Evaluation of liver and spleen stiffness using a ultrasound
guided method: Accuracy of ARFI(R) measurements in liver
disease patients

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AIM: The aim of the study was to analyze the use of ARFI (acoustic radiation force impulse) that allows selecting by US an area of interest, in the evaluation of hepatic and splenic elasticity in a cohort of normal subjects and patients with chronic liver disease.

BACKGROUND:

Transient elastography (TE) is a non-invasive method to evaluate liver fibrosis in patients with chronic liver disease. It is based in the measurement of the progression of a strong high frequency wave of ultrasound through the liver. This progression is also detected by ultrasound, analysing the velocity of the displacement of the wave transmitted. This technique is used in Fibroscan® which is today the system that has been tested in a wide group of different liver diseases such as hepatitis, steatosis and liver cirrhosis (1-2). The values obtained correlates with the stiffness of the liver, measured by liver biopsy, that is mainly caused by fibrosis. Nowadays, this method is used in clinical practice for the follow-up of patients with suspected chronic hepatitis or cirrhosis, considering the method useful not only for stratification of fibrosis, but also as indicative further complications such as gastrointestinal bleeding. Obesity and ascites are causes of impossibility to detect liver stiffness as the depth of the measurement is limited between 2 and 8 cm. When some acute or chronic disease increases intrahepatic pressure, such as acute hypertransaminasemia, biliary obstruction or congestive liver, measurements are non-reliable as they reflects stiffness independent of fibrosis. In average a 10% of the studies performed by Fibroscan® are invalid. The use of US to detect other conditions such as hepatic veins dilation (indicating increased central venous pressure) or ascites could prevent useless or falsely positive TE studies. TE cannot be used for spleen stiffness evaluation, unless a big splenomegaly is present. ARFI is based on a different technology, consisting in evaluating the horizontal displacement of the waves generated by a strong acustic impulse. The analysis of the lateral transmitted wave is performed in a small sample of about 1 cm$^3$ that is located under US guidance at a depth between 3.5 and 5 cm. Previous US-doppler studies have shown that spleen impedance better correlates with liver fibrosis than hepatic impedance (3), suggesting that measurement of spleen stiffness, if feasible, could be useful in predicting portal hypertension.

Recently, ARFI ® has been proposed as an alternative to TE, with the advantage of allowing to select the area of interest. In patients with chronic viral liver disease TE and ARFI have been compared, and the results were similar (3). ARFI might be also used for spleen elasticity evaluation

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Methods and Materials

METHODS: Seventy seven subjects accepted to participate in the study (Table 1): 20 were normal subjects (N), 16 patients had minimal changes (MinC); 10 patients had F2-F3 fibrosis, meaning moderated fibrosis in liver biopsy (ModF) and 30 patients had liver cirrhosis (LC). Final diagnosis was based on liver biopsy (29) or on biochemical, endoscopic, haemodynamic (measurement of the hepatic venous gradient) and clinical criteria.

In all 77 patients 10 ARFI measurements were obtained at the liver; in a subgroup of 35 patients 10 samples were obtained in two segments (7 and 6) to evaluate inter-segments variability, and in 56 patients 10 measurements were also obtained at the spleen.

The equipment used was a Siemens S2000, with a convex probe of 4 MHz. The measurements were obtained transabdominally or subcostally, with the transducer perpendicular to the body surface and taking care of obtaining good contact. The position of the sample was located in areas where liver or spleen were homogeneous on US imaging, avoiding yuxtavascular or near ligaments areas or focal lesions. The depth of the sampling was located between 3.5 and 5 cm from the surface. (Figures 1 to 6).

Data from the US imaging was recorded: Size, pattern and edge of the liver, size of the spleen, presence of ascites or collateral circulation. Biochemical tests analyzed included: Platelet count, prothrombin time, bilirubin, transaminases and total proteins.

Statistical analysis. Differences between groups were assessed by unpaired Student's T test (normally distributed continuous variables) or by U Mann-Whitney test, and by Fisher's test for frequencies. ARFI variability between the two studied segments were evaluated by intraclass correlation coefficient (ICC). P significance was set at 0.05. Statistical analysis was performed by SPSS 16.0 statistical package and by CIA statistical software.
Images for this section:

**Fig 1:** Normal subject. ARFI of the liver

**Fig. 0:** ARFI measurement in segment 6 of a normal liver

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Fig 2- Steatosis. ARFI of the liver

Fig. 0: Steatosis without fibrosis. ARFI values are at normal range.

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Fig 3: Moderated fibrosis: ARFI of the liver.

Liver biopsy:
40% esteatoses
Fibrosis II/IV

Fig. 0: Patient with fibrosis and steatosis in liver biopsy. ARFI values are increased.

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Fig 5: ARFI of the liver in a patient with cirrhosis and obesity

Height: 1.65 m.
Weight: 107 Kg.
Only one segment could be evaluated.

ARFI Values: 3.31 +/- 0.75 m/s
Range: 2.01-4.38

Fig. 0
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Fig. 0: ARFI evaluation of a patient with haemochromatosis. The presence of iron increases the values obtained with ARFI.

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Fig. 6. Liver cirrhosis with ascites and small liver

Values ARFI of the liver:
2.82 +/- 0.5 m/s
Range: 2.13- 4.19

In this case the measurements showed great variability, but all were abnormal.

Fig. 0: Despite the presence of ascites, ARFI could obtain good measurements. With TE the presence of ascites precludes the study.

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Results

The presence of ascites or obesity did not prevent to obtain enough measurements to evaluate the patients (Figures 5 and 6).

The characteristics of age and biochemical tests are shown in Table 2. Age and number of platelets were different for the four groups confirming that fibrosis progresses with age and with time of evolution of hepatic disease.

ARFI mean values for the liver were significantly different in the four groups, allowing differentiating Normal, from Minimal Changes, Moderate fibrosis and Liver cirrhosis (Table 3).

Fifteen out of the 30 patients with LC had ascites or Oesophageal Varices/ intrabdominal collaterals). Values of the liver or spleen were not different in the two subgroups of patients with liver cirrhosis.

In 35 subjects (including patients from the 4 groups) in which 10 measurements were obtained in two different lobules, mean results were similar: Segment 7 : 1.75 +/- 0.86 vs Segment 6: 1.69 +/- 0.79. coefficient of correlations: 0.94. This results show that measuring the liver in the area that could be better studied with US will be representative of the liver stiffness.

The number of measurements performed was 10, following the recommendations for TE. We analyzed the reproducibility of the ten measures which was better in the three groups of patients than in normal subjects, and was moderate to good in any case. These results suggest that 10 measurements are advisable.

The results obtained from liver also correlated with US imaging, being statistically different in patients with smooth border ( 1.29 +/- 0.59) vs. nodular contour ( 2.47 +/- 0.5, p< 0.001). This last finding is commonly associated to liver cirrhosis, and indeed our ARFI results had a range of values similar to those obtained in the group of LC. This confirms our previous study in which irregularity of the contour correlates with Fibroscan® values (5).

The analysis of the ROC curves for ARFI of liver and spleen (Figures 7 and 8) showed a high predictive value of both measurements for diagnosing cirrhosis (liver: AUROC=0.933 p < 0.0001; spleen AUROC=0.956 p< 0.0001).
The best cut-off of ARFI-liver was 1.83 and had a sensitivity 80%, a specificity of 90%, a PPV of 83% , a NPV of 88%; +likelihood ratio 7.68, and - likelihood ratio 0.22.

The best cut-off of ARFI-spleen was established at 2.00, having this value a sensitivity of 89%, a specificity of 87%, a PPV of 86 % and a NPV of 90%; +likelihood ratio 6.89, and - likelihood ratio 0.13. These results suggest that ARFI of the spleen is better to rule out cirrhosis and ARFI of the liver is better for ruling in the diagnosis of cirrhosis.
### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>53% men</th>
<th>46% women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Normal liver</td>
<td>20</td>
</tr>
<tr>
<td>HCV</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>HCV + HIV</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HVB</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ethanol abuse</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other (haemocromatosis, PAF, Autoimmune Hepatitis)</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 0**

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Table 2: Age and biochemical characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Platelets*</th>
<th>Prothrombin</th>
<th>AST</th>
<th>ALT</th>
<th>Total Bl</th>
<th>T. Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>40±11</td>
<td>277±65</td>
<td>96.4±3</td>
<td>22±7</td>
<td>21±10</td>
<td>0.5</td>
<td>74±9</td>
</tr>
<tr>
<td>MinC</td>
<td>46.7±14</td>
<td>262±73</td>
<td>88±14</td>
<td>58.8±68</td>
<td>95±148</td>
<td>0.6±0.2</td>
<td>72.5±4.7</td>
</tr>
<tr>
<td>ModF</td>
<td>52.7±12</td>
<td>172±83</td>
<td>93±9</td>
<td>99±68</td>
<td>131±163</td>
<td>0.8±0.4</td>
<td>82.7±4</td>
</tr>
<tr>
<td>LC</td>
<td>60.2±12</td>
<td>125±65</td>
<td>76.4±14</td>
<td>53±21</td>
<td>49±28</td>
<td>1.6±1.2</td>
<td>72.8±10</td>
</tr>
<tr>
<td>ANOVA</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P=0.01</td>
<td>P=0.003</td>
<td>P=0.039</td>
<td>P&lt;0.001</td>
<td>P=ns</td>
</tr>
</tbody>
</table>

Platelets are expressed in \( \text{mm}^3 \). Prothrombin is expressed as % of normality, AST and ALT as international Units. Total bilirubin and Total proteins in plasma are expressed by mg/mL.

Fig. 0

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Table 3: ARFI results for liver and spleen, and spleen size in the four groups.

<table>
<thead>
<tr>
<th></th>
<th>Liver ARFI</th>
<th>Spleen ARFI</th>
<th>Spleen size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal: n=21</td>
<td>1.10± 0.28</td>
<td>2.3±0.28</td>
<td>9.4±1.5</td>
</tr>
<tr>
<td>Minimal Changes: n=16</td>
<td>1.36±4.4</td>
<td>2.5±0.30</td>
<td>9.97±1.3</td>
</tr>
<tr>
<td>Moderate Fibrosis: n=10</td>
<td>1.78± 0.6</td>
<td>2.4±0.18</td>
<td>10.6±2.1</td>
</tr>
<tr>
<td>Liver Cirrhosis: n=30</td>
<td>2.6± 0.86</td>
<td>3.45±0.5*</td>
<td>14.8±2.2</td>
</tr>
</tbody>
</table>

ANOVA  
P < 0.001  
NS  
P < 0.001

*P< 0.0001 vs. the remaining three groups

Fig. 0

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Fig. 0

AUROC 0.96 (95% CI 0.91-1.00); P<0.0001

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Fig. 0

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Conclusion

Measurement of liver elasticity under US control reflects adequately an increased stiffness due to fibrosis, so allowing differentiating normal from moderated fibrosis and from liver cirrhosis. Spleen stiffness can be successfully evaluated by ARFI, and is higher than liver stiffness in any studied category, and is increased in cirrhotic patients.
References


Personal Information

These group are working in the field of fibrosis, hepatitis and portal hypertension as well as in liver imaging.

Dr Crespo is a fellowship in Hepatology and the remaining authors are working on Ultrasound Unit (Diagnostic Imaging Center at the Hospital Clinic in Barcelona (SPAIN))

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