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Hepatic Doppler Ultrasound in Assessment of the Severity of Esophageal Varices in Cirrhotic Patients

Background/Objective: Endoscopy is the gold-standard technique for the assessment of acutely hemorrhagic esophageal varices in patients with hepatic cirrhosis. The objective of this study is to determine the value of different hepatic vasculature Doppler ultrasonography and their flow characteristics for non-invasive assessment of esophageal varices.

Patients and Methods: Fifty-five (31 male, 24 female) consecutive patients with a mean±SD age of 55±16 (range: 20-88) years, with biopsy-proven hepatic cirrhosis were prospectively studied using Doppler ultrasonography. All of these patients were also examined endoscopically and by echocardiography. None of patients had clinical or echocardiographic signs of right heart failure, tricuspid valve regurgitation or previous history of therapeutic interventions on varices. An ordinal logistic regression (OLR) model was used for determining the adjusted associations between sizes of esophageal varices and hepatic hemodynamic determinants.

Results: There was a significant correlation between the size of esophageal varices and maximum portal vein velocity, which was lower in patients with varices ($p = 0.04$). Other parameters though not statistically significant, were of clinical importance. Those included portal vein mean velocity ($p = 0.08$), hepatic artery volume flow ($p = 0.06$) and hepatic venous waveform pattern ($p = 0.15$). OLR model did not show any significant adjusted associations between these parameters and the size of esophageal varices.

Conclusion: The maximum portal vein velocity and to a lesser extent, hepatic artery volume flow were superior to Doppler ultrasonographic spectral waveform pattern of hepatic vein in differentiating patients with esophageal varices from those with no varices. None of hepatic vasculature Doppler measurements had a significant role in predicting the size of esophageal varices, nonetheless.

Keywords: esophageal and gastric varices, Doppler ultrasound, liver cirrhosis

Introduction

Acute hemorrhage from esophageal varices in patients with liver cirrhosis has a high early mortality rate even when emergently treated.[1] Current guidelines in both Europe and the United States advise that cirrhotic patients undergo endoscopic gastroduodenoscopy every 1–2 years for the presence of esophageal varices.[2,3] The risk of bleeding from these varices is associated with the severity of the liver disease and the size of varices; both these factors are the most important predictors of bleeding.[4,5] It is estimated that approximately 60%–80% of patients with cirrhosis develop esophageal varices during their life at a rate of 5% per year, and the progression from small to large varices occurs in 5%–10% of patients after the first year.[6-9] There is a considerable mortality risk after the first event of bleeding; hence, prophylactic measures is mandatory.[10,11] Upper gastrointestinal tract endoscopy, which is the most common and accurate procedure for evaluation of varices, is somewhat inconvenient for patients.[12,13]

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It also bears a risk, albeit small, of complications like esophageal perforation, aspiration of gastric contents and bacteremia.[14,15] Moreover, sedation with benzodiazepines usually used for this procedure can significantly exaggerate hepatic encephalopathy.[16]

So far, many attempts have been made to find less invasive techniques to assess these patients.[17] Doppler ultrasonography can be regarded as an attractive and non-invasive alternative method and may provide useful functional information. Many investigations reported correlations between different hepatic vasculature Doppler indices and the severity of portal hypertension and the resultant esophageal varices.[18-26] Our study aimed to determine what Doppler indices of hepatic vessels can be used to predict the presence and to evaluate the severity of esophageal varices.

Patients and Methods

Fifty-five (31 male, 24 female) cirrhotic patients were enrolled in this cross-sectional study conducted over 12 months in Taleghani University Hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran.

The patients had heterogeneous etiologies for their cirrhosis; though, there were mostly secondary to either hepatitis B- or hepatitis C-induced chronic hepatitis.

Exclusion criteria included any prior surgical or interventional procedures for treatment of esophageal varices, right ventricular failure, tricuspid regurgitation, presence of portal vein thrombosis or history of Budd-Chiari syndrome.

All patients had undergone percutaneous liver biopsy (as a must to provide histopathologic confirmation of cirrhosis), upper gastrointestinal endoscopy, echocardiography and hepatic vasculature Doppler ultrasonography. All had biopsy-proven hepatic cirrhosis. Esophagoscopy and echocardiography were performed by an expert board-certified gastroenterologist and a cardiologist, respectively, both blinded to the test results.

Endoscopic severity of esophageal varices was classified into four grades (grades I to IV). The severity was in grade I when there were small and non-concentric varices with lacking any intraluminal prolapse; grade II was when there were somewhat intraluminally prolapsed varices with minimal obscuration of gastroesophageal junction; grade III was when there were larger varices showing intraluminal prolapse and substantially obscuring gastroesophageal junction and grade IV was when there were very large varices which completely obscured the gastroesophageal junction.[27] We considered grades I and II as "small varices" and grades III and IV as "large varices." Presence of varices with both grades II and III was regarded as "small and large varices."

All Doppler assessments were performed by a single radiologist using a 3.5 MHz curvilinear transducer of CF-Sonic 7500 ultrasound machine (Fukuda-Denshi Co, Tokyo, Japan).

Patients were examined while fasting and in supine position and quiet respiration. Subcostal or intercostal ultrasonic windows were used to obtain longitudinal view of middle hepatic vein, portal vein and hepatic artery (in front of portal vein) with an ultrasound beam incidence angle of less than 60º. The Doppler sample volume was located in the vessel center, covering at least half of the vessel diameter. In case of velocity determinations, Doppler incidence angle was corrected to reduce measurement errors of velocity.

Measurements of the middle hepatic vein were taken at least two centimeters from its confluence point with other hepatic veins to form the inferior vena cava. Hepatic vein spectral waveforms were classified as triphasic (consisting of two antegrade components directed toward the liver and a single retrograde flow component), biphasic (presenting two antegrade flow components of remarkably different magnitude) or monophasic (showing minimal or no phasic motion of antegrade flow) as shown in Figure 1.

Outer-to-outer main portal vein diameter (mm) was measured in midway between the spleno-portal junction and its intrahepatic bifurcation.[28]

Other evaluated portal flowmetry indices were the maximum and mean portal vein velocities (cm/s) automatically measured on spectral waveforms as well as portal vein volume flow (mL/min) which was automatically calculated, based on the following formula:

$$\textit{Portal vein volume flow} = \textit{Mean velocity} \times \textit{Cross sectional area} \times 60$$

Corresponding measurements are shown in Figure 2.

Hepatic artery indices were also measured just anterior to the site of portal vein measurements. These indices included peak systolic and end-diastolic velocities (cm/s), hepatic artery volume flow (mL/min) and its resistive index, acceleration time (s), acceleration index and pulsatility index (Fig. 3).

For determining crude associations, univariate analysis was performed by One-way ANOVA, Kruskal-Wallis and likelihood ratio Chi-square tests. A p value less than 0.05 was considered statistically significant. An ordinal logistic regression (OLR) model was used for determining the adjusted associations between size of esophageal varices and hepatic hemodynamic determinants.

We used STATA® SE version 8 (1984-2007, Texas, USA) for statistical analyses.

Results

The mean(SD) age of patients was 55(16) (range: 20–88) years. Nine (0.16) patients had no varices; 22 (0.40) had small, 13 (0.24) had large and 11 (0.20) had both small and large varices.

The most frequent concomitant ultrasonic finding in these patients was ascites (Fig. 1-C), which was found in 22 (0.40) patients.

There were no significant associations between size of varices and gender (p = 0.24) or age (p = 0.45) of patients.

The associations between hemodynamic characteristics of portal vein and hepatic artery on one hand and the presence and size of varices on the other hand are summarized in Table 1. There was a significant association between the maximum portal vein velocity and the size of varices (p = 0.04). Although

Table 1. Hemodynamic characteristics of portal vein and hepatic artery in patients with different endoscopic findings of esophageal varices*

	No Varices	Small	Large	Small and Large	P value
Portal Vein					
Diameter (mm)	11.2 (9.9-12.5)	12.7 (11.7-13.7)	11.4 (9.3-13.5)	12.3 (9.3-15.5)	0.38
Volume flow (mL/min)	592 (161-1023)	620 (362-878)	417 (249-585)	405 (194-617)	0.59
Mean velocity (cm/s)	15.5 (10.8-20.2)	11.38 (9.2-13.6)	10.47 (6.6-14.4)	9.78 (7.9-11.6)	0.08
Maximum velocity (cm/s)	19.5 (12-27)†	13.25 (10.7-15.8)‡	12.5 (8-17)‡	11.7 (9.4-14)‡	0.04
Hepatic Artery					
Peak Systolic Velocity (cm/s)	70.6 (51.7-89.6)	60.6 (48.8-72.4)	70.9 (56.2-85.8)	54.8 (35.5-74.1)	0.37
End Diastolic Velocity (cm/s)	19.5 (15.9-23.2)	16.3 (12.9-19.8)	19.9 (16.2-23.6)	16.9 (8.2-25.7)	0.49
Resistive Index	0.69 (0.60-0.79)	0.72 (0.69-0.76)	0.71 (0.68-0.75)	0.69 (0.61-0.78)	0.83
Pulsatility Index	1.46 (1.05-1.87)	1.57 (1.35-1.8)	1.38 (1.18-1.6)	1.46 (1.07-1.84)	0.70
Acceleration Time (s)	69.1 (51.6-86.5)	74.7 (59.9-89.5)	80.6 (66.2-94.9)	67.8 (56.8-78.7)	0.66
Volume Flow (mL/min)	353 (208-500)	203 (125-282)	266 (183-350)	170 (83-257)	0.06
Acceleration Index	0.76 (0.47-1)	0.67 (0.49-0.86)	0.64 (0.52-0.76)	0.52 (0.4-0.65)	0.49

* The numbers in the parentheses represent 95% confidence intervals for measurements.
†, ‡: Difference in subgroups, based on Bonferroni post-hoc test (p value ≈ 0.02)

Table 2. Adjusted associations between important Doppler measures and size of varices in cirrhotic patients based on an ordinal logistic regression model * §

Hemodynamic Measures	Coefficient ($CI_{95\%}$)‡	P value †	Odds Ratio ($CI_{95\%}$)‡
Portal Vein Maximum Velocity (cm/s)	-0.08 (-0.17 – 0.01)	0.09	0.92 (0.84 – 1.01)
Hepatic Artery Peak Systolic Velocity (cm/s)	-0.000 (-0.004 – 0.003)	0.86	0.999 (0.995 – 1.002)
Monophasic Waveform Pattern of Hepatic Vein	0.80 (-0.57 – 2.19)	0.25	2.25 (0.56 – 8.91)
Biphasic Waveform Pattern of Hepatic Vein	-2.38 (-4.91 – 0.16)	0.07	0.09 (0.01 – 1.18)

*model characteristics: Log likelihood = -47.45; LR chi square (4) = 12.46; p value = 0.0143
§ Ancillary parameters (standard error): cut1: -2.99(0.94); cut2: -0.65 (0.79); cut3: 0.80 (0.83)
† Based on Wald test
‡ Confidence intervals for the level of 95%

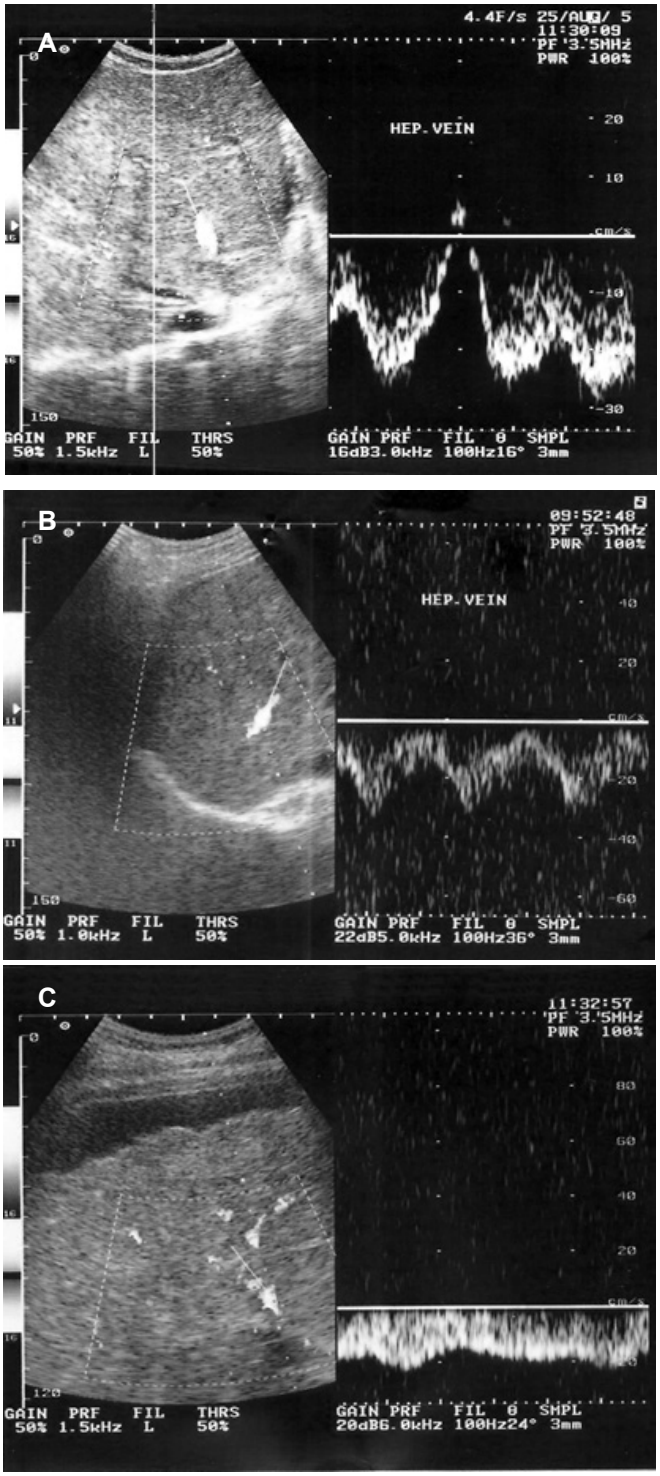

Fig. 1. Doppler spectral waveforms of hepatic vein showing different flow patterns including;

A, A triphasic pattern with two antegrade and a single retrograde flow components.

B, A biphasic pattern with two different in magnitude antegrade flow velocity components.

C, A monophasic pattern with subtle velocity changes during the heart cycle and respiration. Also, note the presence of ascites in **C** seen in front of hepatic parenchyma.

none of other portal vein measurements had statistically significant associations with the size of varices, some of them, such as portal vein mean velocity as well as hepatic artery volume flow, were of clinical importance.

The associations between hepatic venous Doppler spectral waveform and the size of esophageal varices is shown in Figure 4. Approximately, 36% of patients had triphasic pattern; 11% had biphasic form and 53% of patients had monophasic spectrum. No statistically significant association was however found (p = 0.15). If instead of considering three patterns, hepatic venous waveform patterns were classified into two separate dummy variables, *i.e.,* monophasic and biphasic patterns, the difference became statistically significant (p = 0.04). In this way, the waveform pattern may also be a clinically important measure.

Using an OLR model, the adjusted associations among the above-mentioned factors and size of varices were computed (Table 2). The portal vein mean velocity was omitted from the model because of its co-linearity with the maximum velocity. None of the considered measures had a statistically significant association with the severity of esophageal varices (Table 2) and therefore cannot be used for estimation of their size. However, if the classification was reduced to monophasic *vs* biphasic waveforms, with point estimated odds ratios of 2.25 and 0.09, respectively, these two waveform patterns could be used as predictors for size of varices.

Discussion

So far, many applications of ultrasound, including those of endoscopic ultrasound, in the management of esophageal varices in portal hypertension have been reported.[29,30]

Some reports suggested that the portal vein hemodynamics is relevant to the severity of esophageal varices found in endoscopic evaluation. In the majority of studies, portal vein velocity was found to be significantly lower in patients with varices;[18-21] in a few of them, portal vein volume flow was also reported to be lower in patients who had variceal bleeding.[18,19] In study of Korner, the overall sensitivity for prediction of variceal bleeding in case of decreased portal vein mean velocity was 88% and that of its reduced volume flow was 65%.[19]

Our study showed that the maximal portal venous

velocity in cirrhotic patients can differentiate presence from absence of esophageal varices; however, it cannot determine its severity. In fact, this finding can be in concordance with those of Korner, because portal vein maximal flow velocity and mean velocity are proportionate to each other, relevant to its relatively steady flow.

Furthermore, some articles have shown that portal vein diameter is also increased in high grade large varices;[18,22,23] such a finding was not observed in our study.

Iwao, *et al*, showed that not only portal venous velocity was significantly lower, but the hepatic arterial pulsatility index was also significantly higher in patients with esophageal varices.[24] We did not find any other reports regarding associations between hepatic artery flow parameters and presence and/or size of varices.

Our study results did not disclose any significant associations between hepatic artery pulsatility index and esophageal varices status. It revealed that its volume flow may have an important role in detecting the presence of varices, albeit this parameter could not predict the size of varices. This association may be in part attributable to a considerable volume of blood which is pooled in varices, leading to reduced blood flow through the hepatic arteries. Although portal venous velocity was noted to be diminished in those who had varices, their portal vein dilation, secondary to portal hypertension has resulted in absence of significant decrease of portal venous volume flow; in case of hepatic artery, there was no arterial dilation and thus, the volume flow was decreased, as well.

On the other hand, the study performed by Letard, *et al*, demonstrated that there was no relationship between the prevalence of esophageal or gastric varices and the pattern of portal venous flow.[25] Recently, De Bem, *et al*, also revealed that there is no good correlation between Doppler ultrasound parameters of the portal system and the presence of gastroesophageal varices in cirrhotic patients.[26]

Considering the splenic vein, Kayacetin, *et al*, showed that those with esophageal variceal bleeding had significantly greater splenic blood flow volume and splenic vein congestion index.[31] We did not observe such a finding in our study.

The progressive structural changes in the liver in association with an increased resistance through hepatic and portal veins in cirrhosis seem to be the cause of a transform of normal triphasic hepatic vein Doppler waveform into less oscillating spectra. In a study performed by Gorka, *et al*, the diagnostic sensitivity of monophasic hepatic vein Doppler waves for detection of large varices was 92%, while that of biphasic waveforms was reported to be 62%.[18] In our study, hepatic vein Doppler flow pattern changes, if classified into

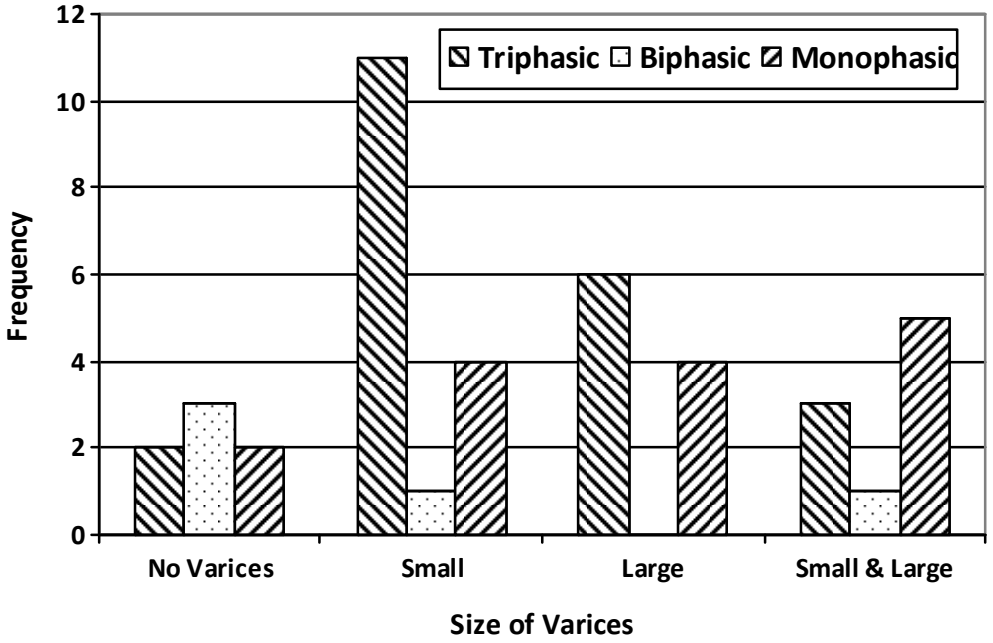

Fig. 4. Hepatic vein Doppler 879 pattern in different subgroups of esophageal varices.

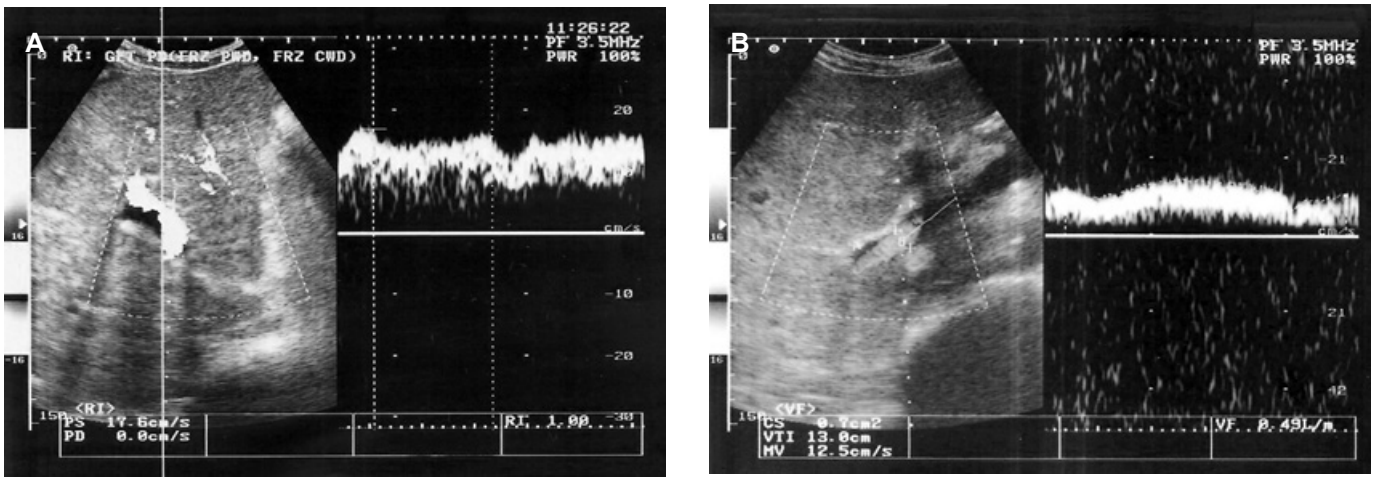

Fig. 2. Doppler spectral waveforms of portal vein showing a relatively steady flow throughout its center.

A, Shows measured maximal portal vein velocity (17.6 cm/s) in a patient.

B, Displays a measured cross-sectional area of 0.7 cm^2, velocity-time integral of 13.0 cm, mean velocity of 12.5 cm/s and volume flow of 490 mL/min of portal vein in another patient.

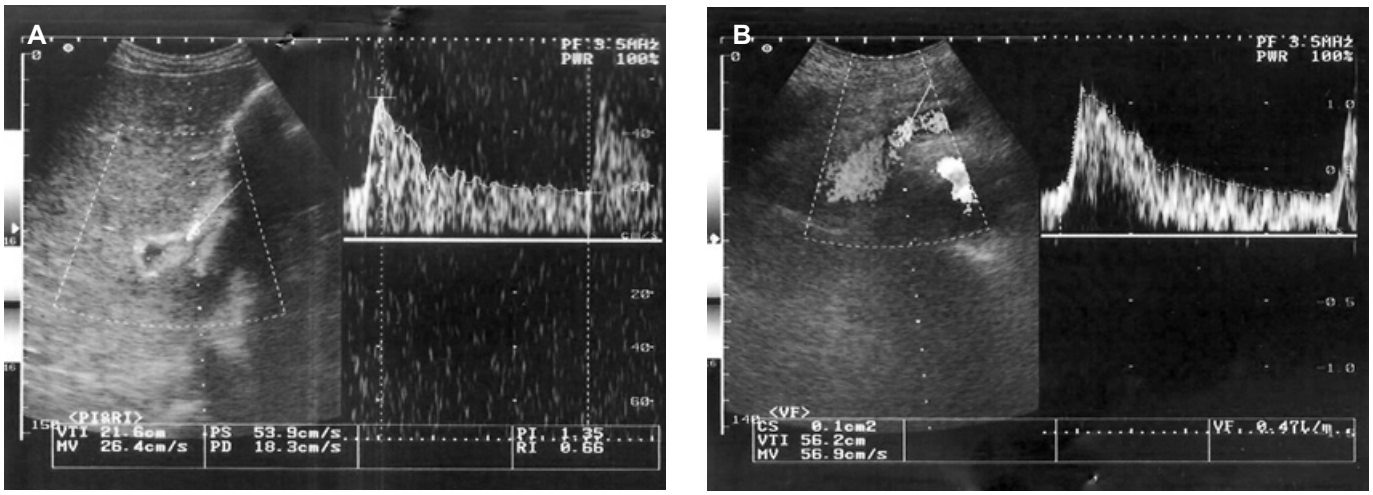

Fig. 3. Doppler spectral waveform of hepatic artery in two different patients.

A, Showing measurement of velocity-time integral of 21.6 cm, mean velocity of 26.4 cm/s, peak systolic velocity of 53.9 cm/s, end-diastolic velocity of 18.3 cm/s, pulsatility index of 1.35 and a resistive index of 0.66.

B, Demonstrating measurement of hepatic artery cross-sectional area of 0.1 cm^2, velocity-time integral of 56.2 cm, mean velocity of 56.9 cm/s, and volume flow of 470 mL/min.

three different types, were unable to predict the severity of esophageal varices or even differentiate their presence from absence, while when the waveform pattern was classified into two types, it could somewhat discriminate varices based on their size. This finding may be attributed to the relatively low sample size of our study. Further assessments, using larger groups of patients may obviate this problem.

Hepatic venous pressure gradient measurements are regarded as an accurate index for detection of hepatic venous changes in these patients.[32] It is also considered a confident technique to predict the likelihood of bleeding of varices and response to medical treatments.[33] Study of Choi, *et al*, displayed that there is no correlation between Doppler measurements and hepatic venous pressure gradient.[34] This may be considered as a confirmation for our findings of lack of correlation between Doppler waveform pattern and esophageal varices status. However, Baik, *et al*, recently showed that Doppler waveform assessment of hepatic vein is useful in the noninvasive evaluation of the severity of portal hypertension and the response to vasoactive agents in patients with portal hypertension and variceal bleeding.[35] On the other hand, Halpern recommended further clinical assessments performance to confirm the results of Baik, *et al*, study to determine whether hepatic venous Doppler waveform tracings can actually be used to assess portal

pressure and monitor patient response to therapy.[36]

The major drawback of our study is a relatively small sample size. Moreover, heterogeneity of etiologies of cirrhosis in our patients may have led to somewhat heterogeneous findings. Therefore, it remains to be seen whether results of other larger studies with more homogeneous patient groups confirm our findings. Another important limitation of this investigation is a history of prior different medical prescriptions which had undoubted effects on their disease process and we did not excluded these group of patients from our study.

In conclusion, we found that the most reliable predictor of presence of esophageal varices is the portal vein maximal velocity. Hepatic artery volume flow can in some extent predict whether there are varices or not. Nevertheless, it was not a reliable predictor for determining the severity of varices. Hepatic vein Doppler waveform pattern does not have any predictive values in this concern if it is classified into three patterns. However, if it is categorized into two types—monophasic *vs* biphasic patterns—it can be used as an acceptable predictor.

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