Comparative study between two point Shear Wave Elastographic techniques: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ

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Abstract

Aim: To compare the feasibility and the liver stiffness (LS) values obtained by means of the two available point Shear Wave Elastographic (pSWE) techniques: ARFI elastography and ElastPQ technique. Material and methods: Our study included 176 subjects with or without chronic liver disease, in which LS was evaluated in the same session by means of ARFI elastography and ElastPQ. Results: Ten valid measurements were obtained in all subjects by means of ARFI elastography and in 97.7% cases by means of ElastPQ (p=0.12). Reliable LS measurements by means of ARFI elastography were obtained in 170/176 subjects (96.5%), so the final analysis included 166/176 subjects (94.3%). The mean LS values by ARFI were significantly higher than those obtained by ElastPQ: 1.46±0.69 m/s vs. 1.32±0.52 m/s, p=0.0004. For a LS cut-off value >1.4 m/second, ARFI elastography had 83.1% accuracy (AUROC=0.822) to differentiate between subjects with or without chronic liver disease, while the best ElastPQ cut-off value to discriminate between these two categories of subjects was >1.23 m/second, with 83.7% accuracy (AUROC=0.851). Conclusions: Both available pSWE techniques have very good feasibility for the non-invasive liver fibrosis assessment and a good performance for predicting the presence of liver pathology. LS values obtained by ElastPQ technique are significantly lower than those obtained by ARFI elastography.

Keywords: liver stiffness, Shear Wave Elastography, ARFI elastography, ElastPQ, liver fibrosis.

Introduction

Non-invasive evaluation of liver fibrosis by using ultrasound-based-elastographic techniques is increasingly used in the last years. Recently, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued guidelines regarding the clinical application of these techniques [1,2]. According to these guidelines, ultrasound based-elastographic techniques are classified in: strain techniques and shear wave elastography techniques. Three types of elastographic techniques are included in the last category: Transient Elastography, point Shear Wave Elastography (pSWE) and shear wave elastography (SWE) imaging (including 2D-SWE and 3D-SWE). In the pSWE category two techniques are included: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ which look very similar, but there are some differences regarding their physical principles.

Regarding ARFI elastography technique, the ultrasound probe 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 and reflects the underlying tissue stiffness (influenced mainly by liver fibrosis), the propagation speed increasing with tissue stiffness. 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 [1,3,4].

Very few information are available regarding the physical principles of ElastPQ technique. According to the data provided by the manufacturer in the application for approval submitted to the US Food and Drug Admin-
istation (FDA), ElastPQ system is relatively similar with Aixplorer system® (SuperSonic Imagine S.A., Aix-en-Provence, France), which is a 2D-SWE. ElastPQ system generates an electronic voltage pulse, which is transmitted to the transducer. In the transducer, a piezo electric array converts the electronic pulse into an ultrasonic pressure wave. When coupled to the body, the pressure wave transmits through body tissues. The Doppler functions of the system process the Doppler shift frequencies from the echoes of moving targets, such as blood, to detect and graphically display the Doppler shift of these tissues as flow. The Doppler mode creates waves in soft tissues and estimates the tissue stiffness by determining the speed at which these shear waves travel.

The usefulness of ARFI elastography for non-invasive assessment of liver fibrosis was demonstrated in the last 2-3 years in international multicenter studies [5] and meta-analyses [6-8], but ElastPQ is a newly developed technique and few data are available [9-12].

The aim of this study was to compare the feasibility and the liver stiffness (LS) values obtained in subjects with or without chronic liver disease by means of the two available pSWE techniques.

**Material and methods**

**Subjects**

Our prospective study included 176 adult subjects with or without chronic liver disease, in which LS was evaluated in the same session (the same day) by means of ARFI elastography and ElastPQ technique. The study group included: healthy volunteers (subjects without a history of liver disease, with a normal abdominal ultrasound examination, but in whom additional tests, such as biological tests, viral markers were not performed); chronic hepatitis patients with various etiologies and fibrosis stages; and patients previously diagnosed with liver cirrhosis by means of clinical, biologic, ultrasonographic, endoscopic, morphologic and/or laparoscopic criteria.

All subjects signed the informed consent and the study was performed in accordance with the latest version of Helsinki Declaration and approved by the local Ethics Committee.

**Acoustic Radiation Force Impulse (ARFI) Elastography**

Acoustic Radiation Force Impulse elastography was performed with a Siemens Acuson S2000™ ultrasound system (Siemens AG, Erlangen, Germany) with a 4C1 transducer, by using Virtual Touch Tissue Quantification application. In each patient, we aimed for 10 valid ARFI measurements. The examination was performed in fasting conditions, in supine position with the right arm in maximum abduction, by intercostal approach in the right liver lobe, 1-2 cm under the liver capsule, with minimal scanning pressure applied by the operator, while the patient was asked to stop normal breathing for a moment, in order to minimize breathing motion (fig 1). The device uses a measuring box of 10/5 mm that is placed in a position chosen by the operator. A median value of 10 valid measurements was calculated (expressed in m/s) and considered as indicative of fibrosis severity. If we could not obtain 10 valid measurements after 20-25 attempts, we considered these cases as failed measurements.

Reliable LS measurements were defined as median of 10 valid measurements with a with a success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) ≥ 60% and an interquartile range (IQR=the range of the middle 50% of the data) <30%. Even if the manufacturers of the ARFI device initially did not recommend the use of technical quality parameters for LS measurements (now they recognize that the use of IQR increases the accuracy of ARFI elastography), we decided to use it since our previous studies [13,14] demonstrated its importance for increasing the accuracy of ARFI technique. Thus, we showed that LS values assessed by ARFI elastography were correlated with histological fibrosis only in patients with good technical parameters (IQR< 30% and SR ≥ 60%) [13].Also we demonstrated that ARFI measurements with IQR >30% are associated with discordance between the severity of fibrosis predicted using the cut-off values proposed by meta-analysis [6] and the histological fibrosis [7].

Liver stiffness measurements by means of ARFI elastography were performed by two operators blinded to any clinical or elastographic data.

**ElastPQ technique**

ElastPQ technique was performed with a Philips ultrasound system (iU22, Philips Medical Systems, Bothell, WA, USA). Similar with ARFI elastography, LS measurements were performed in fasting conditions, in supine position with the right arm in maximum ab-
duction, by intercostal approach in the right liver lobe, 1-2 cm under the liver capsule, with minimal scanning pressure applied by the operator, while the patient was asked to stop normal breathing for a moment, in order to minimize breathing motion (fig 2). We aimed for 10 valid ElastPQ measurements in each patient (expressed either in m/s or kilopascals). ElastPQ technique also uses a box with predefined size (15/5 mm), which the operator places in the liver, avoiding the area immediately under the liver surface.

The manufacturer of the ElastPQ system did not recommend any quality measurements criteria and also no study analyzed this issue, so that we considered as reliable LS measurements the median value of 10 valid measurements, which was expressed in m/s. If we could not obtain 10 valid measurements after 20-25 attempts, we considered these cases as failed measurements.

Liver stiffness measurements by means of ElastPQ technique were performed by the same two operators who were involved in ARFI elastography measurements. During a working day, each operator performed either ElastPQ or ARFI measurements, in different rooms, so that they were blinded to all clinical and elastographic data.

Statistical analysis
All statistical analyses were performed using MedCalc Software, version 12.7.0 (MedCalc program, Belgium). Continuous variables were reported as mean ± standard deviation or median with range intervals according to their normal or non-normal distribution, while categorical variables were reported as number of patients and percentages. Student’s t-test and paired t-test were used for group comparisons of continuous variables with normal distribution, while Mann-Whitney or Wilcoxon test were applied for variables with non-normal distribution. Group comparisons of categorical variables were performed using Pearson’s chi-squared test.

Spearman’s rank correlation coefficient (r) was used to assess the correlation of LS measurements by means of ARFI elastography and ElastPQ.

Areas under receiver operating characteristics (AUROC) curves were built for ARFI elastography and ElastPQ to discriminate between subjects with and without chronic liver disease. The optimal cut-off values were determined using Youden’s index (sensitivity + specificity - 1) from the AUROC curves analysis. DeLong test was used to compare AUROC curves. 95% confidence intervals were calculated for each predictive test and a p-value < 0.05 was considered to denote statistical significance.

Results
Liver stiffness was evaluated by means of ARFI elastography and ElastPQ in one hundred seventy-six subjects with or without chronic liver disease. The main subjects’ characteristics are presented in Table I.

Ten valid measurements (after at most 20-25 shots) were obtained in all subjects by means of ARFI elastography and in 97.7% cases by means of ElastPQ (p=0.12).

Liver stiffness measurements with good technical parameters (IQR <30% and SR ≥60%) by ARFI elastography were obtained in 170/176 subjects (96.5%). In the final analysis we included 166/176 subjects (94.3%) with ten valid ARFI and ElastPQ measurements, and with good ARFI technical parameters. In this cohort of subjects, 99 (59.6%) were healthy volunteers, 42 patients (25.3%) had chronic liver disease with various etiologies and fibrosis stages and 25 patients (15.1%) had liver cirrhosis.

Correlation of LS values by means of ARFI elastography and by ElastPQ technique
A direct, significant correlation (Spearman r correlation coefficient =0.616) was observed between LS values assessed by means of ARFI elastography and by ElastPQ (p<0.0001).

Table I. Subjects’ characteristics. Numerical variables with normal distribution are presented as mean value ± standard deviation, while variables with non-normal distribution are presented as median values and range intervals.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n = 166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 (18-82)</td>
</tr>
<tr>
<td>Gender: – male</td>
<td>n= 61 (34.6%)</td>
</tr>
<tr>
<td>– female</td>
<td>n= 115 (65.4%)</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>22.8 (15.6 – 42.1)</td>
</tr>
<tr>
<td>Etiology: – healthy volunteers</td>
<td>n = 103 (58.5%)</td>
</tr>
<tr>
<td>– chronic hepatitis C</td>
<td>n= 18 (10.2%)</td>
</tr>
<tr>
<td>– chronic hepatitis B</td>
<td>n = 15 (8.6%)</td>
</tr>
<tr>
<td>– chronic alcoholic hepatitis</td>
<td>n = 4 (2.3%)</td>
</tr>
<tr>
<td>– non-alcoholic steatohepatitis</td>
<td>n = 4 (2.3%)</td>
</tr>
<tr>
<td>– cryptogenic chronic hepatitis</td>
<td>n = 7 (3.9%)</td>
</tr>
<tr>
<td>– liver cirrhosis</td>
<td>n = 25 (14.2%)</td>
</tr>
</tbody>
</table>

n-number of patients
Mean LS values by ARFI were significantly higher than those by ElastPQ (paired t-test): 1.46 ± 0.69 m/s vs. 1.32 ± 0.52 m/s, p=0.0004.

Significant correlations between LS values by ARFI elastography and by ElastPQ were also obtained in various subgroups of subjects (Table II).

Mean LS values assessed by ARFI elastography were significantly higher than those obtained by means of ElastPQ in healthy volunteers, in patients with chronic liver disease and also in cirrhotic patients (Table III).

**Performance of ARFI elastography and ElastPQ for the differentiation between healthy volunteers and patients with chronic liver disease**

Both ARFI elastography and ElastPQ had a good value to differentiate between healthy volunteers from patients with chronic liver disease and cirrhotic patients, respectively. Also, both techniques had an excellent value to discriminate patients with chronic hepatopathies with various stages of fibrosis from those with liver cirrhosis (fig 3, fig 4).

For a LS cut-off value > 1.4 m/s, ARFI elastography had 59.7% Se, 99% Sp, 97.5% positive predictive value (PPV), 78.4% negative predictive value (NPV) and 83.1% accuracy (AUROC = 0.822, p=0.0001) to differentiate between subjects with or without chronic liver disease (Fig.5). The best ElastPQ cut-off value to discriminate between these two categories of subjects was > 1.23 m/s, with 74.6% Se, 89.9% Sp, 83.3% VPP, 83.9% NPV and 83.7% accuracy (AUROC = 0.851, p=0.0001). The AUROCs of ARFI elastography and ElastPQ for predicting the presence of liver diseases (chronic hepatitis and liver cirrhosis patients) were similar (p=0.48) (fig 5).

**Discussions**

In the last years, in many European countries the number of liver biopsies decreased [15], as a result of an increasing number of non-invasive methods for liver diseases evaluation. The oldest and most used ultrasound based-elastographic method is TE, but recently published
data showed that ARFI elastography has a better feasibility than TE and similar value for predicting the presence of significant fibrosis and liver cirrhosis [7].

Our present study is the first which compares the feasibility of the two available pSWE techniques and the LS values obtained by these two techniques in various categories of subjects.

Regarding feasibility, the percentage of subjects in which 10 valid LS could be obtained was very good for both techniques: 100% for ARFI elastography and 97.7% for ElastPQ. Also the rate of reliable LS measurements by means of ARFI was very high (>96%) as compared with TE in which only in 70% up to 85% of the cases reliable LS measurements can be obtained with the standard M-probe [16,17].

An issue that should be analysed in future studies is the necessity to use quality criteria parameters for LS measurements by means of ElastPQ technique. The manufacturer did not make any recommendation, but at the end of the examination, beside the median value of LS measurements, the standard deviation is also displayed on the screen. The usefulness of this parameter, or maybe of the IQR parameter, for increasing the accuracy of ElastPQ technique should be evaluated in larger studies, using the liver biopsy as “gold-standard” method.

The other aim of our study was to see if there are significant differences between the LS values obtained by ARFI elastography and ElastPQ technique in patients with or without chronic liver disease. In the present study we decided to use m/s (and not kPa) for expressing LS by means of ElastPQ technique in order to have the same units for measurements performed by both pSWE techniques. Firstly, a good correlation was observed between LS values obtained by both pSWE techniques, but the LS values assessed by ElastPQ were significantly lower than those obtained by ARFI elastography in the entire cohort of subjects, but also in all subgroups of subjects (healthy volunteers, chronic hepatitis patients and cirrhotic patients), one possible explanation being that the physical principles of these two techniques are not identical.

The few available data [9,10] regarding LS assessment by means of ElastPQ in healthy volunteers showed values ranging between 3.3 kPa and 3.8 kPa, higher values being obtained in men. This difference between LS values obtained in men vs. women was also observed in Transient Elastography [18-20] and 2D-SWE (Aixplorer® system) [21], but not in ARFI elastography in which gender did not influence the LS values [22-24].

Knowing that the elastic value (expressed in kPa) is calculated using the formula, 
\[ E = 3\rho V_s^2 \]

where \( V_s \) (expressed in m/s) is defined as the shear wave propagation velocity and \( \rho \) as tissue density (whose approximated value in the human body is 1) [25], the value of 3.3 kPa and 3.8 kPa obtained by ElastPQ technique in healthy volunteers [9,10] are equivalent with 1.05 m/s and 1.12 m/s, relatively similar with our present data. Regarding the values obtained in patients, Ferraioli et al [10] and Ma et al [11] obtained a median value of 12 kPa (equivalent with 2 m/s) and respectively a mean value of 10.8 kPa (equivalent with 1.9 m/s), values lower than the one that we obtained. The probable explanation for these different results is that our study included also patients with decompensated cirrhosis, while in the other two studies only compensated patients were included, in whom the diagnosis of cirrhosis was established by liver biopsy.

Following our study we tried calculate a LS cut-off value assessed by ElastPQ technique able to predict the presence of liver pathology. Published data provide only a cut-off value for predicting the presence of significant fibrosis (F≥2) in Asian patients chronically infected with hepatitis B virus, which is 6.9 kPa (equivalent with 1.51 m/s). The ElastPQ cut-off that we calculated for predicting the presence of chronic liver pathology was lower (1.23 m/s), probably because our study also included healthy volunteers and because the cohort of patients with chronic liver disease included different etiologies of chronic hepatopathies. The LS cut-off value we obtained by ARFI elastography for predicting the presence of significant fibrosis (1.4 m/s) is similar to those published in meta-analysis [6-8]. In our study, both ARFI and ElastPQ cut-offs had a good accuracy for differentiating between subjects with and without chronic liver disease.

In the present study we included patients with different etiologies of liver disease (as encountered in daily clinical practice), thus a more detailed analysis regarding the influence of the etiology of chronic liver disease on the LS values assessed by ElastPQ technique should be analyzed in further studies. The very few data published [10,11] showed that lower values were obtained in chronic hepatitis B patients [11] as compared with a cohort of patients with different etiologies of liver disease [10]. But, it should be considered that these two studies included patients of different race, and it was demonstrated that LS values obtained by ARFI elastography in Asian patients were lower than those obtained in European patients with the same etiology of liver disease and the same stage of liver fibrosis [5].

In conclusion, both pSWE techniques available in this moment have a very good feasibility for the non-invasive liver fibrosis assessment and a good performance for predicting the presence of liver pathology. Liver stiffness values obtained by Elast PQ technique are significantly lower than those obtained by ARFI elastography and future studies are needed to establish
the best LS cut-offs assessed by ElastPQ for predicting different liver fibrosis stages.

Conflict of interest: none

References


