Evaluation of Splenic Stiffness in Patients of Extrahepatic Portal Vein Obstruction Using 2D Shear Wave Elastography: Comparison with Intra-Operative Portal Pressure

Kumble S. Madhusudhan^{*}, Ragini Kilambi[†], Shalimar[‡], Sujoy Pal[†], Raju Sharma^{*}, Deep N. Srivastava^{*}

^{*}Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi 110029, India, [†]Department of Gastrointestinal Surgery, All India Institute of Medical Sciences, New Delhi 110029, India and [‡]Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India

Background/Aims: To compare splenic stiffness (SS) with intra-operative portal pressures (PPs) in patients of extrahepatic portal vein obstruction (EHPVO). **Methods:** Twenty-one patients (14 males; 7 females) of mean age 20.4 years with clinical and sonographic diagnosis of EHPVO were included in this approved prospective study. Endoscopy for esophageal varices (EV) was done in all patients followed by ultrasonographic 2D shear wave elastography (SWE) of spleen. Three values were taken at different areas of spleen avoiding major vessels and mean was calculated. Intra-operative PP was measured from an omental vein during proximal spleno-renal shunt surgery. The PP was compared and correlated with SS along with other parameters. **Results:** The mean SS was 46.04 ± 8.0 kPa and the mean PP was 33.29 ± 4.1 mmHg. There was no significant correlation between PP and SS ($P = 0.61$) and between grades of EV and SS ($P = 0.38$). Significant correlation was seen between grades of EV and PP (0.04). SS also did not show significant correlation with splenic size or duration of disease. **Conclusion:** SS measured by 2D SWE did not correlate with PP and thus may not help in predicting gastrointestinal bleed in patients of EHPVO. (J CLIN EXP HEPATOL 2017;8:250–255)

Extrahepatic portal vein obstruction (EHPVO) is a vascular condition where there is thrombotic occlusion of the main portal vein with or without thrombosis of intrahepatic branches.¹ This occlusion results in pre-hepatic type of portal hypertension which leads to the development of esophageal varices (EV), splenomegaly and collaterals on imaging.^{1,2} Upper gastrointestinal bleeding, due to esophageal or gastric varices, is an important and serious presenting feature of EHPVO, with mortality reaching up to 5%.³ Thus detection of these varices at an early stage and their prevention is necessary.

Upper gastrointestinal endoscopy (UGIE) is the current investigation of choice for the detection of EV. Though it is fairly safe, it is invasive and associated with a very low risk of perforation.⁴ Since EV are a manifestation of increased portal pressure (PP), measurement of PP gives

indirect information on their grade.⁵ PP may be measured directly at surgery or indirectly by measuring intrasplenic pressure, umbilical vein pressure, intravariceal pressure or hepatic vein wedge pressure.^{6,7} All these techniques are invasive, associated with complications and thus cannot be routinely employed. There is thus a need for a reliable non-invasive modality to detect EV. Since, splenic enlargement and stiffness correlates with the extent and duration of portal hypertension in patients of cirrhosis.^{8,9} Measurement of splenic stiffness (SS) should indirectly suggest the degree of portal hypertension and thus EV even in patients of EHPVO. Only few studies have evaluated 2D shear wave elastography (SWE) in assessing SS and have all studied patients with liver cirrhosis.^{10–15} No study in the literature has compared SS with PP, in patients of EHPVO. Thus, we aimed to assess SS using 2D SWE in patients of EHPVO and compare it with intra-operative portal pressures (IOPP).

MATERIALS AND METHODS

This prospective observational study was approved by Institute Ethics Committee and informed consent was obtained from all patients. Patients referred to our department from January 2014 to December 2014 with clinical and sonographic diagnosis of EHPVO admitted for surgery were included in this study. All patients underwent endoscopy for the assessment and grading of EV at the time of admission for surgery. Subsequently, ultrasonography with color Doppler and 2D SWE was done on

Keywords: extrahepatic portal vein obstruction, portal cavernoma, splenic stiffness, shear wave elastography, portal vein pressure

Received: 30 June 2017; **Accepted:** 24 December 2017; **Available online:** 30 December 2017

Address for correspondence: Kumble S. Madhusudhan, Associate Professor, Department of Radiodiagnosis, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India.

E-mail: drmadhuks@gmail.com

Abbreviations: EHPVO: extrahepatic portal vein obstruction; EV: esophageal varices; LS: liver stiffness; PP: portal pressure; SS: splenic stiffness; SWE: shear wave elastography; UGIE: upper gastrointestinal endoscopy
<https://doi.org/10.1016/j.jceh.2017.12.002>

Aixplorer ultrasound machine (Supersonic Imagine, Aix-en-Provence, France) with SC6-1 convex transducer, after overnight fast. On color Doppler study, status of portal vein, collaterals, splenic vein, left renal vein and superior mesenteric veins were evaluated for size, patency and outline. The spleen size was also measured in longitudinal axis.

2D SWE for SS was done subsequently through the abdominal wall (all patients had splenomegaly) with patient in supine position. The SWE box was placed on the splenic parenchyma about 1.5–2 cm deep to the surface in an area free of vessels (Figure 1). With the patient's breath held for 3–5 s, the image was frozen when there was homogeneous color filling. Then a circular region of interest (ROI)—Q box—of size 1 cm diameter was placed on the most homogeneous area within the SWE box to obtain quantitative value of tissue elasticity in kilopascals (kPa) (Figure 1). The measurements were considered reliable when the standard deviation (SD) was less than 10% of the mean SS or when the SD was less than 1 kPa as suggested by the manufacturer. Three such acquisitions were recorded for each patient and average value was calculated.

Subsequently all patients underwent proximal spleno-renal shunt (PSRS) surgery. PP was measured in an adequately sized omental vessel at surgery with the patient in

supine position. The omental vein was cannulated using 24G cannula and connected to the blood pressure transducer of a monitor (Figure 2). Once the line is flushed with heparinized saline, the pressure in the vein was recorded (mean of the systolic and diastolic values) from the monitor (normal PP—5–10 mmHg).⁵ Subsequently the cannula was removed and the vein was ligated. This was followed by splenectomy and spleno-renal shunt.

Statistical analysis was done using SPSS 17 software (SPSS Inc, Chicago, USA). Descriptive statistics was used to summarize patient characteristics of the study group. Intra-class correlation co-efficient was used to test the reliability of SWE. The SS was correlated with IOPP and with splenic vein diameter, splenic size and grade of EV using Pearson correlation coefficient. A *P*-value of less than 0.05 was considered significant.

RESULTS

Twenty-one patients (14 males; 7 females) of mean age 20.4 years (range: 13–34 years) of EHPVO were included in the study. Hematemesis was the most common symptom. The mean duration of symptoms was 8.6 years (range: 1–18 years). The patient demographic characteristics are shown in Table 1.

Figure 1 Ultrasonography of spleen with shear-wave elastography measured through the abdominal wall.

Figure 2 Technique of measuring portal pressure at surgery. (A) Identifying and securing the target omental vein (arrow). (B) Cannulating the omental vein (arrow). (C) Connecting the omental vein to pressure transducer (arrow). (D) Pressure monitor showing the pressure values (arrow).

There were no complications related to the measurement of PP intra-operatively. SS measurement was technically successful in all patients. The mean SS was 46.04 ± 8.0 kPa. All patients had portal hypertension (defined as PP more than 20 mmHg) and the mean PP was 33.29 ± 4.1 mmHg. There was no significant correlation between PP and SS (Pearson correlation coefficient: -0.119 ; $P = 0.61$) (Figure 3).

There was no significant correlation between grades of EV and SS ($P = 0.38$; Pearson correlation coefficient: -0.391) (Figure 4A). SS did not show any significant correlation with splenic size ($P = 0.09$) or duration of the disease ($P = 0.82$). There was significant correlation of PP with grades of EV ($P = 0.04$) (Figure 4B), with splenic size ($P = 0.03$) and with duration of the disease ($P = 0.02$). Neither PP nor SS showed significant correlation with splenic vein diameter. Although there was significant correlation between SS and renal vein diameter, this was a positive correlation. PP did not show significant difference between patients with and without portal biliopathy ($P = 0.14$) and with or without hematemesis ($P = 0.14$). The results of correlation are summarized in Table 2. The intraclass correlation coefficient (Cronbach's alpha) for SS was 0.822 indicating high reliability of the test.

DISCUSSION

Hematemesis, a presentation of portal hypertension, is the major presenting feature in patients of EHPVO and is usually well tolerated.¹⁶ Various direct and indirect

techniques are available for the measurement of portal hypertension with the direct ones being invasive and difficult to practice.^{6,7} Hepatic venous pressure gradient (HVPG) is the best available measure of portal hypertension and EV in patients with cirrhosis.¹⁷ But HVPG measurement is invasive and is not helpful in EHPVO as portal vein is replaced by collaterals. Routine endoscopy is also invasive and may rarely be associated with complications.⁴ Thus, non-invasive modalities are needed for frequent and regular monitoring of portal hypertension and prediction of EV.¹⁸

Although liver stiffness correlates with features of portal hypertension in patients of cirrhosis, it cannot be used in patients of EHPVO, where the level of obstruction is pre-hepatic and liver is normal.¹⁹ On the other hand SS should correlate with PP as splenomegaly and splenic congestion are features of portal hypertension due to any etiology.²⁰ Various ultrasonographic elastography techniques have been used in assessing SS in patients of cirrhosis, including transient elastography (TE), acoustic radiation force impulse (ARFI) and 2D-SWE. Studies have shown good correlation of SS with HVPG and esophageal variceal grades in patients of cirrhosis.²¹ A recent study by Takuma et al, showed better accuracy of SS (measured by ARFI) than LS in detecting portal hypertension in patients with cirrhosis.²² However, a recent meta-analysis has shown that SS has limited accuracy in prediction of EV in cirrhotic patients.²³ Most of these studies have used either TE or ARFI to evaluate SS and 2D-SWE has been used in only few studies.¹⁰⁻¹⁵ 2D SWE is a simple

Table 1 Demographic Parameters and Results of the Study Group.

<i>Parameters</i>	
Mean age (years)	20.4 [13–34]
Sex (Male:female)	14:7
<i>Symptoms</i>	
Mean duration (years [range])	8.6 [1–18]
Hematemesis (n [%])	17 [81]
Jaundice (n [%])	6 [28.6]
Pain abdomen (n [%])	11 [52.4]
Abdominal lump (n [%])	8 [38.1]
<i>UGI endoscopy</i>	
Esophageal varices—median grade	2 (0–4)
No varices	3 [14.3] ^a
Grade I	0
Grade II	10 [47.6]
Grade III	4 [19]
Grade IV	4 [19]
RCS (n)	6 [28.6]
PHG (n)	14 [66.7]
LC extension (n)	7 [33.3]
<i>Laboratory investigations</i>	
Total bilirubin (mg/dL)	1.49 [0.5–4.5]
Serum alkaline phosphatase (IU/L)	233.1 [105–624]
Serum AST (IU/L)	34.4 [15–72]
Serum ALT (IU/L)	31.3 [14–79]
Serum albumin (g/dL)	4.4 [3.1–5.1]
<i>Ultrasonography</i>	
Splenic stiffness (kPa)—Mean [range]	46.0 [33.3–69.9]
Splenic vein patent (n [%])	20 [95.2]
Splenic vein diameter (mm)—Mean [range]	9.2 [6–14]
SMV patent (n [%])	19 [90.5]
Left renal vein diameter (mm)—Mean [range]	7.1 [5–10]
Spleen size (cm)—Mean [range]	19.5 [13.8–25.8]
IHBR dilatation (n [%])	8 [38.1]
Portal pressure (mmHg)—Mean [range]	33.29 [26–43]

^aThe varices were eradicated by previous endoscopic treatment. RCS, red colour sign; PHG, portal hypertensive gastropathy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SMV, superior mesenteric vein.

technique which is routinely used to measure liver stiffness in patients with chronic liver disease. The same can be applied to spleen to measure its stiffness.

Although studies have shown good correlation of SS with HVP and EV in patients of cirrhosis, we did not find any correlation between SS and IOPP or esophageal variceal grade in patients of EHPVO. We measured PP intra-operatively as described in literature.²⁴ As the portal venous system is valveless, measurement of pressure in any of the veins, preferably omental vein, should depict PP. Although there was correlation between PP and EV in our patients, the reasons for absence of correlation between SS

and PP could be a few. In addition to splenic congestion, there are other changes like hyperplasia and fibrosis occurring in the splenic parenchyma in cases of EHPVO.²⁵ As EHPVO is a chronic disease (mean duration of symptoms—8.6 years), these patients have long standing portal hypertension and this may cause further increase in these pathological changes (like fibrosis) thus affecting SS. This may be a reason for non-correlation of SS with IOPP. Although we did not pathologically evaluate the resected spleen for fibrosis, this would be a potential area of future research. No other study is available in the literature comparing SS with IOPP. Another interesting finding

of our study was positive correlation between SS and left renal vein diameter. Larger left renal vein should decompress the portal system, reducing the PP and thus producing lower SS. Thus there should have been inverse relation between left renal vein diameter and SS. We, however,

found positive correlation. This could also be due to higher splenic fibrosis in long standing cases allowing time for collateralization.

TE, although has been widely used, has its limitations. These include difficulty in obtaining reliable values in obese patients, in patients with narrow intercostal spaces and also in patients with ascites.²⁶ There is only one study in literature where SS was measured in patients of EHPVO.²⁷ The authors here used TE and found a mean value of 51.7 kPa for SS. SS showed good correlation with presence of variceal bleed and they suggested a cut off of 42.8 kPa for SS to predict variceal bleeding with a sensitivity and specificity of 88% and 94% respectively. However, they did not correlate SS with any PP measurement. We used 2D-SWE technique which has been shown to be better than TE for measuring liver or spleen stiffness.¹¹ Further, all patients had splenomegaly which allowed us to measure stiffness of spleen through anterior abdominal wall with 100% technical success, unlike other studies where intercostal space was used with lower success rates.¹⁰ This could also be the reason for the lower mean and range of SS values in our study compared to study by Sharma et al. (46.04 ± 8.0 kPa versus 51.7 ± 21.5 kPa, respectively).²⁷ The intraclass correlation of measured SS values by 2D SWE in our study was 0.82 suggesting

Figure 3 Scatter plot showing the distribution of values of splenic stiffness and portal pressure of the study group.

Figure 4 Scatter plots showing correlation of esophageal varices with splenic stiffness (A) and portal pressure (B).

Table 2 Correlation of Various Parameters with Portal Pressure and Splenic Stiffness.

Parameters	Portal pressure		Splenic stiffness	
	Correlation co-efficient	P-value	Correlation co-efficient	P-value
Duration of the disease	0.543	0.01*	0.053	0.82
Esophageal varices	0.480	0.04*	−0.391	0.38
Splenic vein diameter	0.295	0.21	0.226	0.34
Left renal vein size	−0.278	0.22	0.478	0.03*
Spleen size	0.482	0.03*	0.379	0.09

Asterisk (*)—indicates that the correlation was significant.

high reliability of measured readings. The mean SS in our study was higher than the values for normal spleen described in literature (16.6 ± 2.5 kPa).²⁸

The study had few limitations. First, the sample size was small. Second, there was selection bias as we included only those patients who underwent surgery which has specific indications (mostly bleeding which is refractory to endotherapy and portal biliopathy). Third, there was no pathological information on the resected spleen. This may have helped in explaining our results better. Fourth, measurement of PP done at surgery may not be accurate due to the effects of general anesthesia.

In conclusion, SS measured by 2D SWE may not be a good measure of portal hypertension as it did not correlate with esophageal variceal grade and thus may not help in predicting hematemesis in patients of EHPVO.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Sarin SK, Sollano JD, Chawla YK, et al. Consensus on extra-hepatic portal vein obstruction. *Liver Int.* 2006;26:512–519.
2. Gauthier F. Recent concepts regarding extra-hepatic portal hypertension. *Semin Pediatr Surg.* 2005;14:216–225.
3. Mowat AP. Prevention of variceal bleeding. *J Pediatr Gastroenterol Nutr.* 1986;5:679–687.
4. Wolfsen HC, Hemminger LL, Achem SR, et al. Complications of endoscopy of the upper gastrointestinal tract: a single-center experience. *Mayo Clin Proc.* 2004;79:1264–1267.
5. Tandon RK, Saikia N. Measuring intravariceal pressure. *Gastroint Endosc.* 2009;70:414–415.
6. Groszmann RJ. Reassessing portal venous pressure measurements [Editorial]. *Gastroenterology.* 1984;86:1611–1617.
7. Sarin SK, Sethi KK, Nanda R. Measurement and correlation of wedged hepatic, intrahepatic, intrasplenic and intravariceal pressures in patients with cirrhosis of liver and non-cirrhotic portal fibrosis. *Gut.* 1987;28:260–266.
8. Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophageal varices in patients with cirrhosis. *J Clin Gastroenterol.* 2002;34:81–85.
9. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology.* 2013;144:102–111.
10. Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shearwave elastography and transient elastography with liver biopsy correlation. *Radiology.* 2013;269:910–918.
11. Elkrief L, Rautou PE, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. *Radiology.* 2015;275:589–598.
12. Cassinotto C, Charrie A, Mouries A, et al. Liver and spleen elastography using supersonic shear imaging for the noninvasive diagnosis of cirrhosis severity and oesophageal varices. *Dig Liver Dis.* 2015;47:695–701.
13. Grgurevic I, Puljiz Z, Brnic D, et al. Liver and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. *Eur Radiol.* 2015;25:3214–3221.
14. Jansen C, Bogs C, Verlinden W, et al. Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension: a prospective multicentre study. *Liver Int.* 2017;37:396–405.
15. Pawlus A, Inglot M, Chabowski M, et al. Shear wave elastography (SWE) of the spleen in patients with hepatitis B and C but without significant liver fibrosis. *Br J Radiol.* 2016;89:20160423.
16. Sarin SK, Khanna R. Non-cirrhotic portal hypertension. *Clin Liver Dis.* 2014;18:451–476.
17. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology.* 2004;39:280–282.
18. Cho EJ, Kim MY, Lee JH, et al. Diagnostic and prognostic values of noninvasive predictors of portal hypertension in patients with alcoholic cirrhosis. *PLOS ONE.* 2015;10:e0133935.
19. Madhusudhan KS, Sharma R, Kilambi R, et al. 2D shear wave elastography of liver in patients with extrahepatic portal vein obstruction. *J Clin Exp Hepatol.* 2017;7:23–27.
20. Castéra L, García-Tsao G. When the spleen gets tough, the varices get going. *Gastroenterology.* 2013;144:19–22.
21. Colecchia A, Montrone L, Scafoli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV related cirrhosis. *Gastroenterology.* 2012;143:646–654.
22. Takuma Y, Nouse K, Morimoto Y, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. *Radiology.* 2016;279:609–619.
23. Singh S, Eaton JE, Murad MH, Tanaka H, Iijima H, Talwalkar JA. Accuracy of spleen stiffness measurement in the detection of esophageal varices in patients with chronic liver disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2014;12:935–945.
24. Agarwal AK, Sharma D, Singh S, Agarwal S, Girish SP. Portal biliopathy: a study of 39 surgically treated patients. *HPB (Oxford).* 2011;13:33–39.
25. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. *Dig Liver Dis.* 2002;34:144–150.
26. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology.* 2010;51:828–835.
27. Sharma P, Mishra SR, Kumar M, Sharma BC, Sarin SK. Liver and spleen stiffness in patients with extrahepatic portal vein obstruction. *Radiology.* 2012;263:893–899.
28. Pawluś A, Inglot MS, Szymańska K, et al. Shear wave elastography of the spleen: evaluation of spleen stiffness in healthy volunteers. *Abdom Radiol (NY).* 2016;41:2169–2174.