Performance of ultrasonic transient elastography for the noninvasive assessment of liver steatosis

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**Purpose**

- Steatosis is a frequent histological finding in patients with chronic liver diseases (CLD) [1, 2].
- The current "gold standard" for evaluating steatosis is liver biopsy (LB), but it is invasive and may result in severe complications [3]. Furthermore, LB also has potential sampling errors and cannot be readily repeated for adequate patient follow-up [4].
- The non-invasive diagnosis of steatosis (especially blood tests and imaging techniques), has been extensively developed in the last decade.
- Ultrasonography is considered the imaging technique of choice for steatosis screening given its low cost, safety and wide availability [5], but it is operator-dependent [6] and it detects steatosis only if it involves at least 20% of all hepatocytes [7]. The method cannot establish with certainty the degree of fatty infiltration and cannot accurately discriminate steatosis from fibrosis, since both result in increased liver echogenity [8].
- To overcome these limitations, a novel non-invasive tool based on the evaluation of ultrasound attenuation using the Fibroscan® device (Echosens, Paris, France) has been developed, using a novel proprietary algorithm called controlled attenuation parameter (CAP) [9]. This parameter is an estimate of the total ultrasonic attenuation (go-and-return path) at the central frequency of the regular or M probe of the Fibroscan® (3.5 MHz) and is expressed in decibel per meter (dB/m). CAP is evaluated using the same radio-frequency data and the same region of interest, as the region used to assess the liver stiffness (LS) [10].
- We aim to establish CAP performance in predicting each steatosis grade on a group of biopsied chronic liver diseases (CLD) patients.

**Methods and materials**

**Patients**

- 201 consecutive patients with different diffuse chronic liver disease (viral hepatitis C, viral hepatitis B, non-alcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis) examined in our department were prospectively included in this study.
- All of them underwent percutaneous liver biopsy for disease grading and staging.
- All patients were referred for CAP measurement, 1 day prior to liver biopsy.
- Apart from the epidemiological data, the following biological parameters were determined for all patients on the same day as the
CAP measurements: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transpeptidase (GGT), total bilirubin, alkaline phosphatase (AKP), platelet count, fasting blood glucose, fasting serum cholesterol and triglycerides.

- The exclusion criteria were: the evidence of ascites at physical or ultrasound examination (ascites is a physical limitation of the technique because elastic waves do not propagate through liquids) [11], other conditions associated with severe cholestasis or right heart failure - proven to influence the liver stiffness value [12, 13], pregnancy, malignancy or other terminal disease and a LB unsuitable for steatosis grading (when the LB specimen contained <6 portal tracts).

**CAP measurements using transient elastography**

- During the acquisition, patients were positioned in a dorsal decubitus position, with the right arm in maximum abduction. The Fibroscan transducer, covered with a drop of coupling gel, was placed perpendicularly on the intercostal space. Under TM and A-mode control, the operator chose a liver portion within the right lobe, free from any large vascular structure or the gallbladder. Then, the operator pressed the probe button to commence the measurement. The final CAP value considered for analysis was the median of 10 individual CAP values, regardless of the success rate (SR), and was expressed in dB/m (fig 1).
- The measurements were taken using the 3.5 MHz M probe, on which the CAP measurement software was installed, after an overnight fast.
- CAP was computed by the Fibroscan equipment software in an area located between 25 and 65 mm from the skin and in the same region the biopsy specimen was taken from in order to grade and stage the disease.

**Histological study**

- a liver biopsy was performed by using the TruCut technique with a 1.8 mm (14G) diameter automatic needle device - Biopty Gun (Bard GMBH, Karlsruhe, Germany).
- Liver fibrosis stage and necroinflammatory activity grade were evaluated according to the Metavir scoring system in all patients, except those with NASH, evaluated according to the Brunt system [14, 15].
- Fibrosis was staged on a 0-4 scale: F0-no fibrosis; F1-portal fibrosis without septa; F2-portal fibrosis and few septa; F3-numerous septa without cirrhosis; F4-cirrhosis (Metavir score in HCV and HBV patients) or F0-no fibrosis, F1-zone 3 perisinusoidal fibrosis, F2-as above with portal fibrosis, F3-as above with bridging fibrosis and F4-cirrhosis (Brunt score in NASH).
- Necroinflammatory activity was graded as: A0-none; A1-mild; A2-moderate; A3-severe. Lobular inflammation was graded on a 4-point scale on a 200 x field as: 0: no foci; 1: <2 foci; 2: 2-4 foci; and 3: >4 foci.
• Hepatocyte ballooning was graded as: 0: none; 1: occasional ballooned hepatocytes (mainly zone 3); 2: obvious zone 3 ballooning degeneration; 3: widespread ballooning.
• In all patients, steatosis was estimated by visual assessment as a percentage of hepatocytes with fatty accumulation; to be able to pool all patients, steatosis was converted into the following grading system: S0: steatosis in less than 10% of hepatocytes, S1: 11%-33%, S2: 34%-66% and S3: 67%-100% of hepatocytes. The histological type of steatosis was specified, as either pure macrovesicular, mixed (i.e. macrovesicular and microvesicular) or pure microvesicular.

**Statistical analysis**

• The statistical analysis was performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA) and MedCalc software version 12.4.0 (Mariakerke, Belgium).
• Categorical variables were presented as numbers and percentages and were compared using the #2 test. The continuous variables were expressed as mean value, standard deviation, median and range.
• Box plots were used to estimate the CAP distributions between each steatosis grade.
• The relationships between CAP and different histological parameters were characterized using the Spearman correlation coefficients. Variables reaching statistical significance (p<0.05) in univariate analysis were included into a multivariate logistic regression analysis in order to identify those that were independently associated with a certain factor.
• The diagnostic performance of CAP for steatosis prediction was assessed using sensitivity (Se), specificity (Sp), positive (PPV) and negative (NPV) predictive values, likelihood ratios (LR), accuracy (DA) and receiver operating characteristic (ROC) curves. The optimal CAP cut-off values were defined by maximizing the sum of sensitivity and specificity.
Fig. 1: Fibroscan's monitor with CAP and liver stiffness measurement.
Results

# Baseline characteristics of patients

- Of the 201 patients in the study, 118 (58.7%) had been diagnosed with HCV, 48 (23.88%) with HBV, 24 (23.88%) with NASH and 11 (5.47%) with other diffuse CLD (primary biliary cirrhosis, autoimmune hepatitis).
- The majority of patients were female (61.2%)
- Median age: 51 years.
- The median size of the liver biopsy specimens: 15 (12-20) mm

# Correlation between CAP and various histopathological parameters

- Of the histopathologic parameters, CAP correlated significantly only with steatosis ($r=0.568$, $p<0.0001$) and the steatosis type - macrovesicular, mixed or microvesicular - ($r=0.235$, $p=0.02$). No correlation was found between CAP and fibrosis ($r=0.019$, $p=0.8$ according to the Metavir scoring system in HCV and HBV patients, respectively $r=0.158$, $p=0.5$ according to the Brunt scoring system in NASH patients), activity ($r=0.003$, $p=0.9$), ballooning ($r=0.408$, $p=0.09$) or lobular inflammation ($r=0.034$, $p=0.9$).
- Among the histopathological factors correlating with CAP, the multivariate analysis showed that only steatosis influences independently CAP in CLD patients ($p<0.0001$), but not the steatosis type ($p=0.0889$).

# CAP performance in the assessment of steatosis in chronic liver diseases

- The distribution of CAP values for each steatosis grade is represented in Fig. 2. The median (range) CAP values (dB/m) according to the steatosis grades were: 212 (124-359) for S0; 266 (153-353) for S1; 304 (215-359) for S2 and 321 (218-377) for S3. The differences were statistically significant between all the steatosis grades, except S2 vs S3 (Fig. 2).
- Table IV shows the optimal cut-off values as well as the corresponding sensibility, specificity, positive and negative predictive values. Maximal diagnostic accuracy could be obtained for the prediction of #S2 and S3 (82.06%, respectively 81.59%) while, for the prediction of grades #S1, the accuracy reached only 76.11%.
- Fig. 3 shows the ROC curves according to three different steatosis grade thresholds. AUCs were 0.813 for #S1, 0.822 for #S2 and 0.838 for S3.
**Fig. 2:** Box plots of Controlled Attenuation Parameter values for each steatosis grade. The top and the bottom of the boxes are the first and third quartiles, respectively. The length of the box represents therefore the interquartile range including 50% of the values. The line through the middle of each box represents the median. The error shows the minimum and maximum values (range).
**Fig. 3:** Graphs show ROC curves for CAP for different steatosis thresholds: A: S0 vs S1-S3 (cut-off value 260 dB/m); B: S0-S1 vs S2-S3 (cut-off value 285 dB/m); C: S0-S2 vs S3 (cut-off value 294 dB/m).

**Table 1:** CAP cut-off values for the diagnosis of steatosis grades #S1, # S2 and #S3

<table>
<thead>
<tr>
<th>CAP cutoff value (dB/m)</th>
<th>S0 vs S123 (≥ S1)</th>
<th>S01 vs S23 (≥ S2)</th>
<th>S012 vs S3 (≥ S3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se (95% CI) (%)</td>
<td>64.84 (54.1-74.6)</td>
<td>69.70 (51.3-84.4)</td>
<td>83.33 (51.6-97.9)</td>
</tr>
<tr>
<td>Sp (95% CI) (%)</td>
<td>87.27 (79.6-92.9)</td>
<td>85.12 (78.8-90.1)</td>
<td>82.54 (76.4-87.7)</td>
</tr>
<tr>
<td>+LR (95% CI) (%)</td>
<td>5.09 (3.1-8.5)</td>
<td>4.68 (3.1-7.2)</td>
<td>4.77 (3.2-7.1)</td>
</tr>
<tr>
<td>-LR (95% CI) (%)</td>
<td>0.40 (0.3-0.5)</td>
<td>0.36 (0.2-0.6)</td>
<td>0.20 (0.06-0.7)</td>
</tr>
<tr>
<td>PPV (95% CI) (%)</td>
<td>80.8 (69.9-89.1)</td>
<td>47.9 (33.3-62.8)</td>
<td>23.3 (11.8-38.6)</td>
</tr>
<tr>
<td>NPV (95% CI) (%)</td>
<td>75 (66.5-82.3)</td>
<td>93.5 (88.3-96.8)</td>
<td>98.7 (95.5-99.8)</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>0.813 (0.75-0.86)</td>
<td>0.822 (0.76-0.87)</td>
<td>0.838 (0.78-0.88)</td>
</tr>
<tr>
<td>DA (%)</td>
<td>76.11</td>
<td>82.08</td>
<td>81.59</td>
</tr>
</tbody>
</table>
Conclusion

- CAP is a non-invasive method for the assessment of steatosis in chronic liver diseases patients with a diagnosis accuracy of 76.11 - 82.06% and it is independently influenced only by steatosis amount.
- CAP could be an useful clinically tool especially to exclude significant steatosis grades, with a negative predictive value of 93.5-98.7%.
- Nevertheless, other prospective studies conducted on large groups of patients with different chronic liver diseases are mandatory in order to accurately establish CAP performance for steatosis assessment according to the etiology of liver disease, which technical parameters should be met to ensure a high-quality examination and which factors may influence the accuracy of steatosis evaluation using this method.

Personal information

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