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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Ji is a Distinguished Professor in Shanghai University of Traditional Chinese medicine, Shanghai, China. Having received his Bachelor degree from Yangzhou College of medicine in 1991, Dr. Ji undertook his postgraduate training first at Hubei College of Traditional Chinese medicine, received his Master degree in 1994, and then at Shanghai University of Traditional Chinese medicine, received his PhD in 1997. He became Chief Physician in the Gastroenterology Division, Longhua Hospital affiliated to Shanghai University of Traditional Chinese medicine since 2004. His ongoing research interests are applying Evidence-based medicine methods to study the effects, and managing the disease-syndrome pattern establishment of integrative medicine on digestive diseases. Currently, he is the President of the Shanghai Association for the Study of the Liver with integrative medicine.

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Ultrasound liver elastography beyond liver fibrosis assessment

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Abstract

Several guidelines have indicated that liver stiffness (LS) assessed by means of shear wave elastography (SWE) can safely replace liver biopsy in several clinical scenarios, particularly in patients with chronic viral hepatitis. However, an increase of LS may be due to some other clinical conditions not related to fibrosis, such as liver inflammation, acute hepatitis, obstructive cholestasis, liver congestion, infiltrative liver diseases. This review analyzes the role that SWE can play in cases of liver congestion due to right-sided heart failure, congenital heart diseases or valvular diseases. In patients with heart failure LS seems directly influenced by central venous pressure and can be used as a prognostic marker to predict cardiac events. The potential role of LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated also in the hepatic sinusoidal obstruction syndrome (SOS) and in the Budd-Chiari syndrome. In the hepatic SOS, an increase of LS is observed some days before the clinical manifestations; therefore, it could allow an early diagnosis to timely start an effective treatment. Moreover, it has been reported that patients that were successfully treated showed a LS decrease, that reached pre-transplantation value within two to four weeks. It has been reported that, in patients with Budd-Chiari syndrome, LS values can be used to monitor short and long-term outcome after angioplasty.

Key words: Liver stiffness; Shear wave elastography; Heart failure; Liver congestion; Hepatic sinusoidal obstruction syndrome; Fontan circulation; Budd Chiari syndrome; Valvular diseases

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Core tip: An increase of liver stiffness (LS) has been reported in patients with liver congestion. It is a “confounding factor” for the evaluation of liver fibrosis. However, in the setting of right-sided heart failure LS seems directly influenced by central venous pressure and can be used as a prognostic marker to predict cardiac events. It should be

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emphasized that heart failure “per se” may lead to irreversible liver disease. The potential role of LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated also in the hepatic sinusoidal obstruction syndrome and in the Budd-Chiari syndrome.

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INTRODUCTION

Several guidelines have indicated that liver stiffness (LS) assessed by means of ultrasound shear wave elastography (SWE) can safely replace liver biopsy in several clinical scenarios, particularly in patients with chronic viral hepatitis^[1-3]. SWE techniques assess the biomechanical properties of tissue by applying a stress – externally or directly into the body – that generates a tissue deformation and the generation of shear waves whose speed of propagation is directly associated to the stiffness, *i.e.*, in stiffer tissue the shear wave speed is higher. SWE includes transient elastography (TE) and acoustic radiation force impulse (ARFI) techniques. With TE, the stress that generates the shear wave is applied externally on the skin and the measurement is performed in a fixed region of interest (ROI); the system does not give a B-image. With the ARFI based techniques, the shear waves are generated by the push-pulse of a focused ultrasound beam directly into the body. The B-mode image is used to locate the best area for LS measurement. The measurement is performed in a small fixed ROI without an elasticity image, as in point SWE (pSWE), or in a larger ROI in which the elasticity values are color-coded, as in two-dimensional SWE (2D-SWE).

In addition to fibrosis, there are some factors or clinical conditions that may lead to a LS increase. They are known as “confounding factors” for fibrosis staging: Liver inflammation, whose indirect biomarkers are the transaminases values; acute hepatitis; obstructive cholestasis; liver congestion; infiltrative liver diseases^[1,2,4].

The first report of a LS increases due to liver congestion dates back to 2008^[5]. The authors describe the case of a patient, infected with hepatitis C virus after two heart transplants, who had heart failure and showed a very stiff liver – 44.3 kPa at TE – with signs of cardiac hepatopathy but without liver cirrhosis at histology. One year after another heart transplant, a liver biopsy showed that there was a significant improvement of the cardiac hepatopathy, and the TE value was 3.8 kPa, *i.e.*, within the normal range.

Since that report, several studies have investigated the role of the LS in patients with congestive heart disease and without a primary liver disease.

This article analyses the available literature on the role of the SWE techniques beyond liver fibrosis assessment.

HEART DISEASES

Any pathology affecting the right heart may determine an increase of the pressure in the right atrium pressure, the inferior vena cava and the hepatic veins. The liver is covered by a poorly distensible capsule; therefore, hepatic congestion may lead to an increase of stiffness.

Congestive heart disease

Heart failure is a major health problem, with a considerable risk of morbidity and mortality. In patients with congestive heart disease, right heart catheterization is the gold standard to measure central venous pressure (CVP). However, the procedure is invasive, not readily available and not useful for following up patients. An indirect noninvasive parameter of the right atrial pressure (RAP), recommended by the guidelines of the American Society of Echocardiography, is the inferior vena cava diameter > 21 mm together with the collapse of the vessel < 50%^[6].

In patients with right-sided heart failure, the LS measurement could be a useful parameter that can be repeated over short periods of time. The pivotal study reporting

that the LS is directly influenced by CVP was published in 2010 by Millonig *et al*^[7]. They showed that the clamping of the inferior vena cava in landrace pigs significantly increased the LS, and this effect reversed after reopening the vessel. Moreover, in a small group of patients with decompensated congestive heart disease, they found a decrease of the LS in the subjects who responded to the treatment. The decrease of the LS in patients with congestive heart disease who had a clinical improvement after treatment was confirmed in another small series^[8].

It has been reported that the LS, estimated with TE, could be an indirect marker of the RAP in patients with right-sided heart failure^[9]. After excluding patients with organic liver disease, it was found that there was a high correlation between LS and RAP assessed with right heart catheterization ($r = 0.95$), and the regression equation to predict RAP was $(-5.8 + 6.7 \times \text{natural logarithm of LS value})$. The authors found that a LS cut-off value of 10.6 kPa identified RAP > 10 mmHg with sensitivity and accuracy higher than the echocardiographic parameter mentioned above (sensitivity 0.85 *vs* 0.56, accuracy 0.90 *vs* 0.74, $P < 0.05$ for both). However, it should be highlighted that 16 of the 105 (15.2%) patients that were screened were excluded. This is not a negligible percentage and may raise concern on the applicability of the technique in this setting. On the other hand, it should be highlighted that congestive heart disease may lead to organic liver disease, and this latter may be a “confounder” when the LS is used to non-invasively assess the central venous pressure. For that reason, it is of utmost importance to exclude cases with suspected organic liver disease in research studies.

The same group assessed the prognostic value of the LS by TE in a series of hospitalized patients with heart failure^[10]. Of the 226 patients that were screened, 55 (24.3%) were excluded (37 for organic liver disease and 18 for invalid LS measurement). The LS was assessed before discharge in the remaining 171 patients, who were stratified into three groups on the basis of the LS value: Group 1: ≤ 4.7 kPa, corresponding to a RAP of 4.6 mmHg on the basis of the regression equation found in their previous study^[9]; Group 2: 4.7 to ≤ 6.9 kPa, estimated RAP 6.9 mmHg; Group 3: > 6.9 kPa, estimated RAP ≥ 7.0 mmHg. The authors found that the patients in Group 3 were in advanced New York Heart Association functional class and that they had a significantly higher risk of death or readmission to the hospital for heart failure than those in the other two groups. The LS value was able to predict cardiac events with a hazard ratio of 1.13 per 1-kPa increase.

Another study evaluated the prognostic value of the LS in a series of patients with acute decompensated heart failure^[11]. One hundred and fifty-four patients were enrolled, but 27 of them were excluded due to the presence of other factors that could likely increase the LS and 22 due to invalid LS measurement or because they were lost to follow-up. Using an arbitrary LS value of 8.8 kPa by TE, the remaining 105 patients were divided into two groups. In a median follow-up period of about five months, it was found that cardiac events, *i.e.*, death or readmission to hospital, occurred in 54% of patients with LS ≥ 8.8 kPa and 25% of patients with LS < 8.8 kPa ($P = 0.001$). After adjusting for age, sex, and indices related to organ congestion, a LS ≥ 8.8 kPa was still significantly associated with cardiac events.

The LS as a marker of clinical outcome in patients with acute decompensated heart failure was also evaluated in a series of 149 patients in whom TE was performed in the first two days of admission to the hospital and on the day of discharge^[12]. It is reported that, overall, the patients presented a significant decrease of the LS during the hospitalization and that a LS value > 13 kPa on admission and a LS value > 5 kPa at discharge was associated with an increased risk of one-year all-cause death or readmission to the hospital.

Using a pSWE technique in patients with heart failure, it was shown that the changes in LS in patients with heart failure significantly correlated with changes in CVP in multivariate analysis, and that an LS cut-off value of 7 kPa could predict a CVP > 10 mmHg with 89.6% sensitivity and 87.5% specificity^[13,14]. Another group reported that a high LS value on admission was an independent determinant of worse clinical outcomes in patients with acute decompensated heart failure^[15].

The LS cutoffs obtained in these clinical studies are reported in **Table 1**.

All the published studies confirm that the LS can be a marker of congestive heart failure; however, it is not yet clear what cutoff value should be used to define the risk of adverse cardiac events. In fact, this value ranges from > 5 kPa to 8.8 kPa. It is worth mentioning that the “rule of 5” proposed by the Baveno VI consensus on portal hypertension has proposed that LS value with TE up to 5 kPa may exclude liver fibrosis^[16].

It should also be emphasized that there is an interaction between the liver and the heart: heart failure and liver disease often co-exist, and heart failure “*per se*” may lead to irreversible liver disease. Therefore, in some cases, the increase in LS may be due to both liver congestion and liver disease, even when other etiologies of primary liver

Table 1 Congestive heart disease: Liver stiffness cutoffs obtained in clinical studies

Etiology	Ref.	Endpoint	Number of enrolled patients	SWE technique	Number of invalid measurements	Liver stiffness cutoff	Notes
HF	Taniguchi <i>et al</i> ^[9]	Detecting RAP > 10 mm Hg	89 adults	TE	9 (10.1%)	≥ 10.6 kPa	85% sensitivity; 93% specificity
HF	Taniguchi <i>et al</i> ^[10]	Risk of death or readmission to hospital	189 adults	TE	18 (9.5%)	≥ 6.9 kPa	HR per 1-kPa increase: 1.13 (1.09-1.17)
HF + “controls”	Demirtas <i>et al</i> ^[14]	Detecting RAP > 10 mm Hg	60 adults with HF undergoing CRT + 60 adults without HF undergoing PM implantation	pSWE	None	> 7 kPa	89.6% sensitivity; 87.5% specificity
Acute HF	Saito <i>et al</i> ^[11]	Risk of death or readmission to hospital	154 adults (excluded: <i>n</i> = 49)	TE	10 (among excluded patients)	≥ 8.8 kPa	HR: 2.71 (1.43-5.43)
Acute HF	Soloveva <i>et al</i> ^[12]	Risk of one-year all-cause death or readmission to hospital	172 adults (outcome data: <i>n</i> = 145)	TE	16 (9.3%)	> 13 kPa on admission and > 5 kPa at discharge	HR per 1 kPa increase: 1.03 (1.00-1.06)
HF in patients requiring a left ventricular assist device	Nishi <i>et al</i> ^[19]	Incidence of major adverse events	30 adults	TE	None	> 12.5 kPa	AUC: 0.82
Congenital heart diseases	Jalal <i>et al</i> ^[20]	Detecting CVP > 10 mmHg	60 children + 36 adults	TE	None	> 8.8 kPa	92% sensitivity; 96% specificity

HF: Heart failure; TE: Transient elastography; RAP: Right atrial pressure; HR: Hazard ratio; pSWE: Point shear wave elastography; CRT: Cardiac resynchronization therapy; PM: Pacemaker; AUC: Area under the curve; CVP: Central venous pressure.

disease are excluded^[17]. On this regard, it is worth mentioning that liver biopsy data were not available in the majority of the cited articles.

In a small series of patients with end-stage chronic heart failure who underwent left ventricular assist device implantation (28 patients, liver biopsy performed in 16 of them), it was reported that the LS values were affected both by the central venous congestion and the histologic changes of the liver^[18]. On the other hand, in patients with severe heart failure who require a left ventricular assist device, it has been observed that the incidence of major adverse events was lower when the LS was ≤ 12.5 kPa^[19].

Congenital heart diseases and valvular diseases

In a study that included both children (*n* = 60) and adults (*n* = 36) with congenital heart diseases, it was found that the LS significantly correlated with CVP (*r* = 0.75)^[20]. When the two subgroups were analyzed separately, the correlation was significantly higher in the adults (*r* = 0.68 in children *vs* *r* = 0.84 in adults, *P* < 0.0001). Overall, the area under the receiver operating characteristic (AUC) curve of the LS for identifying a CVP > 10 mmHg was 0.97 and the optimal cut-off value of LS for detection of the CVP > 10 mmHg was 8.8 kPa, with 92% sensitivity and 96% specificity.

The LS with a 2D-SWE technique was measured in 79 patients aged < 20 years with congenital heart diseases and without liver disease who underwent cardiac catheterization^[21]. Thirty-four (43.0%) of them had Fontan physiology. As observed in adult patients with heart failure, the CVP was the only factor that independently and significantly correlated with the LS (*r* = 0.78). This quite strong correlation was present also in the subgroups of patients with biventricular disease and those who underwent the Fontan procedure.

In a series of 131 patients with various degrees of tricuspid valve regurgitation secondary to left-sided heart valve disease, it was found that the individuals with severe regurgitation had higher LS than those with moderate regurgitation^[22]. Moreover, the LS values were associated with the parameters that non-invasively assess the severity of tricuspid regurgitation, such as the area of the regurgitant orifice, the right atrial pressure, and the inferior vena cava diameter.

The change over time of the LS value was assessed in a series of 32 consecutive patients undergoing surgery for valve replacement or repair^[23]. All patients had tricuspid valve regurgitation secondary to left-sided heart valve disease. It was

reported that the LS decreased significantly at three months after surgery, from 8.4 kPa to 6.0 kPa ($P = 0.03$).

The LS cutoffs obtained in these studies are reported in [Table 1](#).

Fontan circulation

The Fontan operation^[24] was proposed for the surgical repair of tricuspid atresia and it still is the palliative standard procedure for patients with univentricular physiology.

Advances in the surgical techniques and in the management of patients with Fontan circulation have led to a longer survival of Fontan-palliated patients who may reach adulthood in the majority of cases. However, the altered hemodynamics lead to disfunction of several organs, especially the liver. In fact, cardiac cirrhosis is quite common in Fontan-palliated patients during their adulthood.

Using a 2D-SWE technique, a study has shown that, in patients with Fontan circulation, the LS correlated with the stage of histopathologic fibrosis, and there was a significantly higher LS (15.6 kPa *vs* 5.5 kPa, $P < 0.0001$) than in healthy controls^[25]. Using TE, a study reported a significant correlation between the stage of fibrosis and the interval of time since the Fontan surgery, with a sharp increase in the number of patients with significant liver fibrosis at 5 years after the operation^[26].

It is worth mentioning that the Fontan procedure *per se* leads to a significant increase in the LS due to hepatic congestion^[27,28]. This increase persists chronically; therefore, it could be a confounding factor for the evaluation of liver fibrosis^[27]. In a small series (9 children; age range, 3.5-5.6 years), it was observed that the LS increased from 6.2 kPa \pm 1.5 kPa in the preoperative period to 11.2 kPa \pm 4 kPa at a mean follow-up of 4 mo^[28]. To overcome this limitation in the use of the LS as a marker of fibrosis, the recent update of the Society of Radiologists in Ultrasound consensus (Barr RG, Stephanie R, Wilson SR, Rubens D, Garcia-Tsao G, Ferraoli G. Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement) has proposed that each subject becomes his/her own control, using the percentage of the stiffness changes over time to evaluate the efficacy of the treatment or the progression of disease in this or similar settings.

LIVER DISEASES

LS assessment is a reliable and non-invasive method for the staging of liver fibrosis in several clinical scenarios and it is an accepted biomarker of portal hypertension^[1,2,4,16,29,30]. The potential role of the LS in evaluating liver disease beyond the stage of liver fibrosis has been investigated in the hepatic sinusoidal obstruction syndrome (SOS) and in the Budd-Chiari syndrome.

Hepatic SOS

Hepatic SOS, previously named hepatic veno-occlusive disease, is caused by a toxic damage to the hepatic sinusoidal endothelial cells^[31]. It may occur after hematopoietic stem cell transplantation and has been associated with the use of oxaliplatin in patients with colorectal liver metastases. It has also been observed after the ingestion of alkaloid toxins, or after high-dose radiation therapy^[31]. SOS is a potentially life-threatening disease, which can lead to hepatic congestion and sinusoidal portal hypertension^[32]. The diagnosis is based on clinical criteria including weight gain, hepatomegaly, ascites, and jaundice^[32].

In 2011, Fontanilla *et al*^[33] reported an increase of the LS assessed by a pSWE technique (2.75 m/s and 2.58 m/s) in two adult patients diagnosed with SOS. They observed that the LS decreased, reaching normal values, after successful treatment.

The potential role of LS assessment in this setting has been investigated in rat models of acute and severe SOS or chronic, mild and reversible SOS^[34]. In both SOS models, the LS values were significantly higher than in the matched control rats. In the chronic and reversible SOS models there was a significant decrease of the LS after a treatment-free period of two weeks.

The role of the LS in predicting SOS syndrome has been investigated in a series of 25 pediatric patients who received hematopoietic stem cell transplant and in whom the LS by pSWE technique was assessed at three scheduled time points^[35]. Five of them developed SOS. Respect to the patients who did not develop SOS, they showed a significant increase of LS at day + 5 and at day + 14 after transplant. The LS increase occurred on average 9 and 11 d before clinical and conventional ultrasound diagnosis of SOS. Therefore, a LS increase seems to be an early marker of SOS development, allowing an early diagnosis and the possibility to timely start an effective treatment.

Similar findings were observed in a series of 78 adult patients who underwent hematopoietic stem cell transplantation^[36]. The median baseline LS value assessed by TE was 4.2 kPa. Four patients (5.1%) presented SOS, and in all of them the LS showed

a significant increase, respect to baseline values, 2-12 d before the clinical manifestation of SOS. The three patients that were successfully treated with defibrotide showed a decrease of the LS, which reached pre-transplantation value within two to four weeks after the diagnosis of SOS, whereas in the patient with severe SOS who died 20 d after the diagnosis of SOS there was not any decrease of the LS.

Budd-chiari syndrome

Budd-Chiari syndrome is due to the obstruction to the hepatic venous outflow which can be due to several conditions.

The role of the LS in monitoring short and long-term outcome after angioplasty was assessed in a series of 25 patients with Budd-Chiari syndrome^[37]. There was a significant decrease of the LS values within 24 hours after intervention, from 62.8 kPa to 26.3 kPa. There was also a significant difference between the LS values obtained at 24 h and those at 3 mo after treatment (26.3 kPa *vs* 20.9 kPa; *P* = 0.003).

Likewise, in another series of 32 patients with Budd-Chiari syndrome successfully treated with angioplasty, a significant decrease of the LS two days after the treatment, from 35.2 (10.6) kPa to 20.1 (5.5) kPa, was observed^[38]. The patients were followed up for six months. Respect to baseline values, there was a significant decrease at three months; thereafter the LS values remained stable even though still in the cirrhotic stage.

In a case report, the LS together with the pulsed Doppler waveform of the hepatic veins was used to follow-up, at three-month intervals, a patient who presented re-stenosis of the inferior vena cava after balloon dilation. A sharp increase of the LS (from 14.3 kPa to 20.5 kPa) and a monophasic pattern of the hepatic vein flow at pulsed Doppler were markers of re-stenosis, confirmed by X-ray venography^[39].

CONCLUSION

SWE techniques have largely been used for the assessment of the LS related to liver fibrosis, and their use in the clinical practice is now accepted by guidelines. Several studies have shown that, beyond liver fibrosis assessment, the LS is a useful parameter for the evaluation of liver congestion that occurs in case of right-sided heart failure, some congenital and valvular diseases, hepatic SOS or Budd-Chiari syndrome. In these scenarios, the LS assessment may also play a role in monitoring changes over time; therefore, it could be a marker of clinical outcome.

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