Intrahepatic blood flow assessment by Doppler ultrasonography: relationship among hepatic vein, portal vein, hepatic artery and portal pressure intraoperatively measured in patients with portal hypertension

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Abstract

Background: Abnormality of hepatic vein (HV) waveform evaluated by Doppler ultrasonography has been widely studied in patients with chronic liver disease. The paper investigates the relationship between HV waveform changes, portal vein velocity (PVVel), hepatic artery pulsatility index (HAPI) and portal pressure (PP) measured directly from patients with portal hypertension (PHT), aiming to discuss the cause of abnormal HV waveform.

Methods: Sixty patients who had been clinically diagnosed with PHT and accepted surgical therapy, were investigated. PP was measured intraoperatively. HV waveform was categorized as triphasic, biphasic and monophasic. Two Doppler features PVVel and HAPI were measured and compared with both HV waveform changes and PP.

Results: In patients group, the Doppler flow waveform in middle HV was triphasic in 31.6%, biphasic in 46.7%, monophasic in 21.6%. These figures were 88%, 8%, 2% respectively in healthy subjects. With the flattening of HV waveform, PP and HAPI increased significantly ($r = 0.579$, $r = 0.438$, respectively, $p < 0.0001$), while PVVel decreased significantly ($r = -0.44$, $p < 0.0001$). PP in patients with monophasic HV waveform was significantly higher than those with biphasic and triphasic waveform ($p = 0.004$, $p = 0.003$ respectively). The significant difference was similar for PVVel ($p = 0.007$, $p < 0.0001$). HAPI in patients with abnormal HV waveforms (monophasic or biphasic) was much higher than those with normal HV waveform ($p = 0.001$, $p = 0.022$, respectively).

Conclusion: In patients of PHT, monophasic HV waveform indicates higher portal pressure, even measured directly from the portal venous system. The change trends that flattening of HV waveform accompanied by the increase of HAPI and decrease of PVVel support the inference that parenchymal fibrosis and fat infiltration reduce HV compliance being the cause of the abnormality of Doppler HV waveform from one perspective.

Background

Hepatic vein (HV) is the only draining vessels in liver, which has two supplying vessels, from liver sinus to the inferior vena cava (IVC). The thin-walled veins are anechoic under ultrasonographic scanning, have no valves, and can be distinguished from the portal veins. The spectrum of HVs can reflect changes of blood flow through tricuspid valve during the cardiac cycle leading to pulsatile changes of spectrum. The normal waveform of HVs is triphasic pattern with two hepatofugal phases related to atrial and ventricular diastole, and a short phase of retrograde (hepatopetal) flow caused by the pressure increase in the right atrium at atrial systole. With the increased stiffness of the liver parenchyma, especially around the HVs, hepatic waveform became decreased pulsatile with no retrograde flow, or even to a flat wave form eventually [1-3]. However, the exact cause of abnormality in HVs is still a controversial issue. A study suggested that terlipressin-induced improvement in the waveforms can be counted as a evidence that a hemodynamic effect of high portal pressure rather than a fixed structural abnormality was the pathogenic mechanism responsible [4]. Thus, the purpose of this study was to discuss the cause of HV
waveform changes by evaluating the relationship among changes of intrahepatic
blood flow and portal pressure (PP) measured intraoperatively in patients with portal
hypertension (PHT).

Methods

Patients

Sixty patients with PHT without hepatocellular carcinomas and portal
thrombosis referred to the Division of the Fourth Military Medical University Tangdu
Hospital for surgical portosystemic shunts therapy from Aug 2008 to Jan 2010. The
control group consisted of 30 healthy volunteers (22 men and 8 women) with no
history of chronic liver disease and normal liver function tests. The severity of
cirrhosis was graded according to Child-Pugh classification [5]. All subjects were
included in the study provide informed consent to participate. The study was
approved by the ethics committee of our institution.

Doppler ultrasound

Doppler ultrasonographic examinations were conducted with Acuson Sequire
512 (Siemens Acuson Co., Mountain View, California) and a 3.5 MHz phased array
transducer. All patients and control subjects fasted overnight. Considering that the
respiration manoeuvres can alter the HV flow patterns [6, 7], measurements of the
parameter were made during suspended respiration. We selected the middle HV as the
measuring object as results of the most consistent triphasic flow in healthy people and
the most favorable Doppler angle. The Doppler gate was placed in the vessel at a
point 2–3 cm away from the IVC to measure HV waveform. HV waveforms were
classified as triphasic (reversed flow in at least one phase), biphasic (no reversed flow
and with or without decreased phasic oscillation), or monophasic (flat and with or
without fluttering).

Velocity measurements were conducted at an angle between 30 and 60 degrees.
The mean velocity of portal vein (PVVel) and hepatic artery pulsatility indexes (HAPI)
were calculated automatically by the machine after the waveform trace for three
cardiac cycles. In order to minimize variation and errors, all parameters were
measured by the same observer on the same machine and were calculated as the mean
of three consistent measurements.

Measurement of PP

During the operation, the right gastroepiploic vein was isolated and catheterized
by a pressure gauge to measure the PP by an experienced surgeon, who had no
knowledge of the Doppler results. A liver biopsy was sampled during the surgical
operation. Morphologic changes of the liver were determined during the operation.

Statistical analysis

Results were given as mean ± standard deviation. The results in patients with
PHT and healthy controls were compared using an analysis of variance (ANOVA).
Linear regression analysis was used to assess the correlations among all parameters.
Results were considered significant at \( p < 0.05 \).

Result
The average PP measured directly from the right gastroepiploic vein was 30.02 ± 3.81 mmHg. The main clinical and pathological data for the patients at the beginning of the study was presented at Table 1.

Among 60 patients, the Doppler flow waveform in middle hepatic vein was triphasic in 19 (31.6%), biphasic in 28 (46.7%), monophasic in 13 (21.6%) as Figure1 showed. The flow pattern was triphasic in 22 (88%), biphasic in 2 (8%), and monophasic in 1 (4%) among control subjects. The distribution of the HV flow pattern according to the PP was summarized in Table 2. The statistical results showed that there was no significant correlation between HV waveforms and Child-Pugh scores. PP in patients with monophasic HV waveform was much higher than those with biphasic and triphasic waveforms (p = 0.004 and p = 0.003 respectively), while no significant difference was found between patients with biphasic and triphasic flow pattern (29.39 ± 3.40 vs. 28.94 ± 3.36, p = 0.673). Additionally, a significant linear correlation was found between HV waveforms and PP with r = 0.579 (p< 0.0001).

Although PVVel was slightly lower in patients with PHT compared with healthy controls (15.08 ± 4.12cm/s vs.17.14 ± 3.46cm/s), no statistical significance was observed (p = 0.114), and no significant correlation was observed between PVVel and PP (p =0.597). However, PVVel in patients with monophasic pattern (11.82 ± 3.91 cm/s) decreased significantly compared with biphasic and triphasic patterns (15.33 ± 3.63cm/s, p = 0.007 and 16.96 ± 3.76cm/s, p <0.0001) (Fig 2). Furthermore, PVVel was inversely related with HV waveform (r = -0.44, p < 0.0001).

Statistical analysis also revealed that HAPI in patients with monophasic and biphasic waveforms was significantly higher than that in patients with triphasic waveform (p = 0.001, p = 0.022 respectively) (Fig 3), and significant linear correlations existed both between HAPI and HV waveforms (r = 00.438, p < 0.0001), HAPI and PP (r = 0.427, p = 0.001). On average, HAPI in patients group was much higher compared with that in healthy group (1.63 ± 0.48 vs. 1.166±0.182, p < 0.0001).

Discussion

In patients with chronic liver disease, various studies have been designed for grading evaluation the severity of liver abnormality [8-10] by Doppler ultrasound display. Hepatic vein flow pattern is one of the interests. Three grades hepatic waveforms described by Bolondi et al [11] to indicate the changes from the normal triphasic form to the flat pattern was widely used in previous studies of chronic liver disease [11-13]. Nowadays, more researches were performed to determine whether HV waveform analysis might be useful in the assessment of portal hypertension [8, 14]. In our study, we suggest that an abnormal HV Doppler curve may be a non-specific indicator of liver abnormality, also of PP in PHT patients. Furthermore, an increased stiffness of the liver parenchyma around the HVs was believed to contribute to HV waveform changes by comparing the heamodynamic changes of portal vein and hepatic artery.

Even though measurement of hepatic venous pressure gradient (HVPG) has been accepted as the gold standard for assessing the degree of portal hypertension, because of its invasiveness, it is not suitable for widespread routine clinical use [15–17].
Additionally, in presence of an increased pre-sinusoidal resistance during cirrhotic process, the portal venous pressure can be higher than the wedged hepatic venous pressure [18]. Because of these limitations of HVPG, our study is the first to compare HV waveforms with PP measured directly in portal venous system.

Differed from other results [13,19], the HV waveforms in healthy group also presented three types of flow patterns in our study, while the triphasic HV waveform was in the majority (88%). The only one person who presented monophasic waveform in HV had a much higher triglyceride (TG, 8.56 mmol/L) in the following blood lipid test, might being the cause. The other two persons with biphasic HV waveform had normal lipid profile. In patients with PHT, monophasic HV waveform meant a higher PP, a lower PVVel, and a higher hepatic artery resistance. Hence, flattening change tendency of the HV waveform in patients with PHT indicated a high likelihood of severe portal hypertension and liver stiffness. Of these parameters, HAPI seemed more sensitive to reflect abnormal HV waveforms.

To our knowledge, the exact cause of the changes in the Doppler HV waveform remains unclear. Some investigators have suggested that parenchymal fibrosis and fat infiltration surrounding the hepatic vein wall compress the thin wall and reduced its compliance can be reason [20, 21]. Others think that the pathogenic mechanism causing intrahepatic shunts is responsible for the abnormal waveforms [4, 22]. Two hemodynamic parameters PPVel and HAPI were also assessed in the present study aiming to discuss the mechanism of HV waveform changes. The results showed that the more flatten the HV waveform was, the lower the PVVel and the higher the HAPI became. From our point of view, intrahepatic shunts either from hepatic artery to HV, or from portal vein to HV would cause increased inflow in HV in one hand, while in the other hand, draining by HV through vascular shunts could also decrease the vascular resistance of supplying vessels, consequently leading to an increased velocity in portal vein and a decreased resistance in hepatic artery. However, PVVel and HAPI measured in the study were opposite to the theory. We also attempted to find some correlations between the architectural distortion and HV waveform changes according to a study reporting that patients with small nodules had higher PP [23]. We observed that most of the liver has small nodules in PHT patients, but HV waveform changes was not correlated significantly with this pathological change.

In conclusion, HV waveform changes in patients with PHT can indicate severity of PP to a certain degree. Taking all the intrahepatic hemodynamic changes under PHT into account might provide some information on the HV abnormal waveform mechanism investigation. The study still had several limitations. First, we did not perform echocardiography and X-ray examinations for exclusion of subjects with heart and pulmonary diseases, especially causing the right heart dysfunction. Second, the confirmation of liver disease by liver biopsy was not performed in healthy subjects for ethical reasons. Hence, we could not explain exactly why there were abnormal HV waveforms in control group, only attributed the abnormality to the abnormal blood lipid profile. Follow-up studies are needed to expand the exclusive criteria to all disease causing right heart dysfunction for further validation above Doppler features.
Abbreviations

HV, hepatic vein; IVC, inferior vena cava; PP, portal hypertension; PPVel, portal
vein velocity, HAPI, hepatic artery pulsatility index; PP, portal pressure; HVGP,
hepatic venous pressure gradient

Competing interests
The author(s) declare that they have no competing interests.

Authors’ contributions
LZ performed the ultrasound examination and data analysis. JKY was the surgeon
measured portal pressure. YYD designed the studies. TSC edited the paper.

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Table 1: Clinical characteristics of 60 patients with PHT

<table>
<thead>
<tr>
<th>Patients characteristics</th>
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<tbody>
<tr>
<td>Age (median/range)</td>
<td>47(26-59)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>14/46</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>22/30/8</td>
</tr>
<tr>
<td>Nodularity (small/mixed/large)</td>
<td>41/11/8</td>
</tr>
<tr>
<td>PP (mean±SD)</td>
<td>30.02±3.81mmHg</td>
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</table>

Table 2 Distribution of the HV flow pattern according to the PP

<table>
<thead>
<tr>
<th>HV waveform</th>
<th>Number</th>
<th>%</th>
<th>PP (mmHg)</th>
<th>Significance of PP comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>triphasic</td>
<td>19</td>
<td>32%</td>
<td>28.95±3.36</td>
<td>*p=0.003</td>
</tr>
<tr>
<td>biphasic</td>
<td>28</td>
<td>54%</td>
<td>29.39±3.40</td>
<td></td>
</tr>
<tr>
<td>monophasic</td>
<td>13</td>
<td>14%</td>
<td>32.92±4.05</td>
<td>*p=0.004</td>
</tr>
</tbody>
</table>

Fig 1 HV waveform patterns in patients with PHT. Triphasic pattern (two antegrade waves below the baseline and one presystolic retrograde wave above the baseline). Biphasic pattern with absent reversed pre-systolic wave. Monophasic with a flat pattern.

Fig 2 Comparison of the PVVel among different HV waveforms

Fig 3 Comparison of the HAPI among different HV waveforms
Figure 1

- Triphasic
- Biphasic
- Monophasic
Figure 3

The box plot compares the HAPI values across three groups: Triphasic, Biphasic, and Monophasic. The HAPI values are as follows:

- Triphasic: 1.37 ± 0.33
- Biphasic: 1.67 ± 0.46
- Monophasic: 1.93 ± 0.48

Statistical significance is indicated by the p-values:

- Triphasic vs. Biphasic: p < 0.001
- Triphasic vs. Monophasic: p = 0.022
- Biphasic vs. Monophasic: Not statistically significant