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● *Original Contribution*

LIVER STIFFNESS: A SIGNIFICANT RELATIONSHIP WITH THE WAVEFORM PATTERN IN THE HEPATIC VEIN

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Abstract—The aim of this prospective study was to assess the relationship between liver stiffness and hepatic vein waveform patterns in 42 patients with chronic hepatitis and 55 with cirrhosis. Liver stiffness measurement (LSM) values (FibroScan, Echosens, Paris, France) were significantly lower in the triphasic pattern group (11.3 ± 8.4 kPa) than in the monophasic pattern (32.5 ± 23.5 kPa, $p = 0.001$) and biphasic pattern (25.6 ± 18.1 kPa, $p = 0.001$) groups, indicating no significant relationship with portal pressure. The ability to diagnose cirrhosis represented by the highest area under the receiver operating characteristic curve was 0.921 (83.6% sensitivity, 90.5% specificity, best cutoff value: 16.9 kPa) by LSM and 1.000 (best cutoff value: 19.4 kPa) by LSM combined with the monophasic pattern. This study revealed a close linkage between liver stiffness and hepatic vein waveform findings, resulting in a better understanding of hepatic vein hemodynamics and wider application of its analysis. (E-mail: maru-cib@umin.ac.jp) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Cirrhosis, Portal hypertension, Hepatic vein waveform, Liver stiffness.**

INTRODUCTION

Chronic liver disease, which is increasing in prevalence worldwide, has various etiologies, including viral infection, alcohol abuse and metabolic disorders (Williams 2006). The most advanced condition is cirrhosis, which requires careful management because of possible adverse events, such as cancer, portal hypertension and hepatic failure (Cardenas and Gines 2011; Nissen and Martin 2002; Tandon and Garcia-Tsao 2006). Characterization of chronic liver disease remains a pivotal issue in clinical practice.

Morphologic changes of the liver are closely associated with changes in the inflow and outflow hemodynamics of the liver (Bolondi et al. 1990; Zwiebel et al. 1995), and because it is the only route for outflow of blood from the liver, the hepatic vein (HV) may reflect the comprehensive hepatic hemodynamic changes. Doppler ultrasound (US) is a reliable method for evaluating abdominal hemodynamics in a simple, real-time procedure (Grant et al. 1989; Taylor and Holland 1990), and previous studies have reported that HV waveform patterns are associated with the severity of chronic liver disease (Colli et al. 1994; Kawanaka et al. 2008). However, the factors closely associated with HV waveforms remain unclear.

Development of hepatic fibrosis increases tissue stiffness as liver disease progresses (Bedossa et al. 2003; Poynard et al. 2000). Various tools have become available to assess the elasticity of the liver with US or magnetic resonance imaging (Albrecht et al. 1999; Friedrich-Rust et al. 2009; Huwart et al. 2008; Sandrin et al. 2003). FibroScan (Echosens, Paris, France) may be one of the most popular techniques. Liver stiffness represents not only the grade of hepatic fibrosis, but also the risk of potentially severe outcomes for the patient, such as hepatocellular carcinoma and portal hypertension (Carrion et al. 2006; Chon et al. 2012; Vizzutti et al. 2007).

On this background, we hypothesized that there might be a relationship between HV waveform patterns and liver stiffness. Therefore, this study used Doppler US to examine the features of HV waveforms in patients with chronic liver diseases from the viewpoint of liver stiffness.

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METHODS

Patients

This prospective study was performed from April 2011 to June 2014 with the approval of the ethics committee of our hospital. Informed written consent was obtained from each patient.

The study enrolled consecutive patients who fulfilled the following criteria. (i) Patients had to have chronic hepatitis or cirrhosis, where the diagnosis of chronic hepatitis was made histologically using biopsy samples and the diagnosis of cirrhosis was made histologically using liver samples or both clinical and imaging findings. (ii) Patients had to have undergone both Doppler US and liver stiffness measurement (LSM) using the FibroScan 502. The purpose of Doppler US for patients with cirrhosis was assessment of portal hemodynamics because of clinical signs of portal hypertension, such as endoscopy-detected gastroesophageal varices and hepatic encephalopathy. In patients with chronic hepatitis, however, Doppler US was performed to determine the presence or absence of portal hemodynamic abnormalities at the time of liver biopsy. LSM and blood sampling were performed at the time of routine US or Doppler US.

Exclusion criteria were (i) the presence of ascites detected by US, because of difficulty in obtaining data by FibroScan; (ii) the presence of liver tumors, because of the possible influence on LSM or HV waveform pattern; and (iii) the presence of portal vein thrombosis or vascular abnormalities such as reversed portal flow and arterioportal shunt, because of the possible influence on HV waveform pattern; (iv) use of vasoactive medications, such as beta blockers, because of the possible effect on portal hemodynamics; and (v) pregnancy. Exclusion criteria i–iii were screened for with B-mode US and color Doppler US.

Ultrasound examination

Doppler US was performed with the patient in a supine position, after ≥4 h of fasting, using an SSA-790A (from April 2011 to March 2013) in 17 patients or a TUS-A500 (from April 2013 to June 2014) in 80 patients with a 3.75-MHz convex probe (Toshiba, Tokyo, Japan). Both sets of US equipment employed the same measurement algorithm. The sampling width was set to correspond to the vessel diameter, and the angle between the US beam and the vessel was kept below 60°. The waveform was observed under gentle breathing, in the right HV from the right intercostal space, by positioning the sample volume within 2–3 cm of the junction with the vena cava. The operator took the still image when the stable waveform pattern that repeated on the cardiac cycle was observed. Then, one of the typical waveforms for one cardiac cycle was selected, and the mean, maximum and minimum velocities were calculated by automatic tracing of the wave spectrum.

In addition, the waveform of the portal trunk was detected by longitudinal or oblique scanning of the middle abdomen. Mean velocity (cm/s) was calculated by automatic tracing of the wave spectrum for almost one cardiac cycle. Mean flow volume (mL/min) was calculated by multiplying the mean velocity for 1 s by the cross section of the vessel, and multiplying that product by 60 s.

Spleen size (mm^2) was measured by multiplying the distance from the splenic hilum to the caudal polar angle obtained from two intersecting lines (Maruyama et al. 2014). Splenomegaly was defined as a spleen >2000 mm^2.

Two or more measurements (mean ± SD: 2.4 ± 0.7) were made for the portal trunk, and one or more measurements (1.1 ± 0.3) for the HV. The average value of multiple measurements was used for hemodynamic analysis of the portal vein. Meanwhile, as for the HV, one image of a representative waveform was selected, and the waveform pattern was assessed and then subjected to quantitative velocity analysis.

Hepatic vein waveform analysis

We determined the HV waveform pattern quantitatively by applying the waveform variations calculated as ([maximum flow velocity] – [minimum flow velocity])/(maximum flow velocity) × 100, that is, the monophasic waveform pattern for <25% variations and the biphasic waveform pattern for ≥25% variations. A waveform accompanied by reversed flow was defined as a triphasic waveform pattern (Bolondi et al. 1991) (Fig. 1).

Liver stiffness measurement

The LSM value (kPa) was obtained from the right intercostal space using the FibroScan with an M probe in the supine position, which was selected using B-mode US. A-Mode US, which is built into the equipment system, was used to ensure that the liver was ≥60 mm thick and there was no obstacle to prevent the measurement (*e.g.,* large vessels). The depth for measurement was set 25–45 mm from the body surface. LSM was performed ≥10 times, and the median value of 10 successful measurements was taken as the final data point for this study. When the interquartile range (IQR = distance between upper and lower quartiles/median) was >30% and the success rate was <60%, the accuracy of the measurement was considered not guaranteed and the patient was excluded from the analysis (Friedrich-Rust et al. 2009). LSM was performed by T.S., T.K. and S.K., who are hepatologists with more than 8 y of experience.

Hepatic venography

Hepatic venography was performed within 20 d of US examinations. Because it was conducted to evaluate