Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Non invasive evaluation of portal hypertension using transient elastography

Laurent Castera[1,*], Massimo Pinzani[2], Jaime Bosch[3]

[1]*Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Université Denis Diderot Paris VII, Clichy, France;* [2]*Dipartimento di Medicina Interna, Center for Research, High Education and Transfer "DENOThe", Università degli Studi di Firenze, Firenze, Italy;* [3]*Hepatic Hemodynamic Laboratory, Hospital Clínic-IDIBAPS, University of Barcelona and CIBERehd, Barcelona, Spain*

Summary

The development of portal hypertension is a common consequence of chronic liver diseases leading to the formation of esophageal and gastric varices responsible for variceal bleeding, associated with a high mortality rate, as well as other severe complications such as portosystemic encephalopathy and sepsis. Measurement of hepatic venous pressure gradient (HVPG) and upper GI endoscopy are considered the gold standards for portal hypertension assessment in patients with cirrhosis. However, both types of investigation are invasive and HVPG measurement is routinely available and/or performed with adequate standards only in expert centres. There is thus a need for non invasive methods able to predict, with acceptable diagnostic accuracy, the progression of portal hypertension toward the levels of clinically significant (i.e. HVPG $\geqslant$10 mmHg) and severe (HVPG $\geqslant$12 mmHg) as well as the presence and the size of oesophageal varices. Transient elastography (TE) is a novel non invasive technology that allows measuring liver stiffness and that has gained popularity over the past few years. Although TE has been initially proposed to assess liver fibrosis, a good correlation has been reported between liver stiffness values and HVPG as well as the presence of oesophageal varices, suggesting that it could be an interesting tool for the non invasive evaluation of portal hypertension. This review is aimed at discussing the advantages and limits of TE and the perspectives for its rationale use in clinical practice for the management of patients with portal hypertension.

Introduction

The development of portal hypertension is a common consequence of chronic liver diseases (CLD) characterized by progressive liver tissue fibrogenesis and extensive vascular changes occurring both within the liver and in the splanchnic compartment [1]. Established evidence indicates that CLD are characterized by a progressive intrahepatic vascular remodelling with capillarization of sinusoids, fibrogenesis, neo-angiogenesis, and development of intrahepatic shunts, which would lead to increased hepatic resistance leading to increased portal pressure and decreased effective hepatocyte perfusion leading to liver failure. It is also well established that increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder (so-called "static component"). Indeed, the extensive accumulation of fibrillar extracellular matrix is associated with the active contraction of myofibroblasts, activated hepatic stellate cells, and vascular smooth-muscle cells of the intrahepatic veins in a tissue microenvironment characterized by a net predominance of vasoconstrictors (so-called "dynamic component") [2]. An additional determinant of portal hypertension is the progressive increase in blood flow in the portal veins, which is established through splanchnic arteriolar vasodilatation caused by an excessive release of endogenous vasodilators. The increase in portal blood flow aggravates the increase in portal pressure and contributes to the formation of an extensive network of portosystemic collaterals that may divert as much as 80% of portal blood flow. These are responsible for the formation of esophageal and gastric varices, involved in variceal bleeding, associated with a high mortality rate [3]. In addition, collateral vessels result in shunting of portal blood into the systemic circulation, causing high systemic concentrations of several substances normally metabolized by the liver. These in turn contribute to severe complications of cirrhosis, such as portosystemic encephalopathy.

An increase in portal pressure (i.e. >6 mmHg) can be already detected by the measurement of the hepatic vein pressure gradient (HVPG) in patients with histologically defined advanced fibrosis. However, complications of portal hypertension, i.e. development of esophageal varices, may start when HVPG increases over 10 mmHg, which defines what is known as "clinically significant portal hypertension" (Baveno IV) and clinical decompensation in form of bleeding, ascites, hepatic encephalopathy, and renal impairment, may develop when HVPG increases over a threshold value of 10–12 mmHg [4].

Beyond these classic clinical concepts, the detection of increased portal pressure in the context of chronic fibrogenic

Keywords: Portal hypertension; HVPG; Oesophageal varices; Endoscopy; Transient elastography; FibroScan.
Received 7 December 2010; received in revised form 6 June 2011; accepted 5 July 2011
* Corresponding author. Address: Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Université Denis Diderot-Paris VII, 100 boulevard du General Leclerc, 92110 Clichy, France.
E-mail address: laurent.castera@bjn.aphp.fr (L. Castera).

diseases of the liver has profound implications and currently represents a key reference standard for the development of a pathophysiological classification of cirrhosis [5]. At present the stage of "cirrhosis" is either defined by the histopathological evidence of METAVIR stage F4 or ISHAK S5–S6 or more in general by the presence of the so-called "regenerative" or "cirrhotic nodules". In routine clinical practice, such definition does not allow making the distinction between a fibrogenic process that is still in progress but potentially reversible from a more advanced stage of the liver disease that becomes irreversible. Indeed, cirrhosis encompasses a pathological spectrum which is neither static nor uncompromisingly progressive but rather dynamic and bidirectional, especially when treatment against the causative agent of tissue damage can be introduced with success at this stage of the disease. Thus, there is a pressing need to redefine cirrhosis in a manner that better recognizes its underlying relationship to portal hypertension and tissue fibrosis, and more faithfully reflects its progression, reversibility, and prognosis. The need becomes particularly appropriate given the increasing use of effective antiviral treatments in patients with HBV and HCV cirrhosis and the possibility of introducing effective antifibrotic agents. In this context, it is essential to define favorable or unfavorable endpoints that correlate with a distinct clinical outcome in patients with cirrhosis.

All these considerations apply particularly to the stage of cirrhosis defined as "compensated", characterized by the paucity or absence of clinical signs. Currently, compensated cirrhosis is subclassified in two stages: without varices (stage 1) or with varices (stage 2). In addition, this distinction could be further refined as (a) no portal hypertension; (b) portal hypertension that is not clinically-significant (HVPG <10 mmHg); and (c) clinically significant portal hypertension (HVPG $\geqslant$10 mmHg) [6]. Regardless, in most cases presenting in clinical practice, it is practically impossible to allocate a patient with compensated cirrhosis in one of these substages without performing HVPG measurement and upper GI endoscopy. Both types of investigation are invasive and HVPG measurement is routinely available and/or performed with adequate standards only in expert centres. Along these lines, the need of non invasive methods able to predict with acceptable diagnostic accuracy the progression of portal hypertension toward the levels of clinically significant (i.e. $\geqslant$10 mmHg) and severe (i.e. $\geqslant$12 mmHg) becomes absolutely relevant. In this context, it would be also useful to have non invasive methodologies able to predict the presence or absence of esophageal and gastric varices. However, it should be stressed that the available non invasive methods are not expected to replace either HVPG measurement or upper GI endoscopy, but rather to offer a mean for the rapid discrimination of different steps of progression within the stage of compensated cirrhosis. This will greatly help allocating cirrhotic patients in different categories of risk and guide the need of further evaluation with HVPG measurement and upper GI endoscopy.

How to evaluate portal hypertension

Is HVPG measurement a relevant gold standard for portal hypertension assessment?

HVPG is an accurate, reproducible and safe way of measuring portal pressure in patients with cirrhosis of any aetiology (with the exception of primary biliary cirrhosis) [7]. HVPG is considered to be the best surrogate indicator of prognosis in patients with cirrhosis [8]. This is due to the fact that HVPG elevation has been found in multiple studies to carry independent prognostic value for most relevant events in the course of cirrhosis (Table 1). Briefly, HVPG has been found to correlate with the risk of formation of varices, of clinical decompensation and of development of hepatocellular carcinoma (HCC) in patients with "Stage 1" compensated cirrhosis [4,9,10]. Measurement of HVPG can distinguish sub-stages within compensated cirrhosis, according to whether HVPG is <10 or $\geqslant$10 mmHg, the latter having an increased risk of decompensation, HCC and death. Based on this, it has been proposed that preventive therapies may be started when HVPG is $\geqslant$10 mmHg, since lowering portal pressure below 10 mmHg is likely to result in prevention of clinical decompensation, and death [3]. Relevance of HVPG measurements is further emphasized by the findings that HVPG above 16 mmHg correlates with increased risk of death [7,11,12], that during acute variceal bleeding, HVPG >20 mmHg is the best independent prognostic marker [13–16] and that measurement of changes in HVPG during the treatment of portal hypertension allow to define a group of patients with an optimal outcome (the hemodynamic "responders") [17–21] (Table 1). Recent studies further suggest that patients showing a drop in HVPG $\geqslant$10% of baseline 15 min after the IV administration of propranolol (0.15 mg/kg) ("acute hemodynamic responders") [22,23] also have a lower risk of bleeding and death. Finally, a pre-operative HVPG $\geqslant$10 mmHg denotes a poor prognostic of liver resection in patients with small HCC; HVPG $\geqslant$6 mmHg 1-year after liver transplantation, is the best indicator of a poor outcome [24] and successful treatment of viral cirrhosis [25–27], and alcohol withdrawal [28] are associated with a significant decrease in HVPG. Because of this, it has been proposed that serial measurements of HVPG could be used for assessing progression/regression of fibrosis/cirrhosis in chronic liver diseases of any aetiology [7]. Details on the technique and precautions for accurate measurements are described in depth in recent reviews [7,11].

Is upper GI endoscopy a relevant gold standard for portal hypertension assessment?

Another "gold standard" in the evaluation of portal hypertension is the use of upper GI endoscopy for the detection of varices [6]. By far, endoscopy is the best way of assessing the presence of oesophageal varices (OV), where its accuracy is much greater than that of radiology (including multidetector CT-angiography) [29–31]. Endoscopy has to be complemented sometimes with endoscopic ultrasonography, especially in cases with suspected isolated gastric varices. Endoscopy has the further advantage of allowing to detect indicators of increased bleeding risk (the red colour signs and "wale" marks) that cannot be detected accurately by other imaging techniques [32]. Because of this, it is recommended that any patient with cirrhosis should undergo screening endoscopy at diagnosis, and repeat follow-up examinations if no varices are found or if no preventive treatment is initiated in patients with "low-risk" varices (small varices without red colour signs in a Child A patient) [6].

Both HVPG measurements and upper GI endoscopy are safe but minimally invasive diagnostic techniques that carry patient discomfort, increase the burden for medical providers and increased cost of medical care. Because of this, there is a clinical

Review

Table 1. Correlation between HVPG and complications of portal hypertension in patients with cirrhosis.

Clinical scenario		HVPG value
Compensated cirrhosis		
	Risk of formation of varices	≥10 mmHg
	Risk of clinical decompensation	≥10 mmHg
	Risk of hepatocellular carcinoma	≥10 mmHg
	Risk of variceal bleeding	≥12 mmHg
	Risk of death	≥16 mmHg
Acute variceal bleeding		
	Risk of treatment failure and increased mortality	≥20 mmHg
Treatment of portal hypertension		
a) Pre-primary prophylaxis	Formation of varices	<10 mmHg or decrease in HVPG ≥10%*
b) Primary prophylaxis	First variceal haemorrhage	≤12 mmHg or decrease in HVPG ≥20%*
c) Secondary prophylaxis	Recurrent variceal bleeding, ascites, SBP, death	≤12 mmHg or decrease in HVPG ≥20%*
Resection of hepatocellular carcinoma	Surgical risk (decompensation and death)	≥10 mmHg

*Chronic HVPG response (change in HVPG after 3–12 weeks on therapy); the criteria for a "good" HVPG response after acute IV propranolol is a decrease in HVPG ⩾10% of baseline values.
SBP, spontaneous bacterial peritonitis.

need for non-invasive ways of assessing portal hypertensive patients that could substitute for the need of hemodynamic measurements and endoscopy. Let us state upfront that despite new technological developments, all the efforts done up to now have not resulted in such a substitute. However, as discussed in this review, there have been substantial advances that may result in a much better definition of patients in whom these procedures are indicated, decreasing the number of patients that have to be submitted to HVPG/endoscopy. Specifically, there is substantial evidence indicating that transient elastography (TE) can be quite effective in detecting patients with a high risk of having (or not having) developed clinically significant elevations of HVPG or varices. Details on the principle and technique of TE have been previously described [33,34].

Diagnostic performance of transient elastography for portal hypertension

Detection of clinically significant portal hypertension

The performances of TE for detection of clinically significant portal hypertension are shown in Table 2. A good correlation between liver stiffness values and HVPG has been initially reported by Carrion *et al.* in 124 HCV patients with HCV recurrence after liver transplantation (Pearson coefficient, 0.84; p <0.001) [35]. The AUROCs for the diagnosis of portal hypertension (HVPG ⩾6 mmHg) and clinically significant portal hypertension were 0.93 and 0.94, respectively (Table 2). Several other groups have confirmed these results since in patients with chronic hepatitis C [36] or with other chronic liver diseases [37–39], with AUROCs for detecting clinically significant portal hypertension ranging from 0.76 to 0.99 and TE cut-offs from 13.6 to 34.9 kPa (Table 2). Interestingly, in the only study that analysed the results according to the liver disease etiology [38], cut-offs were higher in alcoholic cirrhosis than in viral cirrhosis (34.9 and 20.5 kPa, respectively). Although these results are in keeping with findings suggesting that cut-offs for cirrhosis diagnosis may be higher in alcoholic liver disease [40,41], they need to be further confirmed in other series.

Another interesting finding is the fact that, although the correlation was excellent for HVPG values below 10–12 mmHg, it hardly reached statistical significance for values above 12 mm Hg [36]. This important observation suggests that beyond a certain degree of portal pressure (i.e. above 10–12 mmHg), the development of portal hypertension becomes at least partially independent from the simple accumulation of fibrillar extracellular matrix responsible for the increase in liver stiffness. It is consistent with the pathophysiology of portal hypertension where several extra-hepatic factors such as the hyperdynamic circulation, the splanchnic vasodilatation, and the resistance opposed to portal blood flow by the portosystemic collaterals contribute to the rise in portal pressure [7,42]. Accordingly, TE is unlikely to be useful in the monitoring the hemodynamic response to drug therapy, the effect of which is mediated primarily by decreasing the splanchnic blood flow [4].

Conversely, repeated liver stiffness measurements over time could be of interest during the first year after liver transplantation to identify patients with severe hepatitis C recurrence at an early stage [43]. Indeed, liver stiffness values together with donor age and bilirubin levels were independent predictors in multivariate analysis of portal hypertension (HVPG ⩾6 mmHg) and fibrosis progression (fibrosis stage >2) in HCV-infected liver transplant recipients. These preliminary results are promising but need to be validated by other groups [44] before implementation in clinical practice.

Detection of oesophageal varices

A correlation between liver stiffness values and the presence of OV has also been reported [36,37,45–50]. AUROCs of TE for diagnosing the presence of OV ranged from 0.74 to 0.85 and cut-offs

Table 2. Diagnostic performance of transient elastography for the detection of clinically significant portal hypertension (HVPG ⩾10 mm Hg).

Authors, [Ref.]	Patients (n)	Etiologies	Study design	Prevalence of clinically significant portal hypertension (%)	Cut-offs HVPG ≥10 mmHg (kPa)		AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR
Carrion *et al.*, [35]	124	HCV-LT	Pro. mono.	21	8.7*	-	0.92	90	81	81	90	4.7	0.12
Vizzutti *et al.*, [36]	61	HCV	Pro. mono.	77	13.6	17.6**	0.99 0.92	97 94	92 81	97 86	92 91	13.7 4.9	0.02 0.08
Sanchez-Condé *et al.*, [39]	38	HIV-HCV	Pro. mono.	74	14.0	23.0**	0.80 0.80	93 83	50 67	84 79	71 71	3.5 2.5	0.62 0.49
Lemoine *et al.*, [38]	44 48	HCV Alcohol	Retro. mono.	77 83	20.5 34.9		0.76 0.94	63 90	70 88	88 97	35 64	2.1 7.5	0.53 0.13
Bureau *et al.*, [37]	150	CLD	Pro. mono.	51	21.0		0.94	90	93	93	91	12.8	0.10

*Hepatic venous pressure gradient (HVPG) ⩾6 mm Hg; **severe portal hypertension HVPG ⩾12 mm Hg.

AUC, area under ROC curve; Se, sensitivity; Sp, specificity; +LR, positive likelihood ratio; −LR, negative likelihood ratio; HCV, chronic hepatitis C; HCV-LT, liver transplant for hepatitis C; CLD, chronic liver diseases; Pro. mono., prospective monocentric; Retro. mono., retrospective monocentric.

Table 3. Diagnostic performance of transient elastography for the detection of oesophageal varices (OV and LOV) in cirrhotic patients.

Authors, [Ref.]	Patients (n)	Etiologies	Study design	Child-Pugh A (%)	End point	Prevalence OV (%)	Cut-offs (kPa)	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR	Saved endoscopy (%)
Kazemi *et al.*, [45]	165	CLD	Retro. mono.	n.a.	OV LOV	45 28	13.9 19.0	0.83 0.84	95 91	43 60	57 48	91 95	1.7 2.3	0.13 0.14	66 69
Vizzutti *et al.*, [36]	47	HCV	Pro. mono.	60	OV	66	17.6	0.76	90	43	77	66	1.6	0.23	74
Pritchett *et al.*, [48]	211	CLD	Retro. mono.	n.a.	OV LOV	n.a. 37	19.5 19.8	0.74 0.76	76 91	66 56	56 91	82 55	2.2 2.1	0.36 0.16	n.a. 69
Bureau *et al.*, [37]	89	CLD	Pro. mono.	34	OV LOV	72 48	21.1 29.3	0.85 0.76	84 81	71 61			2.9 2.1	0.22 0.31	81 71
Castera *et al.*, [46]	70	HCV	Retro. mono.	100	OV LOV	36 19	21.5 30.5	0.84 0.87	76 77	78 85	68 56	84 94	3.5 5.1	0.31 0.27	73 79
Pineda, *et al.*, [47]	102	HIV-HCV	Pro. multi.	76	CROV*	13	21.0	0.71	100	32	25	100	1.5	0.0	44
Nguyen et al. [49]	183 58 103	CLD HCV/HBV Alcohol	Retro. mono.	63	LOV	22 17 25	48.0 19.8 47.2	0.76 0.73 0.77	73 89 85	73 55 64	44 27 44	90 97 93	2.7 2.0 2.4	0.37 0.20 0.23	73 60 69
Malik *et al.*, [50]	124	CLD	Retro. mono.	n.a.	OV	51	20.0	0.85	n.a.	n.a.	80	75	n.a.	n.a.	n.a.

*CROV: clinically relevant OV requiring primary prophylaxis of bleeding, i.e. patients carrying LOV or OV with red signs or Child-Pugh class C.

CLD, chronic liver diseases; HCV, chronic hepatitis C; HIV-HCV, co-infection with human deficiency virus and hepatitis C virus; HBV, hepatitis B virus; AUC, area under ROC curve; Se, sensitivity; Sp, specificity; PPV & NPV, positive and negative predictive values; +LR & −LR, positive and negative likelihood ratios; Pro. mono., prospective monocentric; Pro. multi., prospective multicentric; Retro. mono., retrospective monocentric.
The percentage of saved endoscopy was calculated as the percentage of correctly classified patients by pooling true negative and true positive.

from 13.9 to 21.5 kPa (Table 3). Sensitivity for the prediction of the presence of OV was high (76–95%) but specificity was much lower (43–78%).

A correlation between liver stiffness values and variceal size was observed in some studies [37,45,46,48] whereas it was not in others [36,47,49,50]. Cut-offs for the prediction of the presence of large OV (LOV) were higher ranging from 19 to 48.0 kPa (Table 3). Sensitivity of TE for detecting LOV was also high (77–100%) with much lower specificity (32–85%) (Table 3). In the only study that analysed the results according to the etiology of the underlying liver disease [49], cut-offs for detection of LOV were higher in patients with alcoholic cirrhosis than in those with viral cirrhosis (47.2 and 19.8 kPa, respectively), a finding consistent with what has been reported for clinically significant portal hypertension [38]. Further studies are needed to confirm these findings.

Overall, these results deserve several comments. First, most of these studies have been conducted retrospectively in single centers on heterogeneous populations (mixing viral hepatitis- and alcohol-related liver diseases) with small sample size (<100 in most cases). Second, the prevalence of disease severity (proportion of Child-Pugh A patients ranging from 34% to 100%) and varices (proportion of patients with OV or LOV ranging from 36% to 72% and 19% to 48%, respectively) was highly variable from one study to another. Third, the judgement criteria markedly differed

Review

Table 4. Diagnostic performance of other non invasive tools for the detection of oesophageal varices (OV and LOV) in cirrhotic patients.

Test, [Ref.]	Patients (n)	Etiologies	Study design	Child-Pugh A (%)	End point	Prevalence OV (%)	Cut-offs (kPa)	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR	Saved endoscopy (%)
Platelet count, [54]	510	CLD	Retro. multi.	79	CROV*	28	89	0.65	55	75	49	80	2.17	0.61	66
AST/ALT ratio, [54]	510	CLD	Retro. multi.	79	CROV*	28	1.1	0.64	71	57	60	82	1.63	0.52	61
APRI, [54]	510	CLD	Retro. multi.	79	CROV*	28	1.5	0.57	57	57	35	76	1.30	0.76	57
Forns' index, [54]	510	CLD	Retro. multi.	79	CROV*	28	8.8	0.66	71	62	58	82	1.88	0.47	66
Lok index, [54]	510	CLD	Retro. multi.	79	CROV*	28	1.5	0.70	71	68	50	84	2.25	0.42	69
Fib-4, [54]	510	CLD	Retro. multi.	79	CROV*	28	4.3	0.63	71	56	40	82	1.60	0.53	60
Fibroindex, [54]	510	CLD	Retro multi.	79	CROV*	28	2.5	0.65	51	76	50	75	2.06	0.65	70
Fibrotest®, [55]	99	CLD	Retro. mono.	42	LOV	72	0.85	0.77	84	53	86	50	1.78	0.28	
PC/SDR, [56]	218	CLD	Pro. multi.	51	OV	54	909	0.86	92	67	77	87	2.77	0.13	80
Capsule endoscopy, [57]	288	CLD	Pro. multi.	69	OV LOV	63 27	n.a. n.a.	n.a. n.a.	84 78	88 96	92 87	77 92	7.00 19.50	0.18 0.23	86 79
Lapalus *et al.*, [58]	120	CLD	Pro. multi.	48	OV LOV	62 29	n.a. n.a.	n.a. n.a.	77 77	86 88	90 75	69 90	5.42 6.69	0.28 0.26	 85

*CROV, clinically relevant OV requiring primary prophylaxis of bleeding, i.e. patients carrying LOV or OV with red signs or Child-Pugh class C.

CLD, chronic liver diseases; AUC, area under ROC curve; Se, sensitivity; Sp, specificity; PPV & NPV, positive and negative predictive values; +LR & −LR, positive and negative likelihood ratios; Pro. multi., prospective multicentric; Retro. mono., retrospective monocentric; Retro. multi., retrospective multicentric.
The percentage of saved endoscopy was calculated as the percentage of correctly classified patients by pooling true negative and true positive.

between studies: presence of OV only in two of them [36,50], presence of LOV only in one of them [49] and presence of both in four [37,45,46,48]. However, according to the latest Baveno V recommendations [6], primary prophylaxis for variceal bleeding is indicated in patients with clinically relevant OV (CROV) (i.e. patients with LOV or with small OV and red wale marks or Child C class), a criteria that has been taken into account in one study only [47]. Also the assessment of OV size was rather subjective: no details were provided in most of these studies regarding the quality of this assessment even though endoscopy is known to be an imperfect gold standard with considerable inter-observer variability for detecting and grading varices [51]. Fourth, the proposed cut-offs for detecting OV or LOV were discrepant between studies, thus the optimal cut-off remains to be defined. Finally, the diagnostic accuracy (specificity and likelihood ratios) reported so far is much too low for a reliable use in clinical practice.

Thus, from the data currently available, diagnostic performances of TE are acceptable for the prediction of clinically significant portal hypertension but far from satisfactory to confidently predict the presence of OV in clinical practice and to screen cirrhotic patients without endoscopy.

Comparison of transient elastography with other non invasive tools

Detection of portal hypertension

Several biological parameters have been proposed for the non invasive detection of clinically significant portal hypertension including prothrombin time [37], a score combining platelet count and total bilirubin [52], and FibroTest® [53]. In a population of 61 Korean patients, Park *et al.* [52] have shown that a score combining platelet count and total bilirubin had an AUROC of 0.91 for predicting clinically significant portal hypertension with a 88% sensitivity and 86% specificity at a cut-off of −1.0. In 92 French patients with cirrhosis, the FibroTest® had an AUROC of 0.79 for predicting severe portal hypertension (HVPG $\geqslant$12 mm Hg) [53]. In the only study comparing TE to other non invasive tests, performance of TE and prothrombin time did not differ (AUROC 0.95 *vs.* 0.89, respectively) [37]. Combining TE (at a cut-off of 21 kPa) and prothrombin time (at a cut-off of 82.5%) allowed classifying correctly 73% of patients.

Detection of oesophageal varices

Several non invasive tools have been proposed for the detection of OV including routine biological parameters [54], FibroTest® [55], combination of simple biological and ultrasound parameters [56], and more recently oesophageal capsule endoscopy [57,58]. The performances of these tools are summarized in Table 4. The AUROCs of serum markers ranged from 0.57 to 0.86, with higher sensitivity (51–92%) than specificity (53–76%). In the largest study to date comparing retrospectively a panel of serum markers (platelet count, AST/ALT ratio, APRI, Forns index, Lok index, FIB-4, and Fibroindex) in more than 500 patients with chronic liver diseases, the combination of Lok index (cut-off = 1.5) and Forns index (cut-off = 8.8) had the best diagnostic performance (AUROC of 0.80 and negative predictive value of 90%) for predicting clinically relevant OV [54].

Sensitivity of oesophageal capsule endoscopy for the detection of LOV ranged from 77% to 78% and specificity from 88% to 96% [57,58] (Table 4). These preliminary results suggest that oesophageal capsule endoscopy is a promising tool for the detection of OV. However, further studies comparing this technology to other available non invasive tools such as TE are awaited.

Three studies only compared TE with other non invasive tools thus far [45,46,59]. TE did not perform better for the detection of OV and LOV in patients with chronic hepatitis C than serum markers [46]. For instance, at a cut-off of 30.5 kPa, TE predicted the presence of LOV with 79% accuracy as compared with 79% for prothrombin time, 77% for Lok index, 76% for AST/ALT ratio and platelet count, 64% for FibroTest®, and 63% for APRI, respectively. Similarly, in another study [45], TE performances did not differ from those of platelet count/spleen diameter ratio for detection of LOV. In a cohort of 401 Korean patients with chronic hepatitis B (training set 280; validation set 121), TE had similar diagnostic performances than spleen diameter and platelet count for detection of clinically relevant OV [59]. However, the combination of liver stiffness with spleen diameter and platelet count (referred as LSPS for LSM-Spleen diameter to Platelet ratio Score) increased diagnostic accuracy. Indeed, LSPS had a significantly better AUROC than TE alone (0.95 *vs.* 0.88, respectively; p <0.001). At a cut-off <3.5, LSPS had a 94.0% negative predictive value and a 94.2% positive predictive value at a cut-off >5.5. Overall, upper GI endoscopy could be saved in 90.3% patients. These promising results suggest that like for the diagnosis of liver fibrosis [60], combining two unrelated methods such as TE and serum markers or ultrasonography may increase accuracy for detecting OV but need to be further validated.

Prediction of clinical outcome

Since the initial report [61], suggesting that liver stiffness may be of prognostic value in patients with cirrhosis, other groups have confirmed these findings [62–64]. Very recently, a French study conducted in 100 patients with chronic liver diseases and a 2-year follow-up, reported that liver stiffness values may be as effective as HVPG in predicting clinical decompensation and portal hypertension-related complications [65]. For instance, at a cut-off of 21.1 kPa, TE had a 100% negative predictive value for the occurrence of portal hypertension related complications, suggesting that if such results are further confirmed, TE could be used as a screening test for clinical outcome [66].

Limitations of transient elastography

Liver stiffness measurements can be difficult in obese patients or with narrow intercostal space and impossible in patients with ascites [33]. Although TE reproducibility has been shown to be excellent for inter-observer and intra-observer agreement [67,68], its applicability may not be as good as initially thought. Indeed, in our experience over 5 years in more than 13,000 examinations, liver stiffness measurements were not interpretable in nearly one in five cases (failure to obtain any measurement in 4% and unreliable results not meeting manufacturer's recommendations in 17%) [69]. The principal reasons were obesity, particularly increased waist circumference, and limited operator experience. These results emphasize the need for adequate operator training and for technological improvements in specific patient populations such as those with non alcoholic fatty liver disease.

Finally, as the liver is an organ wrapped in a distensible but non-elastic envelope (Glisson's capsula), additional space-occupying tissue abnormalities, such as oedema and inflammation, cholestasis and congestion, may interfere with liver stiffness measurement (LSM), independently of fibrosis. Indeed, as previously mentioned, the extent of necro-inflammatory activity has been shown to influence TE measurements in patients with viral hepatitis with a steady increase of liver stiffness values in parallel with the degree of histological activity [67,70,71]. Consistent with these results, the risk of overestimating liver stiffness values has been reported in case of ALT flares in patients with acute viral hepatitis or chronic hepatitis B [72–74] as well as in cases of extrahepatic cholestasis [75] or congestive heart failure [76]. Also TE measurements need to be standardized, since in patients with cirrhosis its values increased by over 25% after a light meal, as compared with fasting patients [77].

Conclusions and perspectives

TE is currently insufficient to confidently predict the presence of oesophageal varices in clinical practice but rather, given its likely prognostic value in cirrhosis, to offer a mean for rapid discrimination of different steps of progression within the stage of compensated cirrhosis. This will greatly help allocating cirrhotic patients in different categories of risk and guide the need for further evaluation with HVPG measurement and upper GI endoscopy.

TE is not expected to replace HVPG measurement in assessing the response to the treatment of portal hypertension and the prognosis of acute variceal bleeding. This will remain the domain of invasive procedures and future developments should be aimed at making easier to obtain repeated measurements along the follow-up. There is insufficient data as to whether TE may substitute HVPG in indications such as prognosis of liver resection for HCC, although it is likely that patients with high TE values (i.e. >14 kPa) may be reasonably excluded as candidates for liver resection and may not need and HVPG measurement to confidently identify severe recurrence of HCV after liver transplantation.

Also studies comparing TE with other non invasive methods for the detection of OV are awaited. However, when designing future studies, the weaknesses of the existing gold standard should probably be taken into account. In particular, attention should be paid to improving the interpretation of endoscopy and reducing the variability of results.

Finally, other techniques such as the measurement of spleen stiffness [78] may also become available and deserved to be further evaluated in comparison or in combination with TE.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. Gastroenterology 2008;134:1715–1728.

Review

[2] Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology 2006;43:S121–S131.
[3] Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362:823–832.
[4] Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–488.
[5] Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445–1449.
[6] de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762–768.
[7] Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573–582.
[8] Gluud C, Henriksen JH, Nielsen G. Prognostic indicators in alcoholic cirrhotic men. Hepatology 1988;8:222–227.
[9] Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254–2261.
[10] Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol 2009;50: 923–928.
[11] Bosch J, Garcia-Pagan JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver disease. Semin Liver Dis 2006;26:348–362.
[12] Merkel C, Bolognesi M, Bellon S, Zuin R, Noventa F, Finucci G, et al. Prognostic usefulness of hepatic vein catheterization in patients with cirrhosis and esophageal varices. Gastroenterology 1992;102:973–979.
[13] Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902–908.
[14] Abraldes JG, Villanueva C, Banares R, Aracil C, Catalina MV, Garci APJC, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48:229–236.
[15] Moitinho E, Escorsell A, Bandi JC, Salmeron JM, Garcia-Pagan JC, Rodes J, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology 1999;117:626–631.
[16] Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jimenez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40:793–801.
[17] Bosch J, Masti R, Kravetz D, Bruix J, Gaya J, Rigau J, et al. Effects of propranolol on azygos venous blood flow and hepatic and systemic hemodynamics in cirrhosis. Hepatology 1984;4:1200–1205.
[18] Thalheimer U, Bosch J, Burroughs AK. How to prevent varices from bleeding: shades of grey – the case for nonselective beta blockers. Gastroenterology 2007;133:2029–2036.
[19] Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506–512.
[20] D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. Gastroenterology 2006;131:1611–1624.
[21] Feu F, Garcia-Pagan JC, Bosch J, Luca A, Teres J, Escorsell A, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346: 1056–1059.
[22] La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, Garcia-Pagan JC, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. J Hepatol 2009;51:279–287.
[23] Villanueva C, Aracil C, Colomo A, Hernandez-Gea V, Lopez-Balaguer JM, Alvarez-Urturi C, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. Gastroenterology 2009;137:119–128.
[24] Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilabert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. Hepatology 2006;43: 492–499.
[25] Carrion JA, Navasa M, Garcia-Retortillo M, Garcia-Pagan JC, Crespo G, Bruguera M, et al. Efficacy of antiviral therapy on hepatitis C recurrence after liver transplantation: a randomized controlled study. Gastroenterology 2007;132:1746–1756.
[26] Manolakopoulos S, Triantos C, Theodoropoulos J, Vlachogiannakos J, Kougioumtzan A, Papatheodoridis G, et al. Antiviral therapy reduces portal pressure in patients with cirrhosis due to HBeAg-negative chronic hepatitis B and significant portal hypertension. J Hepatol 2009;51:468–474.
[27] Rincon D, Ripoll C, Lo Iacono O, Salcedo M, Catalina MV, Alvarez E, et al. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. Am J Gastroenterol 2006;101:2269–2274.
[28] Vorobioff J, Groszmann RJ, Picabea E, Gamen M, Villavicencio R, Bordato J, et al. Prognostic value of hepatic venous pressure gradient measurements in alcoholic cirrhosis: a 10-year prospective study. Gastroenterology 1996;111: 701–709.
[29] de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol 2008;49:520–527.
[30] de Franchis R. Cirrhosis: screening for esophageal varices. Nat Rev Gastroenterol Hepatol 2009;6:449–450.
[31] Perri RE, Chiorean MV, Fidler JL, Fletcher JG, Talwalkar JA, Stadheim L, et al. A prospective evaluation of computerized tomographic (CT) scanning as a screening modality for esophageal varices. Hepatology 2008;47:1587–1594.
[32] The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983–989.
[33] Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–1713.
[34] Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835–847.
[35] Carrion JA, Navasa M, Bosch J, Bruguera M, Gilabert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791–1798.
[36] Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–1297.
[37] Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261–1268.
[38] Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28:1102–1110.
[39] Sanchez-Conde M, Montes-Ramirez ML, Miralles P, Alvarez JM, Bellon JM, Ramirez M, et al. Comparison of transient elastography and liver biopsy for the assessment of liver fibrosis in HIV/hepatitis C virus-coinfected patients and correlation with noninvasive serum markers. J Viral Hepat 2010;17: 280–286.
[40] Nahon P, Kettaneh A, Tengher-Barna I, Ziol M, de Ledinghen V, Douvin C, et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol 2008;49:1062–1068.
[41] Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with 7 non-invasive laboratory tests. Aliment Pharmacol Ther 2008:1188–1198.
[42] Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? Hepatology 2007;45:1087–1090.
[43] Carrion JA, Torres F, Crespo G, Miquel R, Garcia-Valdecasas JC, Navasa M, et al. Liver stiffness identifies two different patterns of fibrosis progression in patients with hepatitis C virus recurrence after liver transplantation. Hepatology 2010;51:23–34.
[44] Rigamonti C, Donato MF, Colombo M. Transient elastography in the early prediction of progressive recurrent hepatitis C following liver transplantation. Hepatology 2010;52:800–801.
[45] Kazemi F, Kettaneh A, N'Kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230–235.
[46] Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59–68.

[47] Pineda JA, Recio E, Camacho A, Macias J, Almodovar C, Gonzalez-Serrano M, et al. Liver stiffness as a predictor of esophageal varices requiring therapy in HIV/hepatitis C virus-coinfected patients with cirrhosis. J Acquir Immune Defic Syndr 2009;51:445–449.
[48] Pritchett S, Cardenas A, Manning D, Curry M, Afdhal NH. The optimal cut-off for predicting large oesophageal varices using transient elastography is disease specific. J Viral Hepat 2011;18:e75–e80.
[49] Nguyen-Khac E, Saint-Leger P, Tramier B, Coevoet H, Capron D, Dupas JL. Noninvasive diagnosis of large esophageal varices by fibroscan: strong influence of the cirrhosis etiology. Alcohol Clin Exp Res 2010;34:1146–1153.
[50] Malik R, Lai M, Sadiq A, Farnan R, Mehta S, Nasser I, et al. Comparison of transient elastography, serum markers and clinical signs for the diagnosis of compensated cirrhosis. J Gastroenterol Hepatol 2010;25:1562–1568.
[51] Thabut D, Moreau R, Lebrec D. Screening for esophageal varices: endoscopy, other tools, or endoscopy and other tools? Hepatology 2008;47:1434–1436.
[52] Park SH, Park TE, Kim YM, Kim SJ, Baik GH, Kim JB, et al. Non-invasive model predicting clinically-significant portal hypertension in patients with advanced fibrosis. J Gastroenterol Hepatol 2009;24:1289–1293.
[53] Thabut D, Imbert-Bismut F, Cazals-Hatem D, Messous D, Muntenau M, Valla DC, et al. Relationship between the Fibrotest and portal hypertension in patients with liver disease. Aliment Pharmacol Ther 2007;26:359–368.
[54] Sebastiani G, Tempesta D, Fattovich G, Castera L, Halfon P, Bourliere M, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: results of a multicenter, large-scale study. J Hepatol 2010;53:630–638.
[55] Thabut D, Trabut JB, Massard J, Rudler M, Muntenau M, Messous D, et al. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. Liver Int 2006;26: 271–278.
[56] Giannini EG, Zaman A, Kreil A, Floreani A, Dulbecco P, Testa E, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: results of a multicenter, prospective, validation study. Am J Gastroenterol 2006;101:2511–2519.
[57] de Franchis R, Eisen GM, Laine L, Fernandez-Urien I, Herrerias JM, Brown RD, et al. Esophageal capsule endoscopy for screening and surveillance of esophageal varices in patients with portal hypertension. Hepatology 2008; 47:1595–1603.
[58] Lapalus MG, Ben Soussan E, Gaudric M, Saurin JC, D'Halluin PN, Favre O, et al. Esophageal capsule endoscopy vs. EGD for the evaluation of portal hypertension: a French prospective multicenter comparative study. Am J Gastroenterol 2009;104:1112–1118.
[59] Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol 2010;105:1382–1390.
[60] Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343–350.
[61] Foucher J, Chanteloup E, Vergniol J, Castera L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403–408.
[62] Castera L. Liver stiffness and hepatocellular carcinoma: liaisons dangereuses? Hepatology 2009;49:1793–1794.
[63] Masuzaki R, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology 2009;49: 1954–1961.
[64] Jung KS, Kim SU, Ahn SH, Park YN, Kim do Y, Park JY, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885–894.
[65] Robic MA, Procopet B, Metivier S, Peron JM, Selves J, Vinel JP, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol 2011;55: 1017–1024.
[66] Bosch J. Soft technique, hard end-points. J Hepatol 2011;55:955–956.
[67] Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968–973.
[68] Boursier J, Konate A, Guilluy M, Gorea G, Sawadogo A, Quemener E, et al. Learning curve and interobserver reproducibility evaluation of liver stiffness measurement by transient elastography. Eur J Gastroenterol Hepatol 2008;20:693–701.
[69] Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828–835.
[70] Arena U, Vizzutti F, Abraldes JG, Corti G, Stasi C, Moscarella S, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288–1293.
[71] Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36–44.
[72] Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360–369.
[73] Sagir A, Erhardt A, Schmitt M, Haussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2007;47:592–595.
[74] Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380–384.
[75] Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Buchler MW, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology 2008;48:1718–1723.
[76] Millonig G, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010;52:206–210.
[77] Berzigotti A, de Gottardi A, Delgado MG, Seijo S, Abraldes JG, Garcia-Pagan JC, et al. Liver stiffness increases after a meal in patients with cirrhosis but its change does not correlate with the changes in HVPG (abstract). Hepatology 2010;52:1074A.
[78] Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol 2009;193: 122–127.