Predicting portal hypertension as assessed by acoustic radiation force impulse: correlations with the Doppler ultrasound

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Objective The purpose of this study was to assess the value of acoustic radiation force impulse (ARFI) for evaluating portal hypertension by correlating the elasticity of liver cirrhosis, as measured by ARFI, with haemodynamic indices measured by Doppler ultrasound.

Methods We evaluated the data of a total of 154 prospectively enrolled patients who underwent both duplex Doppler ultrasound and ARFI imaging. The duplex Doppler ultrasound indices, including the mean portal vein velocity, splenic index (SI) and splenoportal index (SPI) were evaluated to determine the statistical correlation with shear wave velocity (SWV) of ARFI. We also analysed the differences in the correlations between the SI, SPI and SWV of the group who had varices. The correlations were assessed with Spearman's rank correlation coefficients.

Results There was an increase of SWV in parallel with the increase of the SI ($\rho=0.409$, $p<0.01$) and SPI ($\rho=0.451$, $p<0.01$). In the patient group who did not have varices ($n=74$), the Doppler indices were found to be more correlated with the SWV (SI: $\rho=0.447$, SPI: $\rho=0.552$, $p<0.01$). However, the group with varices showed no correlation between the SWV and the Doppler parameters.

Conclusion SWV of ARFI was well correlated statistically with Doppler parameters, but is of limited value in predicting portal hypertension directly owing to great variability of Doppler parameters. By evaluating the correlation between ARFI and Doppler ultrasound, we suggest that the SWV might be a non-invasive supplementary tool for predicting portal hypertension.

Received 31 January 2011

Revised 27 June 2011

Accepted 5 July 2011

DOI: 10.1259/bjr/74648924

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Introduction

Portal hypertension is a constant finding in the course of chronic liver disease and it causes serious complications such as variceal bleeding, which is responsible for significant mortality in patients with cirrhosis. Therefore, precise and regular assessment of the severity of portal hypertension is necessary for patients with cirrhosis during follow-up. The hepatic vein pressure gradient (HVPG) has been accepted as the gold standard for assessing the severity of portal hypertension and it is the best predictor of variceal formation [1–3]. However, this method is not feasible in clinical practice because of its invasiveness. Duplex Doppler ultrasound (DDUS) has recently emerged as a useful non-invasive modality to use in outpatient clinics for assessing the portal haemodynamics. Various portal haemodynamic parameters according to DDUS have been introduced. The previous reports on this have shown conflicting results for establishing DDUS as an acceptable modality for estimating the portal pressure. We chose some of the recently introduced parameters that are more acceptable and easier to perform. These were the splenic index (SI) and the splenoportal index (SPI), which are based on the spleen length and portal vein velocity (PVV) [4].

Acoustic radiation force impulse (ARFI) imaging is a radiation force-based imaging method that is provided by conventional B-mode ultrasound. With the increasing interest in finding new non-invasive methods for evaluating liver cirrhosis patients, ARFI can be applied for the measurement of liver stiffness as an alternative to needle biopsy. Many recent studies have shown that ARFI imaging is an accurate non-invasive modality compared with transient elastography and serum fibrosis marker tests [5–8].

The purpose of our study was to determine the correlations between the haemodynamic parameters measured with Doppler ultrasound and the liver stiffness measured with ARFI, and to evaluate the value of ARFI for predicting the presence of portal hypertension in patients with cirrhosis.

Methods and materials

Patients and control subjects

The study received institutional review board approval and informed written consent was obtained from all the subjects. The subjects were drawn from a consecutive series of 200 patients with liver cirrhosis and who visited the outpatient clinic of Dong-A University Hospital for routine follow-up between April 2010 and June 2010. The diagnosis of cirrhosis was established by

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This study was supported by a research fund from Dong-A University.

histological examination or the combination of standard clinical, laboratory and imaging studies, including ultrasound and CT. The patients who did not provide informed consent or who had hepatocellular carcinoma, thrombosis in the inferior vena cava, hepatic vein or portal vein, or heart failure were excluded. After all the exclusions, 154 patients (91 males and 63 females; mean age 55.0 ± 10.4 years) were finally included in this study. The cause of cirrhosis was viral in 133 patients (hepatitis C virus in 30 patients, hepatitis B virus in 102 patients, coinfection of B and C virus in 1 patient), alcohol abuse in 15 patients and cryptogenic in 6 patients. The severity of liver dysfunction, as classified by the Child–Pugh scoring system, was A in 142, B in 8 and C in 4. The patients who had undergone oesophago-gastro-duodenoscopy or CT in the previous 6 months were retrospectively evaluated for the presence of oesophageal or gastric varices. 47 patients were proven to have oesophageal or gastric varices, 74 patients were confirmed to not have varices and the other 33 patients did not undergo endoscopy or CT.

In addition, 15 healthy adult volunteers (10 men and 5 women) who did not have a history of relevant concomitant illness (heart, lung or liver disease or neoplasia) were examined with DDUS and ARFI imaging and they served as a control group in which to obtain benchmark median ARFI velocity and Doppler parameter measurements. The mean age of the control group (25.9 ± 2.4 years) was significantly younger than that of the patient group ($p < 0.001$).

Greyscale and Doppler ultrasound

The examination was performed after the patients had fasted for 4–6 hours. B-mode standard ultrasonography scanning was initially performed using a Siemens Acuson S2000™ with a 4C1 transducer (Siemens Medical Solutions USA Inc., Malvern, PA). The spleen size was depicted after standard screening ultrasonography

scanning of the abdomen. The SI was calculated in square centimetres using the transverse and vertical diameters of the spleen on the maximal cross-sectional images of the spleen (Figure 1) [9].

The portal vein was longitudinally scanned and the Doppler sampling cursor was placed approximately halfway between the venous confluence and the portal bifurcation. The PVV was the mean of three measurements with the patient holding their breath. It was automatically measured by the machine using the time-averaged velocity in two to three cardiac cycles and with an angle correction of $<60^\circ$ [10] (Figure 1).

The SPI was calculated using the data acquired above with the formula $SPI = SI / PVV_{\text{mean}}$ (SI is in cm^2 ; PVV_{mean} is the mean PVV in cm s^{-1}).

All the ultrasound examinations were performed by one of two authors (HJK or JHC, with 7 and 14 years' of experience with Doppler ultrasound, respectively) who were blinded to the clinical data throughout the study. The operators agreed on common rules to perform the ultrasound measurements before the start of the study.

Acoustic radiation force impulse imaging

After the B-mode standard ultrasonography and Doppler ultrasound were done, ARFI elastography was performed with the same curved arrays by the same authors as follows: the right lobe of the liver was accessed through an intercostal space while the patient was in the supine position with the right arm in maximum abduction and with a breath-hold. A region of interest (ROI) was placed 2–3 cm from the liver capsule at the right hepatic lobe, where the liver tissue was at least 5.5 cm thick (Figure 2) [11]. During each evaluation, the operator was careful not to include vessels and biliary structures in the ROI. The velocity of the shear wave from the liver tissue was calculated as the median value of five trials (m s^{-1}).

Figure 1. Measurement of the Doppler parameters. (a) The splenic index was calculated in square centimetres of the transverse and vertical diameters of the spleen on the maximal cross-sectional images of the spleen. The spleen is markedly enlarged in a patient with cirrhosis. (b) The mean portal vein velocity. The portal vein was longitudinally scanned and the Doppler sampling cursor was placed halfway between the venous confluence and the portal bifurcation. The waveform showed a monophasic pattern in a patient with cirrhosis.

Figure 2. Measurement of the shear wave velocity. The region of interest was placed 2–3 cm from the liver capsule at the right hepatic lobe, where the liver tissue was at least 5.5 cm thick.

Statistical analysis

The data are expressed as mean $\pm$ standard deviation (SD). The Doppler ultrasound and ARFI results of the patients with cirrhosis and those of the healthy subjects were compared using the Mann–Whitney *U*-test.

Spearman rank correlation coefficients were used to assess the correlation between the parameters (the SI, the mean PVV and the SPI) measured by Doppler ultrasound and the velocity of the shear wave as measured by ARFI. The same test was used for both the groups with and without varices. The differences between the group with varices and the group without varices were compared with the Mann–Whitney *U*-test. The statistical analyses were performed by using SPSS® software (v. 18.0 for Windows; SPSS, Chicago, IL). *p*-values of <0.05 were considered to indicate significant differences.

Results

The parameters of Doppler ultrasound and ARFI are summarised in Table 1. There was a statistically significant difference between the patients and healthy subjects for all the measurements. The shear wave velocity (SWV) was correlated with the SI ($\rho=0.409$, $p<0.01$) and the SPI ($\rho=0.451$, $p<0.01$; Figure 3). Weak

but significant correlations were found for the mean PVV ($\rho=-0.205$, $p<0.05$). After excluding the patients who were confirmed to have varices ($n=47$) and the patients who were not assessed ($n=33$), the correlation between these two modalities became higher for the SI ($n=74$, $\rho=0.447$, $p<0.001$), the SPI ($n=74$, $\rho=0.552$, $p<0.001$) and the mean PVV ($n=74$, $\rho=-0.25$, $p<0.05$). The results for the patients who had varices showed a statistical difference from those of the patients who did not have varices: the SWV, SI and SPI of the patients who had varices were $2.31 \pm 0.75 \text{ m s}^{-1}$ ($p<0.001$), $73.95 \pm 24.4 \text{ cm}^2$ ($p<0.001$) and 8.48 ± 4.25 ($p<0.001$), respectively, and they were significantly higher than those values of the patients who did not have varices (Table 2). No significant correlation was found between the ultrasound parameters and the SWV for the group of patients with varices (Figure 4).

Discussion

Duplex Doppler ultrasound is a non-invasive technique that can be used for estimating portal hypertension. Various portal haemodynamic parameters assessed by DDUS have been introduced and the previous studies have reported conflicting findings to presently establish DDUS as an acceptable modality for estimating the portal pressure [1–4]. The SI is the sonographic grading assessment to express the spleen size. The spleen size had traditionally been known to be the predictor of chronic liver disease and has been proven to correlate with portal pressure in recent studies [3, 4, 12]. With increasing portal pressure, the portal velocity decreases and fluctuations disappear with flow becoming continuous [4, 13, 14]. The SPI is a recently proposed index that amplifies the opposite effects that the mean PVV and SI exert, and the SPI can predict the presence of oesophageal varix in outpatient clinics [4].

ARFI sonoelastography has recently attracted a great deal of attention for its use to measure liver stiffness. ARFI imaging is an ultrasound-based technique in which the speed of wave propagation is evaluated to study the viscoelastic properties of the targeted tissue. The targeted region, the ROI, is mechanically excited by an acoustic pulse ($\sim 262 \mu\text{s}$) and this generates localised tissue displacement. By measuring the time to peak displacement, the shear wave speed of the tissue can be estimated at each lateral location of the ROI. The SWV is proportional to the square root of the tissue elasticity [5]. Many of the preliminary studies have yielded comparable

Table 1. Comparison of shear wave velocity of ARFI and parameters of Doppler ultrasound between patients with and without cirrhosis

Modality	No cirrhosis ($n=15$)	Cirrhosis ($n=154$)	<i>p</i> -value
ARFI			
Shear wave velocity (m s^{-1})	1.13 ± 0.10	1.89 ± 0.83	<0.001
Doppler ultrasound			
Mean portal vein velocity (cm s^{-1})	17.58 ± 5.26	10.93 ± 3.60	<0.001
Splenic index (cm^2)	41.01 ± 7.25	54.63 ± 22.37	0.027
Splenoportal index	2.64 ± 1.50	5.63 ± 3.45	<0.001

ARFI, acoustic radiation force impulse.

Data are mean values $\pm$ standard deviations.

Figure 3. Correlation between the shear wave velocity (SWV), the splenic index (SI) and the splenoportal index (SPI). Scatter-plots depict substantial correlations (a) between the SWV and SI ($\rho=0.409$, $p<0.01$) and (b) between the SWV and SPI ($\rho=0.451$, $p=0.01$).

results of the ARFI sonoelastographic velocity for determining the severity of liver fibrosis [5–8].

We compared the two modalities ARFI and DDUS on the assumption that the portal hypertension reflects the severity of cirrhosis. To the best of our knowledge, this is the first study that has assessed the correlation between ARFI and DDUS.

The results of the current study show that a significant relationship exists between liver stiffness, as measured by ARFI, and the parameters related to the portal pressure, as measured by Doppler ultrasound. Our study results demonstrated a positive correlation between the median ARFI sonoelastographic velocity, which reveals the liver stiffness, and the flow parameters of Doppler ultrasound, which reflect portal hypertension. Although liver stiffness appears to be a reliable method for identifying fibrosis, the pathophysiological basis for its correlation with portal hypertension remains poorly defined. The structural and biological changes in the liver may be responsible for increased portal pressure [15, 16]. In individuals with cirrhosis, portal hypertension initially develops as the result of an increase in intrahepatic resistance to the portal blood flow due to profound morphological changes that are characterised by fibrosis and regenerative nodules compressing the sinusoids. This leads to vascular obliteration, activation

of hepatic stellate cells and vasoconstriction, and this is all due in large part to intrahepatic nitric oxide deficiency and enhanced vasoconstrictor activity [17]. As a result, the progressive rise in portal pressure represents a reliable indicator of the tissue changes and, to a certain extent, the biological microenvironment of the cirrhotic liver.

While the correlations between Doppler parameters and SWV for patients without varices were approximately 0.557, the other 44.3% of the variation in SI and SPI was not explained by SWV. We hypothesised many factors that may influence Doppler indices, such as intrahepatic shunt and many portal–caval anastomoses other than gastro-oesophageal varices. Doppler parameters are still controversial for patients with cirrhosis owing to variability and reproducibility [12]. These factors may also affect the high variability of SI and SPI.

The results of the measurements of the patients with varices were significantly higher than those for the patients without varices. However, the results demonstrated a stronger correlation between the SWV and Doppler parameters when the patients who had varices were excluded. Further, there were no correlations between the SWV and Doppler parameters in the group of patients who had varices. In advanced cirrhosis, several extrahepatic factors (such as the hyperdynamic

Table 2. Comparison of shear wave velocity of ARFI and parameters of Doppler ultrasound between patients with varices and without varices

Modality	Cirrhosis without varix (n=74)	Cirrhosis with varix (n=47)	p-value
ARFI			
Shear wave velocity (m s^{-1})	1.69 ± 0.81	2.31 ± 0.75	<0.001
Doppler ultrasound			
Mean portal vein velocity (cm s^{-1})	11.58 ± 3.54	9.83 ± 3.96	<0.001
Splenic index (cm^2)	45.33 ± 14.56	73.95 ± 24.4	<0.001
Splenoportal index	4.29 ± 2.06	8.48 ± 4.25	<0.001

ARFI, acoustic radiation force impulse.

Data are mean values $\pm$ standard deviations unless otherwise indicated.

Figure 4. Comparison between (a, b) the group without varices and (c, d) the group with varices. (a, b) Scatter-plots depict stronger correlation (splenic index: $\rho = 0.447$, $p < 0.001$; splenoportal index: $\rho = 0.552$, $p < 0.001$) than that for the total cirrhotic patients in Figure 1, but there was no correlation in (c, d) the group with varices (splenic index: $\rho = 0.211$, $p = 0.154$; splenoportal index: $\rho = 0.253$, $p = 0.087$).

circulation, splanchnic vasodilation and the resistance opposed to portal blood flow by the portosystemic collaterals) contribute to the rise in portal pressure [16, 18]. Beyond a certain degree of cirrhotic transformation, portal hypertension is maintained by these complex haemodynamic changes and these are mediated by nitric oxide [19, 20]. Although liver stiffness and the SWV reflect a progressive rise in portal pressure due to morphological changes, they cannot measure the complex haemodynamic changes of late portal hypertension [21]. Its ability to predict the grade of varices in the case of severe portal hypertension was poor, suggesting a plateau effect in which further increases in liver stiffness are not reflected in the development of the late complications of portal hypertension.

The average of the Doppler parameters (SI, PVV, SPI) were slightly higher and the PVV was lower compared with the results of other studies [3, 4, 12, 22]. We hypothesised this to be the consequence of the populations in different studies. The majority of our patients had hepatitis B virus-related cirrhosis with a Child–Pugh

classification of A, while the subjects of the other studies had cirrhosis related to alcohol or hepatitis C virus. In alcoholic cirrhosis, the developing fibrous septae extend through the sinusoids from the central to the portal regions as well as from portal tract to portal tract. The hallmark of irreversible liver damage in chronic hepatitis is the deposition of fibrous tissue, which starts from the portal tract. Periportal septal fibrosis occurs with time and this is followed by linking of fibrous septa between lobules [23]. As the fibrosis in early cirrhosis starts from the portal tract, this may initially affect the haemodynamic change of the portal vein. However, this hypothesis should be further studied based on scientific evidence.

The major advantages of ARFI and DDUS are that these techniques are painless and rapid, they have no associated complications and they are easily accepted by patients. Both of the techniques can be performed with conventional ultrasound probes during routine ultrasound screening for hepatocellular carcinoma in patients with cirrhosis.

Although there were statistical correlations between both of the modalities, our study had some limitations. First, most of our patients had Child–Pugh class A virus-related cirrhosis. The potential bias due to the predominance of patients with chronic hepatitis B virus may have had an effect on the results. The value of ARFI in patients with other causes and severity of cirrhosis remains to be established. Doppler parameters are still controversial for patients with cirrhosis and definite standards have not been set for predicting portal hypertension. More extensive studies are needed to establish consistent measurements of the Doppler parameters. The study lacks interobserver agreement of Doppler indices and ARFI, although a previous study revealed $6.1 \pm 3.6\%$ for mean PVV and $4.7 \pm 3.2\%$ for the SI [4]. Another limitation is that only simple correlations were performed. Linear regression was not performed because interactions such as collaterals can affect the results.

In conclusion, substantial correlations were observed between liver stiffness and the Doppler parameters. It may have implications for the clinical assessment of patients who are at an early stage of liver cirrhosis that precedes the development of severe portal hypertension. However, because of the scattering of the data, the quantitative measurement of SPI or portal velocity has a limited utility in predicting portal hypertension directly. Further studies, including direct correlation with portal venous pressure, are needed to compare the prognostic values of Doppler ultrasound and ARFI.

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