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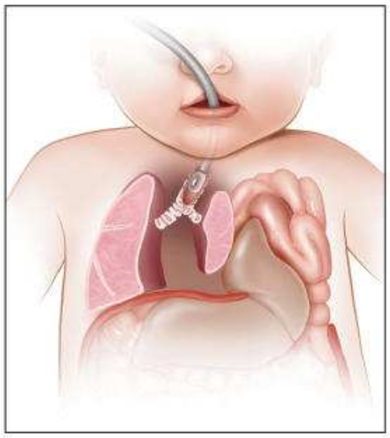

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Changing Waveform During Respiration on Hepatic Vein Doppler Sonography of Severe Portal Hypertension

Comparison With the Damping Index

Soo-Yeon Kim, MD, Woo Kyoung Jeong, MD, Yongsoo Kim, MD, Jeong Nam Heo, MD, Min Yeong Kim, MD, Tae Yeob Kim, MD, Joo Hyun Sohn, MD

Objectives—The purposes of this study were to assess retrospectively whether the waveform change during respiration on hepatic vein Doppler sonography is a parameter of severe portal hypertension as estimated by the hepatic venous pressure gradient (HVPG) and to compare with a hepatic vein damping index (DI) at expiration.

Methods—Spectral Doppler sonography of the hepatic vein was performed on 22 consecutive patients who underwent HVPG measurement for portal hypertension with liver cirrhosis. From the maximum and minimum velocities of systolic hepatofugal venous flow on Doppler sonography, 3 parameters were derived: damping index at expiration (DI_{exp}), damping index ratio (DI_{ratio}), and damping index difference (ΔDI) between inspiration and expiration. Considering an HVPG level of 12 mm Hg or higher as the threshold level for high-grade portal hypertension, we assessed the diagnostic capability of these Doppler sonographic parameters to discriminate using receiver operating characteristic curve analysis.

Results—Area under the curve values for the DI_{ratio} and ΔDI (0.875 and 0.889, respectively) were slightly higher than the area for the DI_{exp} (0.861; $P = .807$ and .682, respectively). When the DI_{exp} was greater than 0.56, the sensitivity and specificity for high-grade portal hypertension were 66.7% and 100.0%, respectively. In the case of the DI_{ratio}, the sensitivity and specificity were 77.8%, and 100.0% at greater than 0.69. The corresponding sensitivity and specificity at a value of 0.25 or less for the ΔDI were 83.3% and 100.0%.

Conclusions—The ratio and difference of the DI of the hepatic vein waveform are helpful parameters in assessing the severity of portal hypertension as well as using the existing DI on its own.

Key Words—Doppler sonography; hepatic venous pressure gradient; liver cirrhosis; portal hypertension

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Abbreviations
AUC, area under the curve; ΔDI, damping index difference; DI, damping index; DI_{exp}, damping index at expiration; DI_{ratio}, damping index ratio; HVPG, hepatic venous pressure gradient; V_{max}, maximum velocity; V_{min}, minimum velocity

The hepatic venous pressure gradient (HVPG) is generally accepted as a surrogate marker of clinical outcomes in patients with portal hypertension and is used to predict variceal development and bleeding arising from severe portal hypertension in cirrhotic patients.[1] Although this method provides useful information about treatment and prognosis, alternatives such as transient elastography[2,3] and Doppler sonography[4,5] have been explored because of the invasiveness of the HVPG.

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Previous work[4] has shown that portal hypertension causes the hepatic venous waveform to become biphasic and then monophasic, and subsequent work[5] showed this finding quantitatively using the damping index (DI). However, the wave patterns obtained in a hepatic vein Doppler sonographic study are influenced by other factors, especially respiration.[6,7] According to previous studies, inspiration can reduce the difference between systolic and diastolic velocities of hepatic venous flow, leading to an increase in damping. Most workers who have used hepatic vein Doppler sonography, including those who introduced the DI as a predictor of a high HVPG,[4,5] observed hepatic venous velocity at the point when breathing was arrested at the end of expiration. On the basis of these studies, we hypothesized that the difference or ratio of damping between expiration and inspiration would be reduced in patients with cirrhosis of the liver because vascular compliance with respect to intrahepatic blood flow is lower (Figure 1).[8,9] Furthermore, we expected that the parameters reflecting changes in blood flow due to respiration would be closely correlated with the severity of portal hypertension.

The purpose of our study was therefore to assess retrospectively the relationship between Doppler sonographic parameters derived from the DI of the hepatic vein waveform and the severity of portal hypertension estimated from the HVPG in cirrhotic patients.

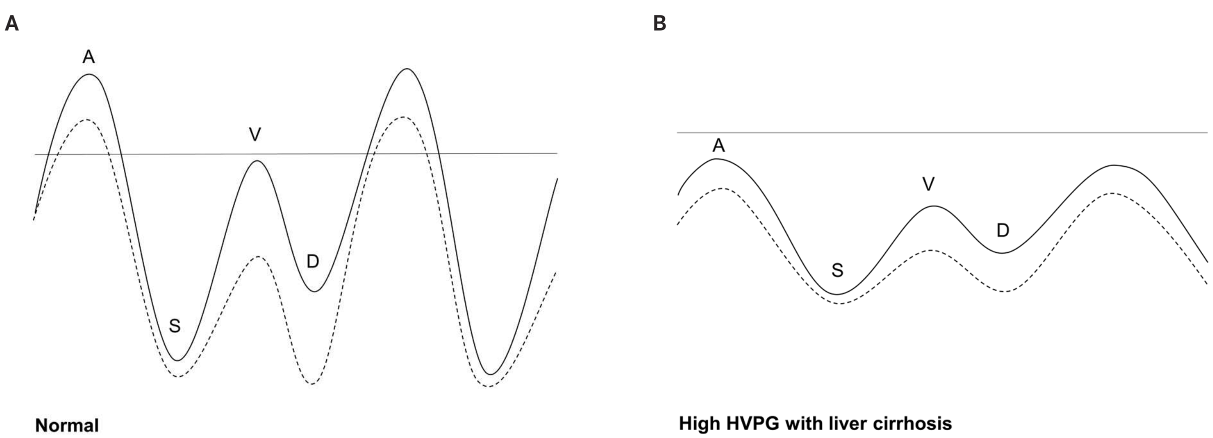
Materials and Methods

Patients

This study was a retrospective analysis of all patients with liver cirrhosis who underwent HVPG examination to check the presence of portal hypertension before medical treatment of portal hypertension between November 2009 and February 2010 in our hospital. The study was conducted with Institutional Review Board approval, and informed consent was waived by the Institutional Review Board.

Twenty-two consecutive patients (17 men and 5 women; mean age, 52.8 ± 11.0 years; range, 35–82 years) from whom both inspiratory and expiratory hepatic vein Doppler waveforms were acquired constituted the patient study group (Table 1). On the clinical record or the results of echocardiography (n = 5), none had valvular heart disease such as tricuspid regurgitation or congestive heart failure. The causes of cirrhosis were alcoholism (n = 16 [72.7%]), hepatitis B (n = 5 [22.7%]), and combined alcoholism and hepatitis B (n = 1 [4.5%]). The diagnosis of cirrhosis was based on histopathologic (n = 1) and clinical (n = 21) findings. Nine patients had Child-Pugh class A disease (40.9%); 11 had class B disease (50.0%); and 2 had class C disease (9.1%). The demographic data for the patient set is given in Table 1.

Figure 1. Study hypothesis regarding the differences between the damping indices of the hepatic vein Doppler waves during respiration in healthy individuals (**A**) and patients with liver cirrhosis (**B**). The solid line is the waveform at expiration, and the dotted line is the waveform at inspiration. Note that the difference in damping between inspiration and expiration is reduced in patients with a high hepatic venous pressure gradient (HVPG) and liver cirrhosis. A indicates atrial contraction; D, ventricular diastole (tricuspid valve open); S, ventricular systole; and V, atrial overfilling.



Hepatic Venous Pressure Gradient Examination

In all patients, HVPG measurement followed the hepatic vein Doppler study on the same day. Hepatic vein catheterization was performed using a 6F balloon tip catheter (Arrow International, Reading, PA). In brief, a sheath introducer was inserted into the right internal jugular vein under a local anesthetic, and a balloon catheter was advanced under fluoroscopic control into the right hepatic vein, where the pressures in both the wedged position and the free position were recorded. All of the measurements were performed by a radiologist (W.K.J.) with 3 years of experience, who measured the values at the plateau using an electronic barometer built into the patient-monitoring equipment (Pulscan-Combo; Scionic Co, Ltd, Seoul, Korea). All measurements were performed in triplicate, and the results were reported as the mean of the 3 measurements. The HVPG was determined by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. The severity of portal hypertension was classified into 2 categories; high-grade portal hypertension, defined as an HVPG of 12 mm Hg or higher; and low-grade portal hypertension, defined as an HVPG lower than 12 mm Hg.[5]

Doppler Sonographic Examination

All hepatic vein Doppler sonographic examinations were performed by the same radiologist (W.K.J.), and patients were examined after they had fasted for at least 6 hours. The examinations were performed in a supine position using an iU22 ultrasound system (Philips Healthcare, Bothell, WA) with a 5–1-MHz convex array transducer placed intercostally. Doppler waveforms were obtained at a Doppler angle of less than 60° and from the proximal right hepatic vein within 3 cm from the inferior vena cava.[9]

Table 1. Demographic Data of the Patients (n = 22)

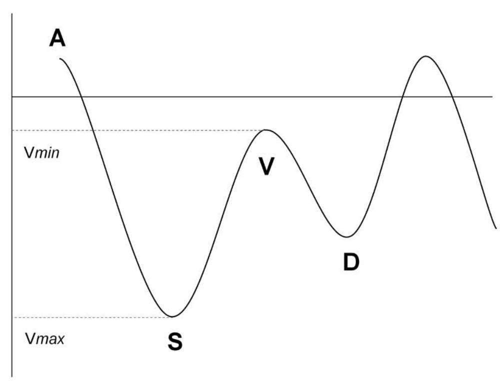
Characteristic	Value
Age, y, mean ± SD (range)	52.8 ± 11.0 (35–82)
Sex (male/female), n (%)	17/5 (77.3/22.7)
Etiology of cirrhosis, n (%)	
Alcohol	16 (72.7)
Hepatitis B virus	5 (22.7)
Alcohol and hepatitis B virus	1 (4.5)
Child-Pugh class, n (%)	
A	9 (40.9)
B	11 (50.0)
C	2 (9.1)
Hepatic venous pressure gradient, n (%)	
≥12 mm Hg	18 (81.8)
<12 mm Hg	4 (18.2)

Doppler waveforms of the right hepatic vein were obtained repeatedly at expiration and inspiration without suspending respiration. To obtain the Doppler waveforms, the following protocol was used. The examiner asked the patient to breathe in to the end of inspiration and checked the location of the right hepatic vein on sonography. Then the sample volume, which was adjusted to about 1 to 2 cm, was located on the target (the specific site of the right hepatic vein), and the transducer was fixed at the intercostal level. Next, the examiner asked the patient to breathe regularly and fully so that the sample volume covered the hepatic vein repeatedly during full inspiration. In the case of the expiratory phase, we asked the patient to breathe out to the end of expiration, moved the transducer to the optimal intercostal space, and then obtained the waveform during expiration in the same manner as for inspiration. All hepatic vein Doppler waveforms were recorded in triplicate.

Hepatic Vein DI

We measured the maximum velocity (V_{max}) and minimum velocity (V_{min}) of systolic hepatofugal flow according to respiratory phase[5,6] and used the mean of 3 consecutive measurements as the representative value. The duration of the waveform obtained was relatively short, especially the inspiratory one, because the Doppler study was performed during free respiration; hence, we selected the waveform at the center of the waveforms obtained with the most obvious wave margin. The DI of the hepatic vein was defined as the ratio of the V_{min} to the V_{max} of the retrograde systolic wave ($DI = V_{min}/V_{max}$), as proposed previously[5] (Figure 2), whereas the expiratory DI was defined as the damping index at expiration (DI_{exp}).[5,7] We considered certain

Figure 2. Schema explaining the damping index. A indicates atrial contraction; D, ventricular diastole (tricuspid valve open); S, ventricular systole; V, atrial overfilling; V_{max}, maximum velocity of hepatic venous flow during ventricular systole; and V_{min}, minimum velocity of hepatic vein flow during ventricular systole, corresponding to the V wave.



Doppler sonographic parameters derived from the DIs at expiration and inspiration, such as the damping index difference (ΔDI) and damping index ratio (DI_{ratio}), as estimates of changes in vascular compliance in the hepatic vein, and these were calculated using the following formulas: $\Delta DI = DI_{insp} - DI_{exp}$, and $DI_{ratio} = DI_{exp}/DI_{insp}$, where DI_{insp} is the damping index at inspiration.

Statistical Analysis

To test the reproducibility of the Doppler parameter measurements, intraclass correlation coefficients between 3 measurements of V_{max} and V_{min} were obtained using a variance component analysis for a 2-way random-effects model without interaction variance. The mean values of Doppler sonographic parameters in high- and low-grade portal hypertension were compared using 2-sample *t* tests on the results of independent samples. To assess the capability of Doppler sonographic parameters to discriminate high- from low-grade portal hypertension, receiver operating characteristic curves were constructed. Area under the curve (AUC) and SE values were calculated, and the AUC values of the Doppler sonographic parameters were compared using a pair-wise method. Cutoff values were also determined for each Doppler sonographic parameter at the highest accuracy, and the sensitivity and specificity of the Doppler sonographic parameters for high-grade portal hypertension were determined from standard formula. $P < .05$ was considered statistically significant. All of the statistical analyses except the intraclass correlation coefficients (calculated with SPSS version 17 software for Windows; SPSS Inc, Chicago, IL) were performed using MedCalc version 11.2.1 software for Windows (MedCalc Software, Mariakerke, Belgium).

Results

High-grade portal hypertension (HVPG ≥12 mm Hg) was observed in 18 patients (81.8%), and low-grade hypertension (HVPG <12 mm Hg) was observed in 4 (18.2%). The median HVPG values were 17.4 mm Hg (range, 12.6–25.3 mm Hg) in the high-grade group and 10.15 mm Hg (range, 5–11.4 mm Hg) in the low-grade group.

The intraclass correlation coefficients for V_{max} and V_{min} were 0.986 and 0.972, respectively, during inspiration, and 0.979 and 0.987 during expiration. The mean values ± SD of the DI_{exp}, ΔDI, and DI_{ratio} in high-grade portal hypertension were 0.63 ± 0.20, 0.11 ± 0.21, and 0.87 ± 0.28, respectively, and the values were 0.39 ± 0.14, 0.40 ± 0.17, and 0.50 ± 0.18 in low-grade portal hypertension (Figures 3 and 4). The mean values of all 3 Doppler sonographic pa-

Figure 3. Spectral Doppler scans of a patient with high-grade portal hypertension during expiration (**A** and **B**) and inspiration (**C**). Solid arrows indicate the maximum velocity during systole, and dotted arrows indicate minimum velocity. The expiratory and inspiratory damping indices were 0.66 and 0.74, respectively. The hepatic venous pressure gradient was 33.0 mm Hg, classified as high-grade portal hypertension.

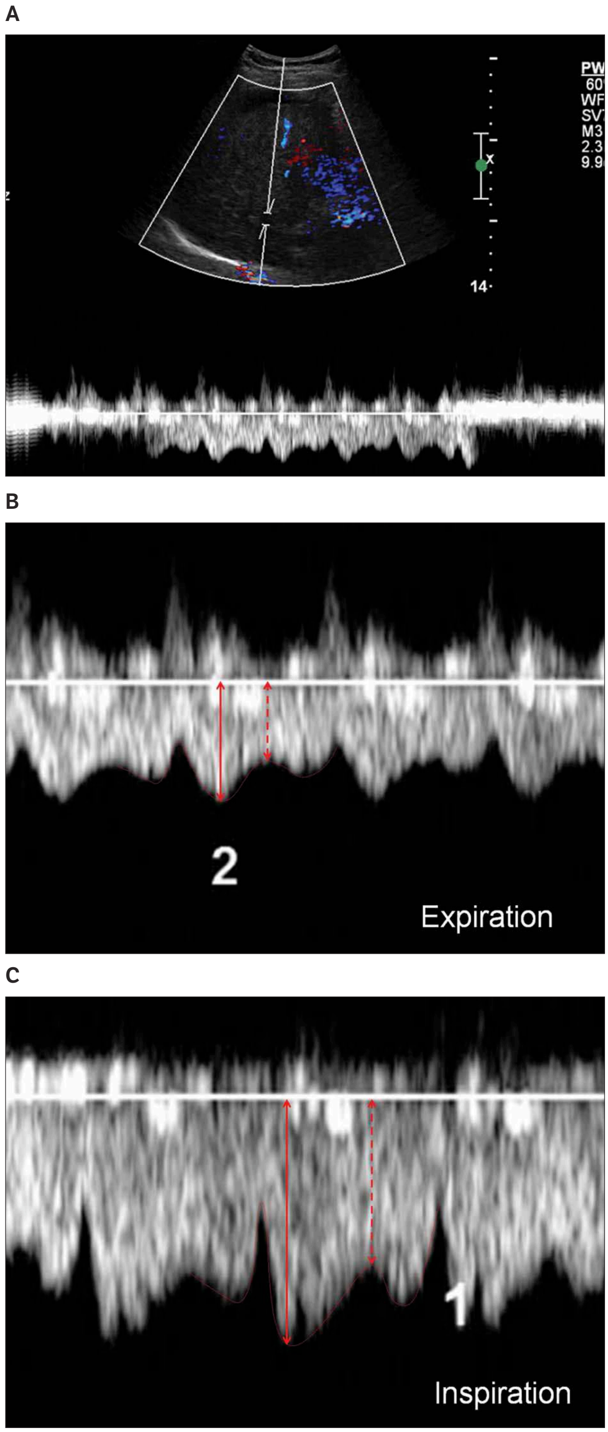
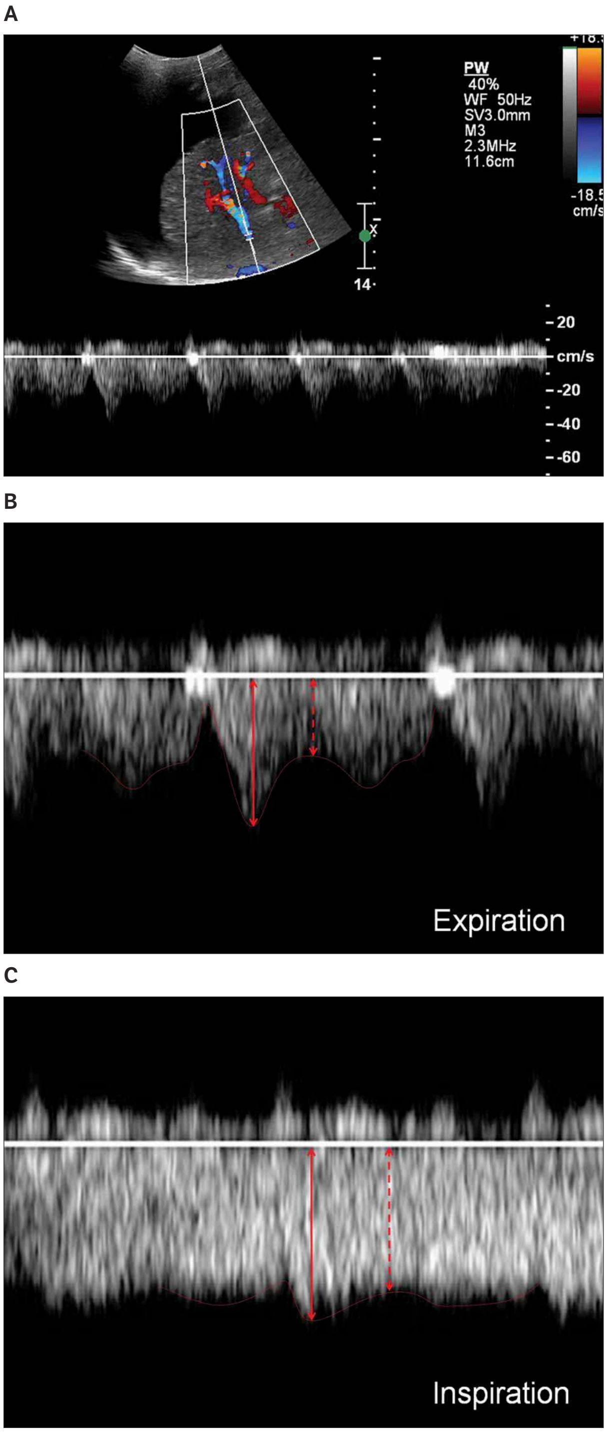


Figure 4. Spectral Doppler scans of a patient with low-grade portal hypertension during expiration (**A** and **B**) and inspiration (**C**). Solid arrows indicate the maximum velocity during systole, and dotted arrows indicate minimum velocity. The expiratory and inspiratory damping indices were 0.56 and 0.82, respectively. The hepatic venous pressure gradient was 10.3 mm Hg, classified as low-grade portal hypertension.



rameters were significantly higher in high-grade portal hypertension (P = .031, .019, and .020, respectively; Table 2).

The receiver operating characteristic curves of the 3 Doppler sonographic parameters used for predicting high-grade portal hypertension suggested that the ΔDI (AUC = 0.889) and DI_{ratio} (AUC = 0.875) might be superior to the DI_{exp} (AUC = 0.861); however, the differences did not reach statistical significance (P = .617 and .745, respectively; Table 3).

The corresponding sensitivity and specificity for DI_{exp} values exceeding 0.56 were 66.7% and 100.0%, respectively. When the cutoff value for the ΔDI was 0.26 or less, the sensitivity and specificity were 83.3% and 100%. Likewise, a cutoff value of 0.69 for the DI_{ratio} yielded sensitivity of 77.8% and specificity of 100% for the presence of high-grade portal hypertension (Figure 5). The relationship between sensitivity and specificity at different cutoff values for the Doppler sonographic parameters is shown in Table 4.

Discussion

Normal Doppler waveforms in the hepatic vein are triphasic, with 2 hepatofugal peaks due to atrial filling in the systolic and diastolic phases and 2 retrograde valleys due to the atrial and ventricular contractions.[10] Although studies have suggested that monophasic waveforms can be caused by histopathologic changes in the liver, particularly fibrosis and clinical deterioration of hepatic function,[8,11] there is debate as to the clinical value of the Doppler waveform as a noninvasive method of detecting hepatic fibrosis.[12] However, in a recent investigation, Baik et al[4] showed a direct correlation between abnormality of the hepatic venous Doppler waveform and HVPG, the latter tending to produce a flattened waveform. In addition, such a monophasic waveform was found to be associated with severe portal hypertension with relatively high sensitivity and specificity. This qualitative assessment revealed the potential of hepatic vein Doppler studies and their ability to provide an assessment of the hemodynamic changes in liver cirrhosis.

In a later investigation by the same group,[5] a quantitative study of the DI_{exp} of the hepatic venous waveform was presented, and the results were encouraging. Specifically, the authors found that the overall accuracy of the DI_{exp} for the presence of severe portal hypertension was high. Accordingly, we designed this study around the quantification of changes in vascular compliance in cirrhotic patients.

Expanding on the original hypothesis of this study, we expected that the quantitative parameters of the hepatic venous Doppler waveforms would be changed by respira-

Table 2. Mean Values of the Doppler Sonographic Parameters

Parameter	High-Grade Portal Hypertension (HVPG ≥ 12mm Hg; n = 18)	Low-Grade Portal Hypertension (HVPG <12 mm Hg; n = 4)	*P*
DI_{exp}	0.63 ± 0.20	0.39 ± 0.14	.031
ΔDI	0.11 ± 0.21	0.40 ± 0.17	.019
DI_{ratio}	0.87 ± 0.28	0.50 ± 0.18	.020

Data are mean ± SD. ΔDI indicates difference between damping indices in the expiratory and inspiratory phases; DI_{exp}, damping index in the expiratory phase; DI_{ratio}, ratio of damping indices in the expiratory and inspiratory phases; and HVPG, hepatic venous pressure gradient.

tion. Specifically, respiration is an important factor that damps hepatic venous flow, and this effect might differ in patients with liver cirrhosis. During inspiration, intrathoracic pressure declines because of expansion of the chest, and venous return increases via the inferior vena cava and hepatic vein. Accordingly, the diastolic flow velocity of the hepatic vein increases, and the flow pattern of the hepatic venous Doppler waveform is damped.[6,7] However, in cases of liver cirrhosis, this effect is accompanied by portal hypertension, and vascular compliance may be reduced by the increased portal venous pressure as well as parenchymal stiffness, which may lead to damping of hepatic venous flow during inspiration. Hence, we faced a dilemma when seeking to account for the damping of hepatic venous flow during inspiration in cirrhotic patients. We hypothesized that the change in damping between inspiration and expiration might depend on the extent of portal hypertension and would decrease further in high-HVPG patients because venous return during inspiration would not increase as much as usual due to the decreased vascular compliance (Figure 1). Therefore, we suggested that the ΔDI and DI_{ratio} might be novel Doppler parameters that could directly reflect the changes in vascular compliance with liver cirrhosis.

In a previous investigation by Kim et al,[5] a DI_{exp} at a cutoff value of 0.6 permitted the diagnosis of severe portal hypertension with sensitivity of 75.9% and specificity of 81.8%. In our study, a cutoff value of 0.56 gave sensitivity of 66.7% and specificity of 100%. Moreover, the AUC analyses of the receiver operating characteristic curves were very similar (0.860 and 0.861, respectively) in the two studies. Therefore, it also could be suggested that the ΔDI and DI_{ratio} in hepatic veins may be useful for assessing the severity of portal hypertension. In fact, a ΔDI cutoff value of 0.25 gave sensitivity of 83.3% and specificity of 100%, with an AUC (0.889) that was possibly higher than that of the DI_{exp}, although within the margin of error ($P = .617$). Therefore, we believe that these new parameters, which directly indicate decreased vascular compliance, could play a comparable clinical role to that of the DI_{exp}.

With respect to the decision to set the cutoff level of high-grade portal hypertension at 12 mm Hg, we can provide the following justification. In general, when the HVPG is higher than 10 mmHg, it is a predictor of variceal development and decompensated liver cirrhosis, and an HVPG of 12 mm Hg or higher is related to variceal hemorrhage. In addition, a comparable study of the DI on hepatic vein Doppler sonography suggested the same cutoff level for severe portal hypertension.[1]

On the basis of the results of our study, we believe that further investigations are desirable. First, although we obtained preliminary evidence of a correlation between the new hepatic venous Doppler sonographic parameters and a high HVPG, the feasibility of Doppler sonography as a noninvasive predictor of variceal bleeding needs to be established; combining it with other noninvasive imaging modalities such as computed tomography and magnetic resonance imaging might be helpful to this end.[12–14] Second, hepatic venous Doppler sonography may be useful not only as an alternative to HVPG measurement but also for establishing a surrogate marker of clinical- or pathologic-grade liver cirrhosis, although the results of some previous investigations using hepatic Doppler sonography have

Table 3. Area Under the Curve Values of the Doppler Sonographic Parameters

Parameter	AUC	SE	95% CI	Pair-Wise Comparison of AUCs, *P*		
DI_{exp}	0.861	0.091	0.648–0.970	} .617 (DI_{exp} vs ΔDI)		} .745 (DI_{exp} vs DI_{ratio})
ΔDI	0.889	0.073	0.682–0.982		} .479 (ΔDI vs DI_{ratio})	
DI_{ratio}	0.875	0.078	0.665–0.976			

AUC indicates area under the curve; CI, confidence interval; ΔDI, difference between damping indices in the expiratory and inspiratory phases; DI_{exp}, damping index in the expiratory phase; and DI_{ratio}, ratio of damping indices in the expiratory and inspiratory phases.

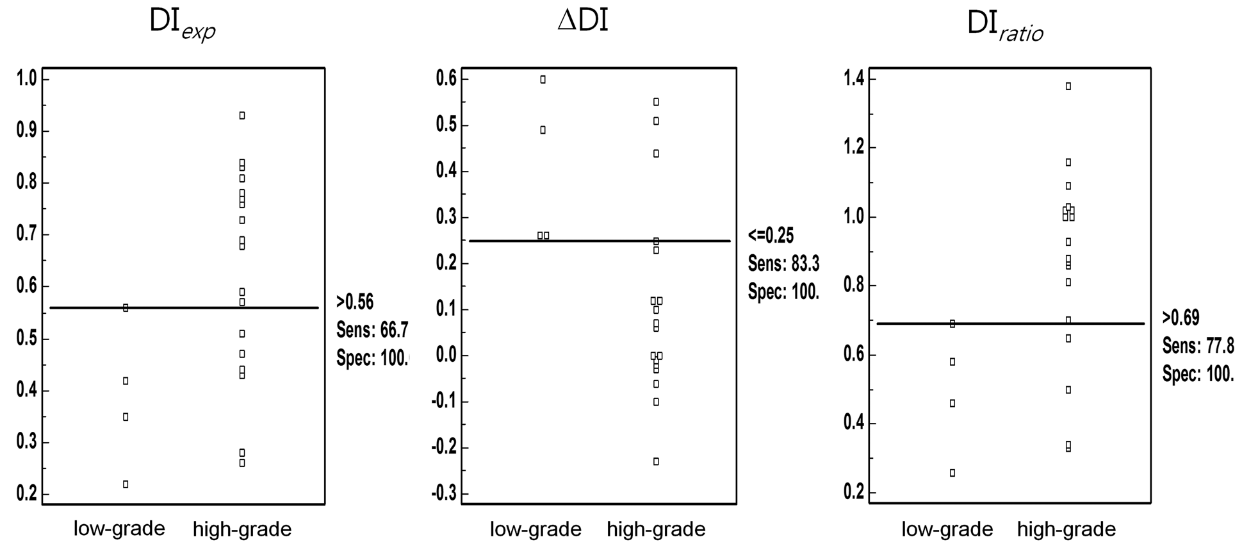


Figure 5. Scatterplots of the sensitivity and specificity for high-grade portal hypertension (≥12 mm Hg) according to the cutoff levels of the various hepatic vein Doppler sonographic parameters. ΔDI indicates damping index difference; DI_{exp}, damping index at expiration; and DI_{ratio}, damping index ratio.

been disappointing.[15,16] Hence, a study comparing Doppler sonography with transient elastography, which has been proven to provide an accurate and noninvasive measure of hepatic fibrosis, would be valuable.[3,17,18]

Our study had some limitations. First, although it was designed to be quantitative, the lack of intraobserver and interobserver validation was a major drawback because all procedures and measurements were performed by the same person. However, some of our results were in agreement with those of previous prospective studies, and this finding may be taken as indirect interobserver agreement. Nevertheless, further investigation to establish the validity of our results is needed. A second limitation was the imbalance between patients (n = 18) and controls (n = 4); however, most of the patients who provided HVPG measurements had decompensated liver cirrhosis and attended our clinic for estimates of their risks of variceal bleeding; therefore, they did not have any choice. This limitation could be overcome by enlarging the study population. Third, the confidence intervals for the sensitivity and specificity of the Doppler parameters were very large. This may have been because the sample was so small; hence, the results of this

Table 4. Cutoff Values for High-Grade Portal Hypertension

Criterion	Sensitivity, %	95% CI, %	Specificity, %	95% CI, %
DI_{exp}				
>0.51	66.7	41.0–86.6	75.0	20.3–95.9
>0.56	66.7	41.0–86.6	100.0	40.2–100.0
>0.57	61.1	35.8–82.6	100.0	40.2–100
ΔDI				
≤0.23	77.8	52.4–93.5	100.0	40.2–100.0
≤0.25	83.3	58.6–96.2	100.0	40.2–100.0
≤0.26	83.3	58.6–96.2	50.0	8.3–91.7
DI_{ratio}				
>0.65	77.8	52.4–93.5	75.0	20.3–95.9
>0.69	77.8	52.4–93.5	100.0	40.2–100.0
>0.70	72.2	46.5–90.2	100.0	40.2–100.0

CI indicates confidence interval; ΔDI, difference between damping indices in the expiratory and inspiratory phases; DI_{exp}, damping index in the expiratory phase; and DI_{ratio}, ratio of damping indices in the expiratory and inspiratory phases.

study should be considered preliminary. The final limitation was that it was difficult to measure the Doppler parameters during free breathing. In particular, the temporal windows in which to measure the inspiratory DI were very small. To overcome this problem, we asked the patients to breathe regularly and slowly, and we obtained the Doppler signals from large sample volumes (≈1–2 cm).

In conclusion, Doppler sonography of the hepatic vein may be helpful in assessing the severity of portal hypertension by combining the ΔDI and DI_{ratio} as a function of respiration as well as using the existing DI on its own.

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