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The mean values of liver stiffness assessed by Acoustic Radiation Force Impulse elastography in normal subjects

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Abstract

The aim of this paper is to establish the values of liver stiffness (LS) assessed by means of ARFI in patients without known liver pathology and considered healthy subjects. **Material and method:** the study group was composed of 82 subjects without known liver pathology, healthy volunteers or patients from other departments of our hospital who did not have altered liver laboratory tests. 76 patients had ARFI valid measurements (47 women and 29 men, mean age 34.5±14.3 years). In each subject abdominal ultrasound was performed (patients with steatosis or any other signs of chronic liver pathology were excluded) as well as ARFI (using Siemens Acuson S2000TM). The median value of 10 measurements was calculated, expressed in m/s; we considered valid only the measurements with IQR<30%, SR>60%, similar to transient elastography. Mean ARFI values and mean values according to age and gender were evaluated. **Results:** valid ARFI measurements were obtained in 76/82 patients (92.6%). The mean value of ARFI measurements in normal individuals was 1.15±0.21 m/s. There were no significant differences between the mean ARFI values in men vs. women (1.16±0.21 vs. 1.14±0.22m/s, p=0.67), also among different age groups (p>0.05). **Conclusion:** In our study the mean LS value obtained by ARFI in healthy subjects was 1.15 m/s.

Keyword: ARFI, liver stiffness, elastography

Rezumat

Scopul acestui studiu este de a stabili valorile durității hepatice determinate prin elastografia ARFI la subiecți necunoscuți cu patologie hepatică, considerați subiecți sănătoşi. **Material şi metodă:** am luat în studiu 82 de subiecți fără patologie hepatică cunoscută, voluntari sănătoşi sau pacienți din alte secții ale spitalului care nu au prezentat teste hepatice modificate. Am obținut masurători ARFI valide la 76 pacienți (47 femei şi 29 bărbați, vârsta medie 34,5±14,3 ani). Am efectuat la fiecare subiect ecografie abdominală (am exclus pacienții cu steatoză hepatică sau orice alt semn de hepatopatie cronică), precum şi ARFI (utilizând aparatul Siemens Acuson S2000TM). Am calculat mediana celor 10 măsurători, exprimată în m/s; am considerat măsurători valide doar cele cu IQR<30%, SR>60%, similar cu elastografia impulsională. Am evaluat valorile medii ale ARFI şi am comparat valorile obținute în funcție de sex şi vârstă. **Rezultate:** La 76/82 subiecți (92,6%) am obținut măsurători valide ale ARFI. Valoarea medie a masurătorilor ARFI la subiecți normali a fost 1,15±0,21 m/s. Nu am găsit diferențe semnificative între valorile ARFI la bărbați vs femei (1,16±0,21 vs. 1,14±0,22m/s, p=0,67), şi la diferitele grupe de vârstă (p>0,05). **Concluzie:** în studiul nostru valorile medii ale durității hepatice obținute prin metoda ARFI la subiecți sănătoşi a fost 1,15 m/s.

Cuvinte cheie: ARFI, duritate hepatică, elastografie

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Introduction

Liver fibrosis is a key element for the therapeutic decision and for the prognosis of patients with chronic diffuse liver diseases. Thus, a correct assessment of fibrosis severity is required, in order to perform a correct staging of the disease. Liver biopsy is still considered the "gold standard" method for the evaluation in chronic diffuse liver diseases, but it has its drawbacks [1]. The specimen

obtained by liver biopsy represents roughly 1/50,000 of the liver and it is a known fact that fibrosis is unevenly distributed through the liver [2]. On the other hand, several studies have proven that there is intra- and inter-observer variability in the grading and staging by liver biopsy [3, 4] and also that there is a large sampling variability [5]. But probably the major disadvantage of liver biopsy is its invasiveness: there is a risk of postbiopsy discomfort for the patients and, sometimes, for serious complications [6-9]. This is why, noninvasive methods for the evaluation of liver fibrosis have been developed in the last few years, in order to replace liver biopsy.

In this new set of diagnostic tools, the elastographic methods: Transient Elastography (TE) (FibroScan) [10, 11], Real-Time Tissue Elastography (HiRT-E) [12-16], Acoustic Radiation Force Impulse (ARFI) (Siemens) [17-20] and MRI elastography [21,22] have begun to play a more and more important role, in the assessing the severity of liver fibrosis. Some of these techniques are already well established, while others still have to prove their usefulness.

Acoustic Radiation Force Impulse Elastography (ARFI) is a new method used for assessment of liver fibrosis, thyroid gland nodules, breast nodules, liver and kidney tumors, for the characterization of atherosclerotic plaques, as well as for the monitoring the results of radiofrequency ablation [12,14,17,20,23-27]. In this method, demonstrated in vivo as clinical feasible in 2002 [27], focused ultrasound is used to apply localized radiation force to small volumes of tissue (2 mm^3), for short durations (less than 1 ms) and the resulting tissue displacements are mapped, using ultrasonic correlation-based methods. The tissue displacements are inversely proportional to the stiffness of the tissue and, thus, a stiffer region of tissue exhibits smaller displacements, rather than a more compliant region. The acoustic pulse is applied in a region of interest, chosen by the examiner, producing shear waves that spread away from the region of interest, perpendicularly to the acoustic push pulse. The moment of interaction between the shear waves and detection waves marks the period of time elapsed between the generating of shear waves and their entire crossing of the region of interest. By recording the shear wave front at several locations and correlating these measurements with the elapsed time, the shear wave velocity – SWV (m/s) can be quantified; generally, the stiffer a region in the tissue, the greater the SWV as it travels through this region. Thus, the measured SWV is an intrinsecal and reproducible property of the tissue [27,28,29]. The technique is integrated in an ultrasound system, Siemens Acuson S2000 and thus has the advantage that the region of interest can be chosen by the operator for ultrasound guidance and also that the procedure can be performed during a routine ultrasound examination.

Several studies have evaluated the clinical usefulness of this method in different fields, including assessment of diffuse liver pathology [17-20,23-26,30-38]. But for a correct clinical application of the method in liver diseases, the normal range of liver stiffness measurements must be established, in order to differentiate the normal liver from the fibrotic liver.

The aim of this paper is to establish the values of liver stiffness (LS) assessed ARFI in patients without known liver pathology and considered healthy subjects.

Material and methods

The study group was composed of 82 subjects without known liver pathology, healthy volunteers or patients from other departments of our hospital, who did not have altered liver tests or history of liver disease and had a normal liver ultrasound aspect. The subjects with enlarged spleen at ultrasound were also excluded. The study was approved by the Local Ethics Committee and patients' informed consent was obtained for the investigations.

In each patient liver stiffness (LS) was measured by means of ARFI in the right liver lobe, 1 cm below the liver capsule, by intercostal approach, with the patient laying in left lateral decubitus, 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. ARFI measurements were performed with a Siemens Acuson S2000™ ultrasound system, using the Virtual Touch™ Tissue Quantification software. In each patient 10 valid ARFI measurements were performed in liver and the median values were calculated, the results being expressed in meters/second (m/s). Only the measuremtents with IQR (interquartile range interval=difference between the 75^{th} and the 25^{th} percentile, essentially the range of middle 50% of the data) < 30% and SR (success rate= ratio of the number of successful acquisitions over the total number of acquisitions) ≥60% were considered as reliable, similar to Transient Elastography (TE) (FibroScan, EchoSens, Paris, France). Abdominal ultrasound was also performed in each subject in the same session and with the same system (patients with steatosis or any other signs of chronic liver pathology were excluded).

Our data 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.

The t test was used to compare the ARFI values.

Mean ARFI values and mean values according to age and gender were evaluated.

Results

Our study group consisted of 82 subjects without known liver pathology, mean age 35.3±14.8 years, 50 women and 32 men (ARFI values ranged between 0.69 and 2.78 m/s). 76 patients (92.6%) had ARFI valid measurements with IQR<30% and SR≥60% (47 women and 29 men, mean age 34.5±14.3 years). Only in one subject (1.2%), we could not obtain 10 valid measurements, but in 5 (6.2%) IQR and SR criterias were not fulfilled.

The mean LS value determined by ARFI in healthy volunteers with IQR<30% and SR≥60% was 1.15±0.21 m/s. ARFI values ranged between 0.69 and 1.6 m/s.

We did not find significant differences between the mean ARFI values in men vs. women (1.16±0.21 vs. 1.14±0.22m/s, p=0.67) (fig 1), also among different age groups (table I, fig 2).

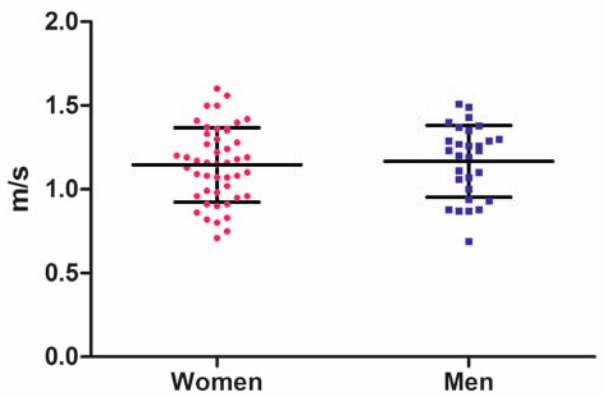

Fig 1. Distribution of ARFI values in healthy volunteers according to the gender groups

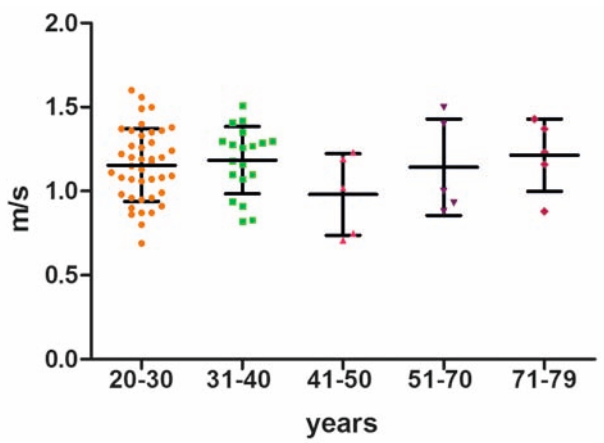

Fig 2. Distribution of ARFI values in healthy volunteers according to the age groups

Table I. Mean values of LS determined by ARFI according to the age groups

Age group (years)	Number of patients	Mean values of LS (m/s)
20-30	42	1.15±0.21
31-40	19	1.18±0.20
41-50	5	0.98±0.24
51-70	5	1.14±0.28
71-79	5	1.21±0.21

From our group, 14 subjects (18.4%) had ARFI higher than the mean value of 1.15±0.21m/s.

In the subgroup of 5 patients with 10 valid ARFI measurements, but with IQR≥30% and/or SR<60%, 4 patients (80%) had ARFI values above the mean value of 1.15 m/s. The values for these 5 patients were 1.68, 2.78, 1.64, 0.92 and 1.54 m/s. If we also included these patients in the statistical data , the mean value of the liver stiffness for healthy subjects was 1.18±0.29 m/s but the decision was taken to exclude these patients because IQR and SR criterias were not fulfilled.

Discussions

Even if several studies have evaluated the place of ARFI in the assessment of liver fibrosis in chronic diffuse liver diseases [17-20,23-26,30-32,34-36,38], there are few published data regarding the normal range of LS in healthy subjects [33,37].

A recent study published by Horster *et al* [33] showed that mean ARFI SWV, in a group of 68 healthy volunteers, with a mean age of 28 years old was 1.19 m/s (range 0.77-1.63), very similar to our results. On the other hand, the authors showed, similar to us, that age and gender did not influence ARFI SWV. The authors performed measurements with two different ultrasound tranducers in three measuring positions and during valsalva manoeuvre. There was no significant difference of ARFI SWS between the 4C1 and 4V1 ultrasound probes in either intercostal or abdominal approach to liver segment 8, but the intercostal approach had the highest success rates (97.2%). The authors also demonstrated that left liver lobe measurements obtained both significantly higher ARFI SWS and value variance (p = 0.0016 and p = 0.0198) as compared to the intercostal approach in right liver lobe. Valsalva manoeuvre did not significantly alter ARFI SWS and variance while skin-liver distance significantly influenced ARFI SWS (p<0.05).

In a prevoius study performed by our group, we also

showed that the best correlation with fibrosis (obtained by liver biopsy), was obtained for measurements made at 1-2 cm (Spearman rho = 0.675, success rate 95.5%) and 2-3 cm (Spearman rho = 0.714, success rate 85.6%) below the capsule, so we concluded that probably the best place for ARFI determinations should be 1-2 cm below the capsule [24].

Several other studies have included also a group of healthy subjects in their series. Thus Goertz *et al* [25] obtained a mean LS value of 1.09 m/s (range 0.79 - 1.32 m/s) in a group of 20 subjects without liver pathology and Fierbinteanu-Braticevici *et al* [30] obtained a mean value of 1.18 m/s for subjects with F0-F1 in liver biopsy. Kim *et al* [32] included in their series 133 subjects with normal liver, in which they performed 5 measurements in the right liver lobe and the mean value of the SWV was calculated in each patients. The mean SWV obtained for the normal liver group was 1.08±0.15 m/s.

The study performed by Friedrich-Rust *et al* [17] included 20 healthy adult volunteers as a reference group. The authors had performed the ARFI measurements in the right liver lobe, though the intercostal space at 2 cm below the liver capsule with 10 valid values for each patient. The median SWV measured in this group was 1.10 m/sec, with a mean value of 1.13±0.23 m/sec, range 0.85-1.42 m/sec.

On the other hand, Gallotti *et al* [37] measured the stiffness of various abdominal organs by ARFI elastography in 35 healthy subjects, obtaining for the liver a mean value of 1.59 m/s, higher then the values from the other studies. Also Grgurevic *et al* [34] established a SWV cut-off value of 1.3 m/s (AUC 0.96), that could reliably differentiate between healthy and non-cirrhotic HCV patients.

One of the discussions is that, unlike in Transient Elastography (TE), the manufacturer of this device did not recommend the use of technical parameters, such as SR (success rate) or IQR (interquartile range interval=difference between the 75th and the 25th percentile, essentially the range of middle 50% of the data), when performing the mesurements. In our experience [38], as shown in our present study, these technical parameters influence the results obtained and can pollute the statistical analysis. So we consider that only the measurements with IQR<30% and SR≥60% should be validated, and also that there is a need for further studies in order to standardize the measurement technique regarding technical parameters, place of determination, number of measurements.

The published data regarding the value of ARFI in predicting the severity of liver fibrosis tried to established cut-off values for the different stages of fibrosis. Thus in the study by Lupsor *et al* [20], 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), while the data published by Friedrich-Rust *et al* [17] showed the following mean values for different fibrosis stages: F0 1.16±0.17 m/sec, F1 1.18±0.18 m/sec, F2 1.34±0.34 m/sec, F3 1.75±0.51 m/sec, F4 2.38±0.74 m/sec. In a Romanian multicentre study [40] including 274 patients with HCV chronic hepatitis, in which we compared ARFI to the liver biopsy, the cut-off values obtained were also 1.19 (F≥1), 1.21 (F≥2), 1.58 (F≥3) and 1.82 (F4). From these data, we can see that the mean SWV value obtained by us for normal subjects is inferior to the cut-off values for F1, but there is an overlapping between the two groups. Future studies may be able to find different factors that may influence the results of ARFI measurements and establish its place in the diagnosis algorithm of patients with chronic diffuse liver diseases.

In conclusion, in our study, the mean LS value obtained by ARFI in healthy subjects was 1.15 m/s, and we did not find significant differences between the mean ARFI values in men vs. women and among different age groups.

Conflict of interest: none

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