Quantitative Diagnosis of Early-Stage Liver Cirrhosis* with Contrast-Enhanced Ultrasound – A Clinical Study

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Abstract
Objectives. To investigate the quantitative diagnosis value of contrast-enhanced ultrasound (CEUS) for early-stage liver cirrhosis.

Material and Methods. A total of 15 healthy subjects and 15 patients with cirrhosis were recruited into the present study, and the hepatic artery, portal vein, hepatic vein and liver parenchyma were dynamically monitored under ultrasonography and then qualified with the QLAB time-intensity curve to obtain the arriving time (AT) and the peak time (PT) of the hepatic artery, portal vein, hepatic vein and liver parenchyma. The hepatic artery to hepatic vein transit time (HA-HVTT = HVAT-HAAT) and portal vein to hepatic vein transit time (PV-HVTT = HVAT-PVAT) were calculated.

Results. The AT of the hepatic vein was significantly shorter than that in controls (P < 0.01); the HA-HVTT and PV-HVTT in cirrhosis patients were also significantly shorter than those in controls (P < 0.01). However, the PT in patients was significantly prolonged when compared with controls (P < 0.05).

Conclusions. The AT of the hepatic vein, the transit time of the liver and the PT of liver parenchyma can be used as non-invasive indicators in the quantitative diagnosis of early-stage liver cirrhosis (Adv Clin Exp Med 2012, 21, 3, 385–390).

Key words: ultrasonography, contrast agent, liver cirrhosis.

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Liver fibrosis is a reversible process in the early development of chronic liver diseases. Therefore, early diagnosis and dynamic monitoring of liver fibrosis may significantly improve the prognosis of chronic liver diseases. No pronounced morphological changes are noted in the early stage of liver cirrhosis, which renders a great challenge in the early imaging diagnosis of liver cirrhosis. It has been shown that there are alterations in the hemodynamics in early-stage liver cirrhosis [1]. Conventional ultrasonography cannot identify the changes in hemodynamics which significantly compromises the sensitivity and specificity of ultrasound in the diagnosis of early-stage liver cirrhosis. With the development of contrast-enhanced ultrasound (CEUS) technology, an ultrasound contrast reagent has been applied in the evaluation of perfusion in organs which may mirror the changes in microcirculation and hemodynamics in early-stage liver cirrhosis to achieve accurate early diagnosis of early-stage liver cirrhosis. In the present study, a series of dynamic parameters of the hepatic artery, hepatic vein, portal vein and liver parenchyma were determined under CEUS to evaluate the microcirculation in early-stage liver cirrhosis and explore the role of these parameters in the diagnosis of early-stage liver cirrhosis.

**Material and Methods**

**Patients and Grouping**

A total of 15 healthy subjects (8 males and 7 females) with a mean age of 44.9 years (range: 28~48 years) were selected in the control group. A total of 15 patients with suspected liver cirrhosis (11 males and 4 females) with a mean age of 55.4 years (range: 31~62 years) were recruited from the Department of Gastroenterology from November 2008 to July 2009 as the liver cirrhosis group. Among them, there was 1 patient with drug-induced liver cirrhosis, 2 patients with alcoholic cirrhosis, 11 patients with posthepatitis B cirrhosis and 1 patient with posthepatitis C cirrhosis. Liver cirrhosis was pathologically proved to be at the early stage.

**Ultrasound Equipment and Contrast Agent**

The Philips IU22 Ultrasonic Diagnostic Apparatus with a diagnostic probe frequency of 3.5~5.0 MHz and mechanical index (MI) of 0.8 was used in this study. The ultrasound contrast reagent (SonoVue; Bracco, Italy) contains the active substance sulphur hexafluoride (SF6) wrapped by phospholipids. Before use, the SonoVue was dissolved in 5 ml of normal saline followed by vortex mixing. Then, 2.4 ml of SonoVue solution (5 mg/ml) was rapidly infused through the cubital vein followed by rapid infusion of 5 ml of normal saline. The VCD and internal station were used to detect immediately after infusion. If necessary, a second infusion was carried out 15 min later.

**Ultrasonography**

Conventional two-dimensional ultrasound was used to scan the liver. The morphology of the liver and its capsule, echo of liver parenchyma as well as the intrahepatic vessels were detected. Then, color Doppler ultrasound was used to detect the flow rate of the hepatic artery, portal vein and hepatic vein followed by achieving a preliminary diagnosis. The location of the probe was adjusted to obtain a favorable image of the right liver lobe in which the hepatic artery, portal vein and hepatic vein can be identified. Then, the mode was switched to CEUS followed by infusion of the contrast. The hepatic artery, portal vein, hepatic vein and liver parenchyma were dynamically monitored, and all images were stored for use.

**Data Acquisition**

The data was analyzed by 2 ultrasound practitioners independently. The changes were dynamically analyzed with the software (QLAB-intensity curve). The arriving time (AT) and peaking time (PT) of the hepatic artery, portal vein and liver parenchyma were determined under CEUS to evaluate the microcirculation in early-stage liver cirrhosis and explore the role of these parameters in the diagnosis of early-stage liver cirrhosis.

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**Statistical Analysis**

Statistical analysis was carried out with SPSS 11.0 statistical software and qualitative data was presented as and analyzed with a paired t test. A value of P < 0.05 was considered statistically significant.

**Results**

There were no significant differences in the ATs of the hepatic artery and portal vein (Figure 1
In the cirrhosis patients, the AT of the hepatic vein was significantly shorter than that in the controls ($P < 0.01$) (Table 1 and Figure 3). The HA-HVTT and PV-HVTT in cirrhosis patients were markedly shorter than those in controls ($P < 0.01$) (Table 2 and Figure 4). However, there were no significant differences in the PTs of the hepatic artery, portal vein and hepatic vein between the two groups. Moreover, the PT of the liver parenchyma was markedly prolonged in cirrhosis patients when compared with controls ($P < 0.05$) (Table 3).
Table 1. ATs in cirrhosis patients and healthy controls (x ± s)

Tabela 1. AT u chorych na marskość wątroby i w grupie kontrolnej

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=) (Grupa kontrolna)</th>
<th>Patient group (n=) (Grupa badana)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic artery(s) (HAAT)</td>
<td>14.66 ± 1.90</td>
<td>14.84 ± 4.00</td>
<td>0.145</td>
<td>0.881</td>
</tr>
<tr>
<td>(Tętnica wątrobowa)</td>
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</tr>
<tr>
<td>Portal vein(s) (PVAT)</td>
<td>18.59 ± 3.45</td>
<td>20.49 ± 5.71</td>
<td>0.989</td>
<td>0.336</td>
</tr>
<tr>
<td>(Żyła wrotna)</td>
<td></td>
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</tr>
<tr>
<td>Hepatic vein(s) (HVAT)</td>
<td>29.00 ± 3.81</td>
<td>21.58 ± 4.18*</td>
<td>4.544</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: *P < 0.01 vs controls.  *P < 0,01 vs grupy kontrolnej.

Fig. 4. A) Time-intensity curve after infusion of ultrasound contrast in controls; B) Time-intensity curve after infusion of ultrasound contrast in cirrhosis patients (yellow: hepatic artery; red: portal vein; green: hepatic vein)

Ryc. 4. A) Krzywa zależności intensywności od czasu po podaniu kontrastu ultrasonograficznego w grupie kontrolnej, B) krzywa zależności intensywności od czasu po podaniu kontrastu ultrasonograficznego u chorych na marskość (żółty: tętnica wątrobowa; czerwony: żyła wrotna; zielony: żyła wątrobowa)

Table 2. Transit time in cirrhosis patients and healthy controls (x ± s)

Tabela 2. Czas przejścia u chorych na marskość wątroby i w grupie kontrolnej

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=) (Grupa kontrolna)</th>
<th>Patient group (n=) (Grupa badana)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA-HVTT</td>
<td>14.34 ± 2.66</td>
<td>6.74 ± 2.34*</td>
<td>7.431</td>
<td>0.000</td>
</tr>
<tr>
<td>PV-HVTT</td>
<td>10.41 ± 3.49</td>
<td>5.65 ± 3.31*</td>
<td>3.427</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Note: *P < 0.01 vs controls.  *P < 0,01 vs grupy kontrolnej.

Table 3. PTs in cirrhosis patients and healthy controls (x ± s)

Tabela 3. PT u chorych na marskość wątroby i w grupie kontrolnej

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=) (Grupa kontrolna)</th>
<th>Patient group (n=) (Grupa badana)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic artery(s) (HAPT)</td>
<td>26.75 ± 7.80</td>
<td>28.19 ± 7.92</td>
<td>0.346</td>
<td>0.732</td>
</tr>
<tr>
<td>(Tętnica wątrobowa)</td>
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<tr>
<td>Portal vein(s) (PVPT)</td>
<td>35.35 ± 6.80</td>
<td>35.02 ± 10.70</td>
<td>0.153</td>
<td>0.879</td>
</tr>
<tr>
<td>(Żyła wrotna)</td>
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<tr>
<td>Hepatic vein(s) (HVPT)</td>
<td>45.71 ± 7.71</td>
<td>43.02 ± 11.10</td>
<td>0.576</td>
<td>0.056</td>
</tr>
<tr>
<td>(Żyła wątrobowa)</td>
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<tr>
<td>Liver parenchyma (Mp. wątrobo)</td>
<td>34.01 ± 7.57</td>
<td>45.55 ± 7.6Δ</td>
<td>2.508</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Note: P < 0.05 vs. controls.  *P < 0,05 vs grupy kontrolnej.
Discussion

When diffuse lesions occur in the liver, the clinical manifestations are difficult to identify due to the potent compensation of liver function. Traditionally, ultrasound practitioners diagnose liver fibrosis according to changes in two-dimensional images and hemodynamics. However, two-dimensional ultrasound cannot be used to quantitate liver fibrosis and hemodynamics is frequently affected by several factors [2–4]. Therefore, the sensitivity and specificity of two-dimensional ultrasound are poor in the diagnosis of early-stage liver cirrhosis. Liver biopsy is the gold standard in the diagnosis of liver fibrosis and cirrhosis. However, liver biopsy is invasive and has poor repeatability limiting its wide application. With the development of CEUS technology, numerous clinical studies have shown application of ultrasound contrast can reflect the perfusion. Therefore, researchers have applied CEUS in the evaluation of microcirculation in early-stage liver cirrhosis, which may be beneficial for the early diagnosis of liver cirrhosis [5].

Albercht et al. [6] applied the transit time of ultrasound contrast reagent in the diagnosis of liver cirrhosis. In their study, the time to the signal of contrast in the hepatic vein of less than 24 seconds had a sensitivity of 100% and specificity of 96% in the diagnosis of liver cirrhosis. In the present study, the ATs of the hepatic vein in controls and patients were 29 seconds and 21 seconds, respectively. The analysis showed the AT of the hepatic vein in cirrhosis patients was significantly shorter than that in controls, which was consistent with the study mentioned above.

Hirota et al. [7] divided 40 patients into a non-cirrhosis group and a compensated cirrhosis group. After intravenous infusion of ultrasound contrast, the time to the signal of contrast in the hepatic artery, portal vein and hepatic vein was determined and the transit time of the liver was calculated. Their results showed the transit time in compensated cirrhosis patients was significantly shorter than that in non-cirrhosis patients. Present results revealed the HA-HVTT and PV-HVTT were 6.7 seconds and 5.6 seconds, respectively, in cirrhosis patients and 14.3 seconds and 10.4 seconds, respectively, in controls. Analysis showed the HA-HVTT and PV-HVTT in cirrhosis patients were markedly shortened when compared with controls, consistent with the study of Hirota et al. These findings imply the pathological alterations in liver fibrosis and cirrhosis result in changes in hemodynamics. The reasons may be as follows:

At the early stage of liver cirrhosis, the intrahepatic hemodynamics is altered. The liver sinusoids are capillarized resulting in a shunt between the portal vein and hepatic vein (blood in the portal vein enters the hepatic vein). In addition, liver fibrosis may cause reconstruction of hepatic lobules resulting in neovascularization and formation of communicating branches between arteries and veins as well as subsequent arteriovenous shunt [8]. Under normal conditions, the ultrasound contrast enters the portal vein. Through the branches of the portal vein, the ultrasound contrast enters the liver sinusoids and subsequently the inferior vena cava via the hepatic vein. Due to alterations in hemodynamics at the early stage of liver cirrhosis, on one hand, the ultrasound contrast from the portal vein enters the hepatic vein via capillarized liver sinusoids bypassing the normal liver sinusoids. On the other hand, the ultrasound contrast from arteries enters the hepatic vein via the communicating branches between arteries and veins. These changes finally result in a significant shortening in the transit time of the liver and the AT of the hepatic vein.

In patients with liver fibrosis or cirrhosis, hyperdynamic circulation in all tissues is also a critical reason resulting in the shortened transit time of the liver. Portal hypertension in liver cirrhosis is characterized by the disorder of blood circulation in not only the liver and portal system, but the systemic blood vessels. In the disorder of circulation in systemic blood vessels, dilatation of peripheral arteries may cause hyperdynamic circulation characterized by increased cardiac output, elevated blood flow, increased heart rate and decrease of blood pressure and systemic vascular resistance.

The enhancement in the liver parenchyma may be attributed to the phagocytosis of the ultrasound contrast by the Kupffer cells, resulting in a retardation of ultrasound contrast in the sinusoid space or vessel walls, which may present a hyperecho under ultrasonography. In the present study, the PT of the liver parenchyma in cirrhosis patients was significantly prolonged when compared with controls, which was consistent with the results of Sugimoto [9]. They proposed there was hyperplasia and cell hypertrophy in cirrhosis, resulting in an increase in intrahepatic vascular resistance. Moreover, the fiber separation may cause changes in the anatomy of the liver. At this time, there is hyperplasia of fibrous connective tissues and collagen deposition in the perisinusoidal space involving capillary-like channels of hepatic sinusoids. These changes lead to reduction of vessel volume, which further increases portal pressure and decreases the blood supply to the portal vein [10–11]. Thus, the blood flow in hepatic sinusoids is slowed and the time of ultrasound contrast in the liver is prolonged, resulting in prolongation of the PT of the liver parenchyma.
Taken together, CEUS can be performed to detect the AT, transit time of the liver and the PT of liver parenchyma. These parameters can be used as indicators in the diagnosis of early-stage liver cirrhosis. However, the sensitivity and specificity of this method should be further investigated due to small sample size in the present study.

References


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