

Hemodynamic Changes of Hepatic Veins as Predictors of Large Oesophageal Varices in Liver Cirrhotic Patients

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Background and study aim:

Oesophageal varices (OV) are morbid and mortal complications of portal hypertension. Oesophago-gastroduodenoscopy (OGD) is the main diagnostic yet semi- invasive tool; different non-invasive methods were developed for early prediction and assessment of OV yet not fully evaluated. This work aims at assessment of changes of hepatic venous wave patterns as early predictors of large OV in cirrhotic patients without history of variceal bleeding.

Patients and methods: A number of 50 previously diagnosed liver cirrhotic patients were subjected to detailed history taking. After exclusion criteria only 46 patients were included in the study. They were subjected to routine investigations, OGD, abdominal ultrasound (US) and

Color Doppler studying of the hepatic veins (HV).

Results: Out of the total number (46 liver cirrhotic patients included in the study), the triphasic waves were detected in (26.1%), biphasic waves in (43.5%) and monophasic waves in (30.4 %). Small varices were detected in (65.2 %), while large varices were detected in (34.8 %). The sensitivity of loss of the triphasic waveform in detecting large varices was high (93.8 %), specificity was (36.7 %), the positive predictive value was (44.1 %) and the negative predictive value was high (91.7 %).

Conclusion: The loss of hepatic venous triphasic waveform - detected by Color Doppler Abdominal Ultrasound Study- is a weak predictor of large OV in liver cirrhotic patients without history of variceal bleeding.

INTRODUCTION

Oesophageal varices (OV) are one of the most awful complications of liver cirrhosis. Its incidence in cirrhotic patients ranges between 60- 80%. Upper gastrointestinal bleeding (UGB) - caused mainly by rupture of OV and to less extent by gastric varices - is disastrous implying a mortality rate of 17- 57% of these prone patients [1]. OV are the direct result of portal hypertension and their presence is usually correlated with the severity of liver disease. About 45% of patients with Child-Pugh A cirrhosis were found to have OV while this percentage jumps to 85% in those with Child- Pugh C [2]. The frequency of bleeding from large OV is 50-53% while that of small OV is 5-18% that can be attributed to the increased variceal wall tension in large OV [3,4].

Because of the dramatic destiny of OV, it is highly recommended to screen all liver cirrhotic patients for the presence of OV at the time of diagnosis and periodically by Oesophagogastrroduodenoscopy (OGD). If OV were not detected in the first endoscopic screening, reevaluation after three years is recommended in compensated liver cirrhotic patients and annually in decompensated liver cirrhotic patients [5-7]. OGD is the gold standard diagnostic method of OV. However, many drawbacks were recorded against OGD including its invasiveness, risk of perforation, aspiration and bacteremia. Moreover, it is not accepted by many patients [8,9] and the cost of repeated screening stressed the need to develop non- invasive techniques for early prediction of recent, developing and large OV to reduce the frequency of

OGD so that it can be preserved for highly suspected cirrhotic patients [10,11]. Many clinical, radiological and chemical predictor methods were advocated either separately or in combinations such as platelet count, studying the spleen with portal vein diameter and Child-Pugh class [12-15].

Multiple Doppler indices were suggested to assess the severity of portal hypertension in cirrhotic patients including the study of hepatic venous waveform changes [16-19]. The normal hepatic venous waveform pattern is triphasic (two negative waves and one positive wave) according to variations in the central venous pressure of the cardiac cycle, but it changes to the biphasic and monophasic pattern in cirrhotic patients (Fig. 1). These changes are attributed to the progressive loss of hepatic compliance. Monophasic waves were found to correlate with the severity of liver disease (high scores of Child-Pugh classification) and poor survival rate [20-23].

This work aims at evaluating the changes of hepatic venous waveform as early predictors of large OV in liver cirrhotic patients without history of variceal bleeding.

PATIENTS AND METHODS

This is a collaborated work between Tropical Medicine, General Surgery and Radiology Departments, Faculty of Medicine, Zagazig University.

Inclusion criteria: The already diagnosed liver cirrhotic patients attending to Tropical outpatient clinic or admitted in the ward of Tropical Medicine Department, Zagazig University Hospitals were included in the study. The diagnosis of liver cirrhosis was already established by clinical approach, laboratory investigations, routine abdominal ultrasound, endoscopic data and liver biopsy.

Exclusion criteria: Patients with history of variceal bleeding, hepatocellular carcinoma, portal vein thrombosis, endoscopic variceal ligation or sclerotherapy were excluded from the study. Patients with cardiac, respiratory or renal diseases or those under treatment with drugs affecting portal haemodynamics (eg. propranolol) were also excluded.

All included patients were subjected to thorough history taking, clinical examination, routine

laboratory investigations, routine abdominal US and Child- Pugh classification. Then they were subjected to:

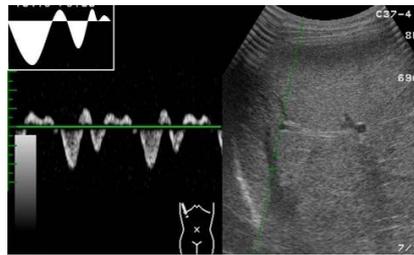
***Oesophagogastroduodenoscopy (OGD):** OV were graded according to the guidelines of the American Association for the Study of Liver Diseases (AASLD) considering them small if less than 5 mm diameter and large if more than 5 mm diameter [24].

***Abdominal ultrasound examination:** It was done according to the following steps.

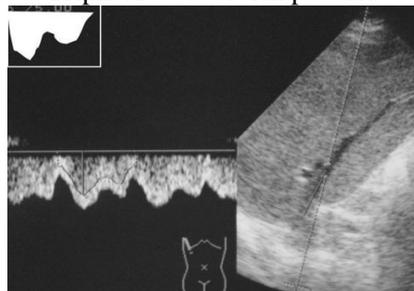
1. After 6-8 hours fasting, all patients were subjected to routine B- mode abdominal ultrasound (US) examination of the liver assessing the size, echogenicity, border irregularity and exclusion of focal lesions.
2. Doppler ultrasound using the 3.5 MHz convex probe (GE, Logic III US, expert, USA). The portal vein first assessed for exclusion of thrombosis then the probe was placed in the right intercostal spaces for tracing of the hepatic veins. Color Doppler was used to identify the pattern of blood flow in the hepatic veins.
3. Spectral analysis of the hepatic venous waveform pattern was obtained from the right hepatic vein 3 - 6 cm from its junction with inferior vena cava [25]. The middle hepatic vein was used for spectral analysis in some cases instead of tracing of the right hepatic vein.
4. Doppler study of waveforms of hepatic veins was recorded for at least 5-10 seconds during quiet breathing or at the end-inspiratory point with breath holding if quiet breathing is not possible. Three records were usually taken for each patient.
5. Color Doppler flow mapping was interpreted as a blue hepatic vein waveform indicating flow away from the US probe and a red hepatic vein waveform indicating flow toward the US probe.
6. Hepatic venous waveforms were classified into:
 - Triphasic (normal) waves with reversed flow in at least one phase. It is considered triphasic if recognized in at least one of three records.
 - Biphasic waves without reversed flow and with or without diminished phasic oscillation.

It is considered biphasic if recognized in at least one of three records.

- Monophasic or flat pattern with or without fluttering. It was considered if the three records are monophasic.



Triphasic waveform pattern.



Biphasic waveform pattern.



Monophasic waveform pattern.

Figure (1): Hepatic venous waveform pattern

Statistical Analysis:

The relation between US wave and OV Size and some factors (age, sex, duration of illness, severity of liver disease) were done using the Pearson chi square test. The role of lost triphasic pattern in predicting large varices was determined by sensitivity, specificity, positive and negative predictive values and Kappa (K) measure of agreement.

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive} + \text{false positive}}$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative} + \text{false negative}}$$

Probability equal or less than 0.05 is considered significant. Data analysis was done using Statistical package for social

sciences (SPSS, version 15.0; Chicago, IL, USA).

Ethical approval:

Informed consent was taken from each patient. The research protocol was duly approved by the ethical committee of Zagazig University Hospitals.

RESULTS

A total number of 50 patients were suggested for the study. After exclusion criteria, 46 patients were included in the study. Males were 24 patients (52.2%), while females were 22 patients (47.8%). Their ages ranged between 19 and 62 years (35.17 ± 13.9). According to Child-Pugh classification, Child-Pugh class A included 24 patients (52.2%), Child-Pugh class B included 10 patients (21.7%) and Child-Pugh class C included 12 patients (26.1%). The duration of illness was less than 4 years in 17 patients (37%), 4-8 years in 17 patients (37%) and more than 8 years in 12 patients (26%). Patients with small OV were 30 patients (65.2%) while those with large OV were 16 (34.8%). Patients with monophasic waves were 14 (30.4%), biphasic waves were 20 (43.5%) and those with triphasic waves were 12 (26.1%) (Table 1).

Table (2) showed that large OV were mainly represented among patient age group 25- 50 years while small OV were mainly represented among patients less than 25 years. Small OV were more prevalent than large OV among all age groups. However the differences were non-significant.

Large OV were mainly represented among patients with duration of illness more than 8 years, while small OV were mainly represented among patients with duration of illness less than 4 years. Large OV were more prevalent than small OV among patients with duration of illness more than 8 years, while small OV were more prevalent than large OV among patients with duration of illness 4-8 years or less than 4 years. The differences were significant.

Large OV were more prevalent among Child-Pugh class C patients, while small OV were more prevalent among Child-Pugh class A patients. Large OV were more prevalent among Child-Pugh class B and C patients, while small OV were more prevalent among Child-Pugh

class A patients. The differences were highly significant.

There was a non – significant difference regarding the size of OV between males and females.

Table (3) showed that triphasic waves were the most prevalent pattern among Child-Pugh class A patients, while biphasic waves were the most prevalent pattern among Child- Pugh class B and C patients. The differences were significant.

Biphasic waves were the most prevalent pattern among males, while triphasic waves were the most prevalent pattern among females. However the differences were non- significant.

Monophasic waves were the least prevalent pattern among patients younger than 25 years, while biphasic waves were the most prevalent pattern among patients 25- 50 years. Monophasic and biphasic waves were equally presented in patients older than 50 years, while triphasic waves were not encountered among this age group. All the differences were non- significant.

Biphasic waves were the most prevalent pattern among patients with duration of illness less than 4 years, while monophasic waves were the least prevalent pattern among patients with duration of illness 4- 8 years and biphasic waves were the most prevalent pattern among patients with

duration of illness more than 8 years and no triphasic waves were encountered among this group. However, the differences were non-significant.

Biphasic waves were the most prevalent pattern among patients with small OV, while monophasic waves were the least prevalent pattern among patients with large OV and Biphasic and triphasic waves were equally presented in this group. All the differences were non-significant.

Table (4) shows that the sensitivity of monophasic waves to detect large OV was 42.9 %, while specificity was 57.9 %. The positive predictive value (PPV) was 85.7 %, while the negative predictive value (NPV) was 91.7 %.

The sensitivity of biphasic waves to detect large OV was 90 %, while the specificity was 50%. The PPV was 45%, while the NPV was 91.7 %.

The sensitivity of loss of triphasic waves (presence of monophasic or biphasic waves) to detect large OV was 93.8 %, while the specificity was 36.7 %. The PPV was 44.1 %, while the NPV was 91.7 %.

The overall result was the non- significant agreement between the results of OGD findings and the results of Doppler Abdominal US.

Table (1): Distribution of age, sex, duration of liver cirrhosis, Child- Pugh classification, OV size and Doppler US waveform among studied patients.

	Total No of patients (46)	
	No	%
Sex		
Male	24	52.2
Female	22	47.8
Age/year		
<25	17	37.0
25- 50	19	41.3
50+	10	21.7
$\bar{X}\pm SD$ (Range)	35.17 \pm 13.9 (19-62)	
Child- Pugh classification		
A	24	52.2
B	10	21.7
C	12	26.11
Duration of liver cirrhosis/years		
< 4	17	37.0
4- 8	17	37.0
8+	12	26.0
OV size		
Small	30	65.2
Large	16	34.8
Doppler US waveform		
Monophasic	14	30.4
Biphasic	20	43.5
Triphasic	12	26.1

Table (2): Relation between age, sex, duration of liver cirrhosis, child- Pugh classification and OV size.

Total = 46 patients	Large		Small		X ²	P-value
	No (16)	(34.8%)	No (30)	(65.2%)		
Age/years						
<25	5	29.4	12	70.6	0.76	0.68
25- 50	8	42.1	11	57.9		
50+	3	30.0	7	70.0		
Duration of liver cirrhosis /years						
<4	3	17.6	14	82.4	7.79	0.02*
4- 8	5	29.4	12	70.6		
8+	8	66.7	4	33.3		
Child- Pugh classification						
A	2	8.3	22	91.7	15.58	0.000**
B	6	60.0	4	40.0		
C	8	66.7	4	33.3		
Sex						
Male	8	33.3	16	66.7		
Female	8	36.4	14	63.6		

*significant

** highly significant

Table (3): Relation between hepatic venous waveform detected by Doppler US and some factors including age, sex, Child- Pugh classification, duration of liver cirrhosis and OV size.

Total No = 46 patients.	Mono		Bi		Tri		X ²	P
	No 14	(30.4%)	No 20	(43.5 %)	No 12	(26.1 %)		
Child- Pugh classification								**
A	7	29.2	5	20.8	12	50	17.63	0.001
B	4	40.0	6	60.0	0	0.0		
C	3	25.0	9	75	0	0.0		
Sex								
Male	9	37.5	13	54.2	2	8.3	8.2	0.1
Female	5	22.7	7	31.8	10	45.5		
Age								
<25	5	29.4	6	35.3	6	35.3	5.62	0.22
25-50	4	21.1	9	47.4	6	31.6		
50+	5	50.0	5	50.0	0	0.0		
Duration of liver cirrhosis /years								
<4	4	23.5	7	41.2	6	35.3	5.89	0.21
4- 8	5	29.4	6	35.3	6	35.3		
8+	5	41.7	7	58.3	0	0.0		
OV-size								
Small	6	37.5	9	56.3	1	6.3	5.02	0.08
Large	8	26.7	11	36.7	11	36.7		

** highly significant

Table (4): Validity of US hepatic venous waveform for the diagnosis of large OV.

Total no=46 Waveform	True +ve	True -ve	Sensitivity	specificity	PPV	NPV	Kappa	P
Monophasic alone	6	11	42.9 %	57.9 %	85.7	91.7	0.33	0.04 *
Biphasic alone	9	11	90.0 %	50.0 %	45.0	91.7	0.31	0.03 *
Combined Monophasic-Biphasic.	15	11	93.8 %	36.7 %	44.1	91.7	0.24	0.02 *

*significant

DISCUSSION

OV bleeding in liver cirrhotic patients is a critical medical emergency associated with a high mortality rate [26]. Large OV is an additional risk factor that predicts impending variceal bleeding [27]. Non- invasive prediction of large OV is a stressing need to allow early medical or OGD interference in patients with impending variceal bleeding [28].

Our study showed that Large OV were significantly associated with longer duration of liver cirrhosis while small OV were significantly associated with shorter duration of liver cirrhosis. This can be explained by the time availability for the development of portal hypertension and the formation of large OV.

These results agree with those of Palmer [29] and Cales et. al., [30] who found that longer duration of liver cirrhosis was significantly, associated with the occurrence of large oesophageal varices.

Our study showed that large OV were more prevalent than small OV among Child-Pugh class B&C patients while small OV were more prevalent than large OV among Child-Pugh class A patients and the differences were highly significant. This means that large OV were more prevalent among patients with more severe liver disease while small OV were more prevalent among patients with less severe liver disease. This can be explained by the progressive increase in variceal wall tension with increased severity of liver disease and the eventual increase in portal hypertension. Our results agree with

those of Zaman et. al., [31] and Cherian et. al., [28] who found that advanced Child-Pugh class and low platelet count were associated with the presence of large OV.

Our study showed that hepatic venous triphasic waves were more encountered than other waves among Child- Pugh class A patients while biphasic waves were the most encountered among Child- Pugh class B&C patients. The differences were highly significant. This means that there was a relation between loss of hepatic venous triphasic waves and the severity of liver disease. This can be explained by the progressive decrease of hepatic compliance with the eventual increased severity of liver disease. This result agrees with that of Bhutto et. al., who found a significant relation between hepatic venous waveform pressure changes and the severity of hepatic dysfunction [32].

Our study showed that hepatic venous biphasic waves were the most encountered than other waves among patients with small OV, while monophasic waves were the least encountered among patients with large OV, however the differences were insignificant. The negative predictive values of biphasic and / or monophasic hepatic venous waveforms to diagnose large OV were very high that denote a poor agreement between loss of hepatic venous triphasic waves and the size of OV and that the loss of hepatic venous triphasic waves is a weak predictor of large OV. This result agrees with that of Bhutto et. al., [32] and Shabestari et. al., [33] who found an insignificant relation between hepatic venous waveform changes and the grading of oesophageal varices.

On the other hand, these results do not agree with those of Gorka et. al., [34] in a Saudi Arabian study, and Josepf et. al., [25] in an Indian study, who found that the loss of hepatic venous triphasic waves is a highly sensitive predictor of large OV. In the same direction Baik et. al., [35] - in their South Korean study- found that the assessment of Doppler US hepatic venous waveform is a useful non-invasive predictor of the severity of portal hypertension. This controversy can be attributed to many environmental, pathological and nutritional differences that can affect the pathogenesis of portal hypertension and hepatic venous waveform changes. The different inclusion and exclusion criteria could add to the different results such as studying patients with recent

variceal bleeding while our study included only cirrhotic patients without previous history of variceal bleeding.

CONCLUSION

Loss of hepatic venous triphasic waves - detected by Color Doppler Ultrasound- is a weak predictor for the diagnosis of large OV in liver cirrhotic patients without history of variceal bleeding.

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Ethical approval: Approved.

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