is a rapid method of assessment of liver fibrosis, totally free of adverse events, comfortable for the patient and for the examiner (with a duration of approximately 5 minutes), and especially with the advantage that this method for the evaluation of liver fibrosis is integrated in an ultrasound machine (existing in some ultrasound laboratories). So, immediately after an ultrasound evaluation of the liver, we can perform ARFI measurements and obtain information concerning the severity of liver fibrosis, without having to acquire another device like the FibroScan.

The new prototype machine of ultrasound performing elastography (ShearWave Elastography on the Aixplorer® system), can maybe overpass some inconveniences of the previous machines (a patented technological breakthrough where the ultrasound beam formation no longer requires dedicated hardware, except for the transducer, but is all done in software). Aixplorer® uses the SonicTouch™ technique, which pushes the tissue at increasing focused depths at supersonic speed (permitting a deep evaluation of the liver). This generates a shear wave in tissue and the velocity of the tissue is translated into a color-coded map of tissue elasticity, in real-time and in kilopascals, at the same time. So, this machine can be a synthesis between all the devices that use ultrasound waves for liver stiffness measurement.

Conclusion

Our study demonstrates that, at the present time, liver elasticity evaluation by means of ARFI is not superior to Transient Elastography (FibroScan) for the assessment of liver fibrosis. We found out that there is a statistically significant correlation between histological fibrosis and ARFI measurements, and that the best performances of this method are in the prediction of severe fibrosis and cirrhosis. The big advantage of ARFI is probably the fact that this system is integrated in an ultrasound machine that exists already in some ultrasound departments.

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