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● *Original Contribution*

HEPATIC PERFUSION PARAMETERS OF CONTRAST-ENHANCED ULTRASONOGRAPHY CORRELATE WITH THE SEVERITY OF CHRONIC LIVER DISEASE

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Abstract—In the study described here, we introduced a new ratio acquired with contrast-enhanced ultrasonography (CEUS): a liver parenchyma blood supply ratio that differentiates arterial and portal phases. Our purpose was to determine whether this ratio and other liver parenchyma perfusion parameters acquired with CEUS can be correlated with the severity of chronic liver disease. Twelve patients with non-cirrhotic chronic liver disease, 35 patients with cirrhosis (child class A: n = 10; child class B: n = 13; child class C: n = 12) and 21 healthy volunteers were examined by CEUS. Time–intensity curves were drawn for regions of interest located in liver parenchyma and right kidney cortex using QLAB quantification software. The arterial and portal phases were differentiated by the time to the maximum enhancement of right kidney and liver parenchyma perfusion data acquired from the time–intensity curves: the intensity of liver parenchyma perfused by hepatic arterial flow (I_{ap}), the intensity of total perfusion of liver parenchyma (I_{peak}), the intensity of liver parenchyma perfused by portal venous flow (I_{pp}) and the ratio of portal perfusion to total perfusion of liver parenchyma expressed by the parameters I_{pp}/I_{peak}, I_{peak}, I_{pp} and I_{pp}/I_{peak} significantly decreased in patients with cirrhosis and in patients with non-cirrhotic chronic liver disease, whereas I_{ap} increased. The parameters I_{pp}, I_{peak}, I_{pp}/I_{peak} and I_{ap} correlated with the severity of chronic liver disease ($r = -0.938$, $p < 0.001$; $r = -0.790$, $p < 0.001$; $r = -0.931$ $p < 0.001$; $r = 0.31$, $p < 0.05$). The diagnostic accuracy rates for cirrhosis expressed as areas under receiver operating characteristic curves were 0.93 for I_{peak}, 0.98 for I_{pp}, 0.98 for I_{pp}/I_{peak}, and 0.69 for I_{ap}. Liver parenchyma perfusion parameters obtained by CEUS were correlated with the severity of chronic liver disease and have the potential to assess cirrhosis non-invasively. (E-mail: qianlinxue2002@163.com) **© 2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast-enhanced ultrasonography, Cirrhosis, Hepatic perfusion.**

INTRODUCTION

Liver cirrhosis is the final stage of progression of chronic liver disease and is common in China. Three percent of patients with compensated cirrhosis progress to decompensation annually. To determine adequate medical therapy and to prevent bleeding from esophageal varices, it is important to diagnose liver cirrhosis accurately and promptly. Needle biopsy of the liver is regarded as the gold standard for the diagnosis of cirrhosis. However, it is invasive and has poor reproducibility, with false-negative rates ranging from 9.3% to 51% (Pagliaro et al. 1983; Zaitoun et al. 2001). Therefore, a non-invasive method for estimation of the severity of chronic liver disease is needed.

During the progression of chronic liver disease, alterations involving the microvascular bed of the liver are already evident during the pre-cirrhotic stages of hepatic fibrogenesis (Ridolfi et al. 2012). The increase in intrahepatic vascular resistance decreases the portal fraction of liver perfusion (Rokey and Weisiger 1996). This decrease in portal perfusion is partially compensated by an increase in hepatic arterial flow (Eipel et al. 2010). Many imaging techniques have been used to evaluate hepatic perfusion, including computed tomography (CT) (Nakashige et al. 2004; Tsushima et al. 1999; Van Beers et al. 2001), magnetic resonance imaging (Hagiwara et al. 2008) and isotope scintigraphy (Iwasa et al. 1995; Ziegler et al. 1996). However, these techniques have disadvantages such as high cost and low resolution, which in turn leads to poor precision.

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Because it is non-invasive, inexpensive and reproducible, ultrasound (US) has become the preferred imaging modality for the diagnosis of chronic liver disease. However, conventional US is somewhat limited in the assessment chronic liver disease. As an important supplement to conventional ultrasound, contrast-enhanced ultrasound (CEUS) techniques have great potential in the evaluation of hepatic perfusion and can overcome some of the limitations.

Many temporal indices have been found to be helpful in the diagnosis and evaluation of liver fibrosis and cirrhosis (Lim et al. 2005; Staub et al. 2009). However, to assess quantitative changes in different phases of hepatic perfusion in chronic liver disease, temporal indices are not enough. In the present study, we focused on the contrast enhancement phases in the time–intensity curve (TIC) of hepatic parenchyma, and used the intensity indices I_{ap}, I_{pp} and I_{pp}/I_{peak} and the conventional parameter I_{peak} to assess chronic liver disease.

METHODS

Patients

Forty-seven patients with biopsy-proven cirrhotic and non-cirrhotic chronic liver disease who were admitted to our hospital between October 2009 and April 2013 were enrolled in the study. Twenty-one healthy volunteers were enrolled in a normal group. The patients were divided into Child A, Child B and Child C groups using Child–Pugh criteria, which are based on serum bilirubin, serum albumin, prothrombin time (international normalized ratio [INR]) and the presence of encephalopathy, and ascites (Kim and Lee 2013; Pugh et al. 1973). Patients with any known disease that might influence the intra- or extrahepatic or renal circulation, such as focal liver lesions and cardiac, renal or portal diseases; patients who had undergone treatments such as transjugular intrahepatic portosystemic shunt (TIPS) and splenectomy; and patients who had taken antihypertensive drugs such as beta blockers during the preceding 2 wk were excluded from the study. The study protocol conformed to the guidelines outlined in the 1975 Declaration of Helsinki and was approved by the medical ethics committee of Beijing Friendship Hospital Affiliated to Capital Medical University. All patients gave written informed consent before being enrolled in the study. The baseline characteristics of the patients are summarized in Table 1.

Table 1. Clinical data of subjects (n = 68)

Datum	Control group (n = 21)	Non-cirrhotic group (n = 12)	Cirrhotic group (n = 35)
Age (y)	39.63 ± 14.10	48.06 ± 7.80	52.39 ± 11.67
Sex (male/female)	13/8	8/4	24/11

Materials

The ultrasound contrast agent used was SonoVue (Bracco, Milan, Italy). The agent was prepared by mixing the powder with 5 mL 0.9% physiologic saline to form a suspension. Examinations were conducted with a Philips IU 22 ultrasound system (Philips, Amsterdam, The Netherlands) and a 2- to 5-MHz transducer. The imaging technology was pulse inverse harmonics imaging (PIHI).

Procedures

To minimize variation, the settings of the scanner such as mechanical index (MI) (the MI used in the present study was 0.05), dynamic range and gain and frequency were kept constant, and the time gain compensation was off. Before the contrast examination, every subject was instructed on breath holding and shallow breathing to minimize the variation caused by motion.

With the patient lying with the left side down, the operator selected an appropriate slice that could clearly show part of the liver and part of the right kidney at the same time and then fixed the transducer. The contrast suspension, 2.4 mL, was injected through an antecubital vein using a 20G needle followed by a rapid flush of 5 mL saline (Claudon et al. 2008). A timer was started, and a real-time dynamic image storage system activated. As soon as the liver or kidney began to enhance, the patient was asked to hold his or her breath for at least 30 s and then to breathe softly. Images were recorded for 1.5 min and stored. The film was analyzed separately by two experienced doctors using QLAB quantification software (Philips). The intra-class correlation coefficients of the data obtained by the two doctors were analyzed to evaluate concordance.

Data acquisition

The liver is supplied by two vessels, the hepatic artery and the portal vein. Therefore, the TIC of liver parenchyma has two components. When the contrast agent from the hepatic artery arrives, the curve begins to rise, and when the contrast agent from the portal vein arrives soon afterward, the curve continues to rise until it peaks (Fig. 1). If we could separate the two components, we could separately quantify the changes in these two components. Because renal perfusion is similar to hepatic artery perfusion, we use the time to maximum enhancement of the right kidney to differentiate the arterial and portal phases (Fig. 2). This method was introduced by Miles et al. (1993) using CT.

CEUS analysis

We selected two regions of interest (ROIs) in the right kidney and the liver, respectively (Fig. 3), and