Liver Stiffness Measurement by Transient Elastography in Clinical Practice

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Abstract

The aim of our study was to evaluate the results of transient elastography assessment of liver stiffness (LS) in various categories of patients. Material and method. We performed transient elastography in 986 patients. We evaluated: the percentage of cases in which valid measurements could be obtained; the values of LS in 40 patients with no history of chronic liver disease (“normal” patients); 44 inactive HBsAg carriers; 173 patients with proven liver cirrhosis; and the correlation between liver biopsy results and LS in 93 patients with chronic HCV hepatitis. Results. We obtained valid measurements of LS in 94.6% of the 986 cases. Male gender, younger age and low BMI were positive predictive factors for obtaining valid measurements. The mean values of LS were: 5.2±1.3 kPa in “normal” patients, 5.8±2.6 kPa in inactive HBsAg carriers, 37.2±20.9 kPa in patients with liver cirrhosis. In patients with chronic HCV hepatitis, we found that the mean value of LS in those with METAVIR F≥2 was 8.5±4.2 kPa, higher than in those with F<2: 5.3±1.4 kPa (p=0.0017). In patients with F≥3, the mean value of LS was 11.1±4.3 kPa, significantly higher than in patients with F<3: 6.1±2.5 kPa (p<0.0001). Conclusions. Liver stiffness, as a marker of fibrosis, can be evaluated by means of transient elastography in a great majority of patients. It is a useful method for the exclusion of significant liver fibrosis and for predicting liver cirrhosis. As compared to liver biopsy, transient elastography can discern significant fibrosis from no or mild fibrosis.

Key words

Transient elastography – chronic liver diseases – liver biopsy.

Introduction

Chronic liver diseases are frequent diseases in the general population, especially in areas with a high incidence of infection with hepatitis viruses. According to WHO data, in Romania approximately 5% of the population is infected with hepatitis B virus (HBV) and 4-5% with hepatitis C virus (HCV) [1]. Besides chronic viral hepatitis, alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) must be taken into consideration as frequent causes of liver damage. It is estimated that NASH incidence is rising, currently affecting 2-3% of the adult population [2-4].

In the evolution of chronic viral and non-viral hepatitis, liver fibrosis is a very important factor associated with prognosis. Therefore, a precise evaluation of the severity of fibrosis in those patients is compulsory, in order to perform a correct staging and eventually to decide the treatment. Currently, liver biopsy (LB) seems to be the optimal method to evaluate changes in fibrosis over time [5]. Nevertheless, LB has its shortcomings: the intra- and interobserver variability [6, 7]; the sampling variability [8]; its invasive character, with morbidity and mortality higher than 0.

Considering all these facts, non invasive methods for the evaluation of liver fibrosis have been developed in the last few years, in order to replace LB. The most promising non-invasive methods are the FibroTest – ActiTest [9] and the transient elastography (TE) [10, 11].

Material and methods

Since a FibroScan device (EchoSens, Paris, France) was recently acquired in the Department of Gastroenterology and Hepatology Timişoara, we evaluated the clinical value of this method over an 8 month period. Between June 2007 and January 2008 we performed a TE evaluation of liver stiffness (LS) in 986 successive patients.

We analyzed LS in various diseases, and compared the results obtained with other “classic” methods of evaluation of liver fibrosis, namely LB.

We assessed the following: a. the percentage of cases in which valid measurements (VM) of LS could be obtained by
The demographic data and the characteristics of our patients are presented in Table I.

### Table I. Demographic data, BMI and technical parameters of TE measurements of the patients included in our study

<table>
<thead>
<tr>
<th>Category</th>
<th>Total number</th>
<th>Females</th>
<th>Males</th>
<th>Mean age (years)</th>
<th>BMI (kg/m²)</th>
<th>SR (%)</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>986</td>
<td>48.7% (480)</td>
<td>51.3% (506)</td>
<td>50.7±13.9</td>
<td>26.1±5</td>
<td>83.5±19.4</td>
<td>28±3.8</td>
</tr>
<tr>
<td>“Normal” patients</td>
<td>40</td>
<td>23 (57.5%)</td>
<td>17 (42.5%)</td>
<td>37±16.9</td>
<td>22.7±4</td>
<td>85.6±17.9</td>
<td>0.9±0.7</td>
</tr>
<tr>
<td>Inactive HBsAg carriers</td>
<td>44</td>
<td>23 (52.3%)</td>
<td>21 (21.7%)</td>
<td>39.4±13.2</td>
<td>25.5±4.5</td>
<td>84.2±19.8</td>
<td>1.2±0.8</td>
</tr>
<tr>
<td>Patients with liver cirrhosis</td>
<td>181</td>
<td>65 (35.9%)</td>
<td>116 (64.1%)</td>
<td>56.1±11.7</td>
<td>26±4.9</td>
<td>83.1±19.7</td>
<td>6.4±6.3</td>
</tr>
<tr>
<td>Patients with HCV chronic hepatitis</td>
<td>93</td>
<td>63 (67.7%)</td>
<td>28 (32.3%)</td>
<td>47.7±12.3</td>
<td>25.8±4.7</td>
<td>85.1±18.6</td>
<td>1.4±0.9</td>
</tr>
</tbody>
</table>

SR - success rate; IQR - interquartile range.
patients with significant fibrosis (at least F2 META VIR) from patients with no or mild fibrosis (F0 and F1), with a sensitivity of 56.5%, specificity of 94.7%, PPV of 97.5% and NPV of 37.5% (Fig.2). For a cut-off value of 8.8kPa, the AUROC analysis showed an accuracy of 85.4% in differentiating patients with severe fibrosis (≥ F3), from patients with at most moderate fibrosis (F0, F1 and F2), with a sensitivity of 63.3%, specificity of 87.9%, PPV of 73.1% and NPV of 82.3% (Fig.3).

Table II. Mean values of LS acording to fibrosis in HCV patients

<table>
<thead>
<tr>
<th>Fibrosis (META VIR)</th>
<th>Number of cases</th>
<th>Mean value of LS (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F=0</td>
<td>5</td>
<td>5.1±0.8</td>
</tr>
<tr>
<td>F=1</td>
<td>14</td>
<td>5.3±1.5</td>
</tr>
<tr>
<td>F=2</td>
<td>39</td>
<td>6.5±2.8</td>
</tr>
<tr>
<td>F=3</td>
<td>16</td>
<td>9.3±3.5</td>
</tr>
<tr>
<td>F=4</td>
<td>14</td>
<td>13.2±4.4</td>
</tr>
</tbody>
</table>

Discussion

As expected, the rate of VMs obtained is not 100%, failure to obtain VMs being associated with the presence of obesity and with the lack of adequate intercostal spaces. In a study performed on 2,114 LS measurements by means of TE, failure to obtain VM was reported in 4.5% of the cases [12]. The univariant analysis showed that it was associated with BMI>28 (p<0.001), diabetes mellitus (p=0.01), age >50 years (p<0.001), steatohepatitis (p=0.001). Failure to obtain VM was not operator dependent and was not associated with the patient gender, or with the transaminase level. In the multivariate analysis, the only factor associated with failure to obtain VM was BMI>28 (p=0.001) [12].

In our study, a similar percentage failure to obtain VM was observed (5.6% of the cases). Male gender, younger age and low BMI were the factors that had a positive influence on obtaining VM by TE. The height of the patients did not influence the ability to obtain VM.

We assessed the value of TE in patients with not known history of chronic liver disease, in order to determine the normal values of LS in healthy subjects. The subgroup of “normal” subjects did not undergo any complementary investigation (such as abdominal ultrasound, liver laboratory work-out or viral markers). In these subjects, the mean value of LS was 5.2±1.3 kPa, ranging from 3 to 8.1 kPa. We observed a wide range of values in “normal” subjects, as well as the fact that a rather large proportion of the patients with not known history of chronic liver disease had LS > 6 kPa (22.5%). In all these cases the questions to be answered are: what are the limits of “normal” LS as measured by TE or whether, in these cases, we encountered a rather atypical Gauss distribution of LS. Further LS evaluation of “normal” subjects, in order to cover all age groups, and further investigation of individuals with higher values of LS in order
to exclude a latent liver disease are necessary.

Transient elastography was developed to evaluate mainly patients with chronic HCV hepatitis. Lately, TE has been successfully used for the assessment of fibrosis in other chronic liver diseases [13-15] especially in chronic HBV hepatitis [13]. In the inactive HBsAg carriers evaluated in the present study, the mean value of LS was 5.7±2.7 kPa, ranging from 3.5 to 20.1 kPa. The great majority of cases had LS < 8 kPa (thus excluding significant fibrosis), and only in two cases the LS was > 8 kPa (confirmed by repeated, “blinded”, measurements). These two patients should undergo LB to see if they really have significant fibrosis, or if it is only an artefactual error. The mean value of LS in “normal” patients was not significantly different from that in inactive HBsAg carriers (5.8 vs. 5.2 kPa, p=0.172). Therefore, the TE evaluation of LS in these patients could be a good surveillance method for the evolution of liver disease.

Although in advanced liver cirrhosis the clinical signs are diagnostic, compensated liver cirrhosis is not always easy to diagnose. Liver biopsy can miss diagnosis in up to 20% of the cases [6], and diagnostic laparoscopy is an invasive method. The studies that investigated the utility of abdominal ultrasound for the diagnosis of liver cirrhosis found an accuracy of 80.7% [16, 17]. Transient elastography seems to be a promising diagnostic method in these patients. Using a cut-off value of 14 kPa, 89.6% of our patients were correctly classified. If the cut-off value of 13 kPa was used, 92.5% of patients were correctly classified. According to various authors, the cut-off value of LS for the diagnosis of cirrhosis varies between 13 and 17.6 kPa. In a study performed by Foucher et al., the cut-off value was established at 17.6 kPa [18]. In this study, NPV and PPV for the diagnosis of cirrhosis were 92% and 91%, respectively.

In a recent meta-analysis [19], the sensitivity of TE for the diagnosis of liver cirrhosis was 87% (95% CI 84%-90%), the specificity 91% (95% CI 89%-92%), the positive likelihood ratio 11.7 (95% CI, 7.9-17.1) and the negative likelihood ratio 0.14 (95% CI 0.10-0.20).

We also studied the correlation between the LS values measured by means of TE and the severity of fibrosis as assessed by LB in patients with HCV chronic hepatitis. In a prospective multicentric French study performed on 327 HCV patients who were evaluated by means of percutaneous LB and valid TE examination, a significant correlation was found between fibrosis and the LS measured by TE (r=0.55) (p=0.001) [20]. This study tried to establish cut-off values for LS that could differentiate between various stages of fibrosis. The cut-off value of 8.7 kPa differentiated F0 and F1 from F2, F3 and F4 with a sensitivity of 55%, specificity of 84%, PPV 87% and NPV of 51%. The conclusion of this study was that the evaluation of LS by means of TE is a useful method for the assessment of liver fibrosis in patients chronically infected with HCV.

In our study the optimal cut-off value for significant fibrosis (at least F2 META VIR) was 6.8 kPa. The diagnostic performance of the LS measurement in our patients, for cut-off values of 6.8 kPa (optimal in our study), 7.1 kPa (optimal in a study by Castera et al) [11] and 8.7 kPa (optimal in a study by Ziol et al) [20] are presented in Table III.

### Table III. Diagnostic performance of TE mesurements for predicting significant fibrosis (at least F2 META VIR) in patients with chronic HCV hepatitis

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.8 kPa</td>
<td>56.5%</td>
<td>94.7%</td>
<td>97.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>7.1 kPa</td>
<td>54.3%</td>
<td>94.7%</td>
<td>97.4%</td>
<td>36.3%</td>
</tr>
<tr>
<td>8.7 kPa</td>
<td>39.1%</td>
<td>100%</td>
<td>100%</td>
<td>31.1%</td>
</tr>
</tbody>
</table>

All these data, added to previous studies [11, 21, 22], demonstrate the value of TE in the non-invasive evaluation of fibrosis. Accordingly, TE could be used in patients with chronic HCV hepatitis to differentiate patients that should be treated (F≥2) from those that do not need treatment (F≤1).

### Conclusions

The liver stiffness evaluation by means of transient elastography allows to obtain valid measurements in the great majority of scanned patients. It is a good method for excluding with sufficient accuracy significant fibrosis and also for predicting the presence of liver cirrhosis. In patients with chronic HCV hepatitis, when evaluating it in comparison with liver biopsy as the “gold standard”, transient elastography can differentiate between significant fibrosis and absent or mild fibrosis. Liver stiffness assessment by transient elastography is a useful non-invasive method for the evaluation of chronic liver disease in clinical practice.

### Conflicts of Interests

None of the authors have any conflicts of interest.

### References


