Spectral Dampness on Hepatic Vein Doppler according to Clinical stages of the Acute Hepatitis A Patients: Comparison to the Laboratory Findings

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Purpose

Acute viral hepatitis induced by hepatitis A virus (HAV) infection may occur sporadically or epidemically, especially in the developing countries. The HAV infection is commonly transmitted via the fecal-oral route, and the exposure to HAV infection provides the immunity for this disease, unlike hepatitis B or C virus infection. However, because many people who live in the developed countries do not have an anti-HAV IgG antibody, the outbreak of this disease can be possible in the area which rapidly makes economic development, like South Korea. As is well known, the prodromal symptoms by the HAV infection occurs after about 4 weeks of the incubation period, and followed by clinical jaundice. Then, the serum bilirubin level usually diminishes within 2 week. According to some recent studies (1-3), the necro-inflammation of hepatocytes and cholestasis due to acute viral hepatitis could influence on the stiffness of the liver parenchyma, so high value of elasticity was measured on the transient elastography in these patient with high serum levels of alanine aminotransferase and bilirubin. Hepatic vein Doppler study could also represent liver stiffness by acute viral hepatitis through change in vascular compliance (4), and the authors said that the wave pattern of hepatic venous flow was flattened monophasically in the patient with acute viral hepatitis. Accordingly, the purpose of this study is to investigate the relationship between damping indices (DI) on the hepatic vein Doppler ultrasonography and the clinical stages in the hepatitis A patients.
Methods and Materials

Subject

Thirty-nine consecutive patients who were serologically proven as hepatitis A infection from August 2009 to January 2010 were enrolled. Their mean age was 30.7 ± 6.2 years, and the ratio between males and females was 24 to 15. All patients of the subject took serum biochemical tests including serum alanine transaminase (ALT) and total bilirubin on admission, and also took an ultrasonography with Doppler study in several days after admission (mean interval between the first laboratory test and ultrasonography, 2.13 ± 1.81 days; range 0-10 days). The blood tests were repeated daily or every other day during acute inflammatory stage with high level of ALT and the interval was lengthened to 1 week. Average of the number of laboratory tests per patient during admission was 4.79 ± 1.42 times (range, 2-7 times), and mean interval between the first and last laboratory tests was 11.33 ± 7.38 days (range, 2-37 days). The period from onset of prodromal symptoms (e.g. fever, malaise, muscle pain) to ultrasonographic exam was 6.90 ± 3.57 days (range, 3-21 days) except one patient who did not remember the onset of prodromal symptoms. The demographic characteristics about subject were summarized in Table 1 on page 5.

Doppler Ultrasonographic Examination

All grayscale and hepatic venous Doppler US examinations were performed by one radiologist (W.K.J), and the patients were examined after they had fasted for at least six hours. The examinations were performed in a supine position using an iU22 ultrasound system (Philips Medical System, Bothell, WA) with a 5-1-MHz convex-array transducer placed intercostally. Doppler waveforms were obtained at a Doppler angle of less than 60°, and from the proximal right hepatic vein within 3cm from the IVC (5). Doppler waveforms of the right hepatic vein were obtained repeatedly at expiration and inspiration without suspending respiration. To obtain the Doppler waveforms, the following protocol was used. The examiner asked the patient to breathe in to the end-inspiration, and checked the location of the right hepatic vein on the US. Then, the sample volume, which was adjusted to about 1-2 cm, was located on the target (the specific site of the right hepatic vein) and the transducer was fixed at the intercostal level. Next, the examiner asked the patient to breathe regularly and fully so that the sample volume covered the hepatic vein repeatedly during full inspiration. In the case of the expiratory phase, we asked the patient to breathe out to the end-expiration and moved the transducer to the optimal intercostal space, then obtained the waveform during expiration in the same manner as for inspiration. All hepatic vein Doppler waveforms were recorded in triplicate.

Hepatic Vein Damping Index
We measured the maximum ($V_{\text{max}}$) and minimum velocities ($V_{\text{min}}$) of systolic hepatofugal flow according to respiratory phase (6,7) (Fig. 2 on page 5) and used the mean of three consecutive measurements as the representative value. The duration of the waveform obtained was relatively short, especially the inspiratory one, because the Doppler study was performed during free respiration; hence we selected the waveform at the center of the waveforms obtained with the most obvious wave margin. The damping index (DI) of the hepatic vein was defined as the ratio of the minimum velocity to the maximum velocity of the retrograde systolic wave ($DI = V_{\text{min}}/V_{\text{max}}$), as proposed previously (7) (Fig. 3 on page 5). We considered certain Doppler US parameters derived from the DIs at expiration and inspiration, such as the difference (#DI) and sum of DIs (#DI), as estimates of changes in vascular compliance in the hepatic vein, and these were calculated using the following formulae: #DI = DI_{\text{insp}} - DI_{\text{exp}}, and #DI = DI_{\text{exp}} + DI_{\text{insp}}.

**Correlation with Laboratory findings and Clinical Stages of Acute Hepatitis A**

The Doppler parameters including $DI_{\text{exp}}$, $DI_{\text{insp}}$, #DI and #DI were correlated with the results of laboratory tests on the ultrasonography levels: serum ALT level as well as serum total bilirubin. As a statistical analysis, Pearson's correlation test was used. Clinically, acute hepatitis was classified into three stages: pre-icteric (necroinflammatory), icteric (bilirubin $\geq$ 5 mg/L after surge of ALT level), and recovery phases (bilirubin < 5 mg/L) (Fig. 4 on page 6), and investigated the relationship with Doppler. Used statistical method was an analysis of variation (ANOVA) test and a post hoc test was also performed by Tukey HSD method. $P$-values of less than 0.05 were considered statistically significant.
Table 1. Characteristics of the subject

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.7 ± 6.2 years</td>
</tr>
<tr>
<td>Sex (Male : Female)</td>
<td>24 : 15</td>
</tr>
<tr>
<td>Interval from onset of prodromal symptom to US</td>
<td>6.90 ± 3.57 days</td>
</tr>
<tr>
<td>Interval between the first laboratory exam to US</td>
<td>2.13 ± 1.81 days</td>
</tr>
<tr>
<td>Follow-up times of laboratory exams</td>
<td>4.79 ± 1.42 times</td>
</tr>
<tr>
<td>Interval between the first and last laboratory exams</td>
<td>11.33 ± 7.38 days</td>
</tr>
</tbody>
</table>

Fig. 0: Table 1. Characteristics of the subject

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Fig. 0: Changes of DI between inspiration phase and expiration phase without breath hold.

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**Fig. 0:** Measurement of damping index (DI) of hepatic vein waveform. DI = the minimum velocity / maximum velocity of the systolic hepatic vein wave.

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**Fig. 0:** Clinical stages of acute hepatitis A. the red line indicates the change of serum ALT level, and the yellow line does the change of serum total bilirubin level.

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Results

Correlation with Laboratory Findings of Acute Hepatitis A

Mean values of peak ALT and total bilirubin level were 3,221 ± 2,229 IU/L and 7.82 ± 4.32 mg/L, respectively. Mean values of ALT and total bilirubin level on the US were 2,358 ± 1,663 IU/L and 4.56 ± 2.26 mg/L, respectively. The level of serum ALT on the US was moderately correlated with $\text{DI}_{\text{exp}}$ ($r=0.330$) and $\#\text{DI}$ ($r=0.343$) with statistical significances (p-values, .040 and .032, respectively) (Fig. 1-2). However, $\text{DI}_{\text{insp}}$ and $\#\text{DI}$ were not correlated with ALT level ($r=0.293$ and 0.065; p-values, .070 and .693, respectively). In the other hand, serum total bilirubin level on the US was moderately correlated with $\text{DI}_{\text{insp}}$ ($r=0.389$; p-value=.014) and $\#\text{DI}$ ($r=0.440$; p-value=.005) significantly (Fig. 3-4), but $\text{DI}_{\text{exp}}$ and $\#\text{DI}$ were not correlated with total bilirubin level ($r=0.063$ and 0.278; p-values, .705 and .087, respectively) (Table 2 on page 12).

Correlation with Clinical Stages of Acute Hepatitis A

According to the clinical stages of acute hepatitis A, there were 19 patients (48.7%) on pre-icteric phase, 16 patients (41.0%) on icteric phase, and 4 patients (10.3%) on recovery phase. The mean values of $\text{DI}_{\text{insp}}$, $\#\text{DI}$, and $\#\text{DI}$ were significantly different among three clinical stage (p-value=.005, .025 and .029, respectively)(Fig. 6-8), but $\text{DI}_{\text{exp}}$ and were not different significantly (p-value= .352). Looking into the result of post hoc test of $\text{DI}_{\text{insp}}$, $\#\text{DI}$, and $\#\text{DI}$, all of the mean values of $\text{DI}_{\text{insp}}$, $\#\text{DI}$, and $\#\text{DI}$ were significantly different both between pre-icteric and icteric phase (p-value=.004, .022, and .023), but there was no significance of the difference between icteric and recovery phase (p-value=.222, .311, and .470) (Table 3 on page 16).
Fig. 0: Correlation between expiratory DI (Diexp) during respiratory phase and serum ALT. *, p

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Fig. 0: Correlation between sum of DIs (#DI) during respiratory phase and serum ALT. * p

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**Fig. 0:** Correlation between inspiratory DI (DInsp) during respiratory phase and serum bilirubin. *, p

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Fig. 0: Correlation between difference of DIs (#DI) during respiratory phase and serum bilirubin. *, p

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<table>
<thead>
<tr>
<th>Laboratory findings on US examination</th>
<th>Correlation coefficient (r)</th>
<th>( \text{DI}_{\text{insp}} )</th>
<th>( \text{DI}_{\text{exp}} )</th>
<th>( \Sigma \text{DI} )</th>
<th>( \Delta \text{DI} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>( r )</td>
<td>0.293</td>
<td>0.330</td>
<td>0.343</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>( \text{P-value} )</td>
<td>.070</td>
<td>.040</td>
<td>.032</td>
<td>.693</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>( r )</td>
<td>0.389</td>
<td>0.063</td>
<td>0.278</td>
<td>0.440</td>
</tr>
<tr>
<td></td>
<td>( \text{P-value} )</td>
<td>.014</td>
<td>.705</td>
<td>.087</td>
<td>.005</td>
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</table>

**Fig. 0**: Table 2. Correlation coefficients between hepatic venous Doppler parameters and ALT and bilirubin levels

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**Fig. 0:** A box-and-whisker plot of means of inspiratory DI. *, p

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**Fig. 0:** A box-and-whisker plot of means of #DI. *, p

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**Fig. 0:** A box-and-whisker plot of means of #DI. *, p

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<table>
<thead>
<tr>
<th>Clinical stages</th>
<th>Mean value of Doppler parameters</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DI_{insp}</td>
<td>DI_{exp}</td>
<td>\Sigma DI</td>
<td>\Delta DI</td>
</tr>
<tr>
<td>Pre-icteric stage</td>
<td>0.30 ± 0.28</td>
<td>0.13 ± 0.23</td>
<td>0.43 ± 0.48</td>
<td>-0.16 ± 0.20</td>
</tr>
<tr>
<td>Icteric stage</td>
<td>0.61 ± 0.23</td>
<td>0.24 ± 0.21</td>
<td>0.84 ± 0.38</td>
<td>-0.37 ± 0.22</td>
</tr>
<tr>
<td>Recovery stage</td>
<td>0.36 ± 0.33</td>
<td>0.13 ± 0.10</td>
<td>0.48 ± 0.39</td>
<td>-0.23 ± 0.28</td>
</tr>
<tr>
<td>(P)-value (pre-icteric vs. icteric)</td>
<td>.004*</td>
<td>.351</td>
<td>.022*</td>
<td>.023*</td>
</tr>
<tr>
<td>(P)-value (icteric vs. recovery)</td>
<td>.222</td>
<td>.664</td>
<td>.311</td>
<td>.470</td>
</tr>
</tbody>
</table>

**Fig. 0:** Table 3. Results of comparison of means among clinical stages. *, p

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Conclusion

On the icteric phase, the damping index of hepatic venous flow tends to be increased. Serum ALT and bilirubin might be moderately correlated with derivatives of hepatic vein damping index.
References


Personal Information

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