Non invasive diagnosis of portal hypertension in cirrhotic patients

Diagnostic non invasif de l’hypertension portale au cours de la cirrhose

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Summary
The measure of disease progression in chronic liver disease represents a key challenge in any of the different stages of evolution. Indeed, a correct and reliable measure of the stage of the disease has relevant implications for assessing the effectiveness of the current therapeutic regimens and for predicting the occurrence of complication. Accordingly, a current major effort is directed at evaluating methodologies characterized by no or low invasiveness to be employed as clinical discriminators in patients populations potentially requiring invasive assessment. This appears particularly relevant in patients with compensated cirrhosis, where the only reference standard is the measurement of portal pressure by hepatic venous pressure gradient (HVPG). In this particular context, transient elastography (TE) appears to be promising and needs to be further investigated, possibly in combination with other non-invasive methodologies such as serum markers algorithms and/or imaging techniques. On the other hand, the application of non-invasive methods for monitoring the response to vasoactive treatment for the reduction of portal pressure and the prevention of related complications seems at the moment not realistic.

Résumé
L’évaluation de l’aggravation des hépatopathies chroniques à chacun des stades de la maladie est primordiale. En effet, une évaluation correcte et fiable de chaque stade de la maladie a une implication concrète pour mesurer l’efficacité des traitements et pour prédire la survenue des complications. Ainsi, de plus en plus de travaux de recherches sont effectués pour évaluer de nouvelles méthodes peu ou non-invasives. Cela est particulièrement important chez les malades avec cirrhose compensée pour lesquels
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]. Although tissue fibrosis is an essential element in the cirrhotic transformation of the liver, it is per se devoid of significant functional (and clinically relevant) effects. Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules [2]. Key morphological features of cirrhosis include: diffuse fibrosis, regenerative nodules, altered lobular architecture and establishment of intrahepatic vascular shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver [3]. The vascular shunts are determined by the topography of the vascularized fibrotic septa and represent an essential feature of cirrhosis [4]. Other relevant characteristics comprise: capillarization of sinusoids and perisinusoidal fibrosis, vascular thrombosis andobliterative lesions in portal tracts and hepatic veins, under-perfusion of lobular parenchyma and consequent tissue hypoxia [5-6]. Altogether these changes are responsible for the development of portal hypertension and relative complications. Portal hypertension is indeed the principal mechanism leading to the death of cirrhotic patients.

An increase in portal pressure can be detected by the measurement of HVPG already in patients with histologically defined advanced fibrosis. However, complications of portal hypertension, i.e. development of esophageal varices, ascites, hepatic encephalopathy, bleeding, and renal impairment, occur over a threshold value of 10-12 mmHg. Over these limits cirrhosis becomes clinically decompensated and bleeding from ruptured esophageal or gastric varices constitutes the major clinical event causing death [7-9]. Along these lines, it is evident an accurate determination of the degree of portal hypertension holds prognostic information in cirrhotic patients in different stages of the disease [10].

HVPG measurement represents the gold standard methodology to assess portal hypertension and its severity [11-12] (Table 1). HVPG is a widely accepted “splanchnic sphygmomanometer” to monitor the effectiveness of vasoactive drugs in primary and secondary prophylaxis of variceal bleeding [10, 13]. Moreover, HVPG may provide useful prognostic information in compensated and decompensated cirrhotic subjects. In patients with compensated cirrhosis,
an HVPG greater or equal to 10 mmHg is the most important predictor of the development of varices [14] and clinical decompensation (i.e. for each 1 mmHg in HVPG increases the risk of decompensation by 11%) [15]. In decompensated cirrhotic patients, HVPG obtained at the time of variceal bleeding predicts outcome [16] and is an independent predictor of death [17]. An HVPG of at least 20 mmHg appears to be the best cut-off in this scenario. Importantly, HVPG measured one year after liver transplantation predicts the risk of developing decompensation better than liver biopsy, and the risk of decompensation three years after liver transplantation appears to be less than 5% in those patients with an HVPG < 6 mmHg [18]. In the study of Rincon et al., a significant decrease in HVPG was observed after antiviral therapy especially in those patients with more pronounced virological and/or biochemical responses. Therefore, HVPG could evaluate both the efficacy portal pressure reducing drugs and response to agent preventing the progression of chronic liver diseases.

Upper gastrointestinal endoscopy is the best method for evaluating the presence of complication of portal hypertension including gastroesophageal varices and portal hypertensive gastropathy, and its routinely employed as a first-level approach to assess this syndrome [19-20]. Indeed, esophageal varices are present in about 40% of compensated cirrhotic patients and in 60% of those presenting with ascites at the initial diagnosis of cirrhosis [21-22]. Moreover, upper gastrointestinal endoscopy discloses the characteristics of the varices (i.e. dimension and presence of red signs). Detection of these signs offers important predictive information for the occurrence of variceal bleeding [23-25]. Additionally, upper gastrointestinal endoscopy allows to assess the presence, extent, and severity of portal hypertension gastropathy. The pressure in esophageal varices can be safely measured at upper gastrointestinal endoscopy through pressure-sensitive gauges, or with an inflating-deflating balloon sited distally on the endoscope. The first approach has been more extensively validated in prospective studies. The main drawback of this methodology concerns the procedural difficulty, especially in patients with small varices. However, variceal pressure measurement is a reproducible methodology when strict criteria are employed to define adequate measurements [26, 27]. Variceal pressure was shown to significantly correlate with portal pressure [28]. Nevertheless, variceal pressure is significantly lower than portal pressure, probably due to the resistance opposed by collateral vessels feeding the varices. Variceal pressure was shown to provide prognostic information in different clinical settings: a. development of first variceal bleeding; b. evolution of an acute variceal bleeding episode; c. risk of bleeding recurrence in patients receiving pharmacological prophylaxis [29-31]. Moreover, variceal pressure could be employed to assess the effectiveness of pharmacological therapy [26, 31-32]. The prognostic value of the variceal pressure response to pharmacological prophylaxis was as powerful as that of the HVPG response. HVPG and variceal pressure measurements identify different patients populations with favourable outcome, therefore they should be considered complementary rather than mutually exclusive [31].

Endosonography allows the visualization of gastroesophageal varices, perigastric/periesophageal collateral veins, portal venous system, and azygos vein. However, this approach does not seem to add further prognostic information in terms of portal hypertension related complication when compared with upper gastrointestinal endoscopy [33, 34]. Interestingly the combined use of endosonography and variceal pressure measurement allows an estimate of variceal wall tension, the driving force for variceal rupture.

Even if HVPG measurement and endoscopy are safe and relatively simple, both are invasive (conscious sedation markedly increases the acceptability of both procedures), require a specific training, and could be not cost-effective in some clinical settings. Therefore, an expert recommendation of the Baveno IV Consensus Conference [35] was to develop non-invasive methodologies (Table 2) able to identify subjects with clinically significant portal hypertension (i.e. with esophageal varices) and to monitor the effectiveness of drug therapy (especially β-blockers).

Non-invasive approaches for the assessment of portal hypertension in cirrhotic patients

Physical examination

Several clinical signs observed at physical examination suggest the presence of portal hypertension. These include splenomegaly, abdominal wall collateral circulation, ascites, and peripheral edema. In addition hypotension and tachycardia may reflect a hyperdynamic circulation in advanced cases. A systematic review of the diagnostic accuracy of physical examination for the detection of cirrhosis with portal hypertension established that physical findings are characterized by low sensitivity for the diagnosis of compensated disease [36].

Laboratory

In portal hypertensive patients, the presence of hypersplenism is responsible for leuco-thrombocytopenia. In this clinical context, an independent correlation between platelet count and the prevalence/grade of esophageal varices was observed [21, 37]. Along these lines, Giannini et al. reported a 100% negative predictive value for the prediction of esophageal varices for a platelet count/spleen diameter ratio above 909 [38]. The effectiveness of this ratio has been externally validated [39]. However, in terms of clinical utility, the relevance of this index in reducing the number of screening upper gastrointestinal endoscopies needs to be further evaluated. More recently, was reported that even if HVPG correlate somewhat with platelet, changes in platelet cannot be used as a surrogate for HVPG changes or as a predictor of varices presence/development in cirrhotic patients [40]. The degree of hepatocellular failure, as indicated by low plasma levels of albumin, prolonged prothrombin time and high bilirubin plasma levels, or patient categorization according to the Child-Pugh score have been shown to correlate with portal pressure and with the prevalence/ grade of esophageal varices in cirrhotic subjects [41-43].
Interestingly, some of these laboratory parameters are included in algorithms designed for the prediction of liver fibrosis in CLD [44]. Therefore, studies investigating a possible predictive and/or prognostic value of these algorithms in subjects with advanced CLD should be encouraged.

**Ultrasound and duplex-Doppler**

Ultrasound Colour Duplex Doppler (USD) is a non-invasive technique which allows the study of splanchnic organs and vessels. At the present state of technological development, USD has a complementary role in the diagnosis of advanced fibrosis/cirrhosis and represent the preferred screening methodology for the examination of patients with suspected portal hypertension. In addition, ultrasound examination provides information about liver, biliary, or pancreatic diseases that may be the cause of portal hypertension, and is able to better define indirect signs of portal hypertension such as splenomegaly, ascites, and the presence of portocollateral vessels. Among these parameters, spleen length has been proposed as an independent predictive marker of esophageal varices.

The main limitations of USD measurements are the high inter- and intra-observer variability. Furthermore, factors related to different physiologic status of the patient (posture, phase of respiration, relationship with meals) largely affect the findings. Some USD parameters have been found to have a high specificity and sensitivity for the diagnosis of cirrhotic portal hypertension, and particularly: dilated portal vein (diameter > 13 mm) [45]; lack or reduced respiratory variations of splenic and superior mesenteric vein diameter [46]; reversal of portal blood flow; reduced portal vein velocity [47]; portal-systemic collateral circulation [48]; altered hepatic venous Doppler pattern [49]; increased intraparenchymal hepatic and splenic artery impedance [50-52]; increased intraparenchymal renal artery impedance [53]; increased congestion index of portal vein [54]; and reduced mesenteric artery impedance [55]. Finally, a good correlation between portal blood flow and HVPG has been reported [55]. Regardless, a critical analysis of different studies performed in cirrhotic patients has yielded conflicting and not conclusive results concerning the usefulness of USD for assessing portal hypertension [49, 53, 55-58]. This is at least in part due to differences in the selection of patients with different degrees of hepatic decompensation and/or to the inclusion of patients presenting with confounding factors such as concomitant cardiovascular or renal diseases, treatment with vasoactive agents or diuretics. In order to overcome these limitations we performed a study in a cohort of 54 HCV cirrhotic subjects carefully selected in order to minimize factors that potentially influence reliability of USD parameters [59]. The correlation between HVPG and selected USD parameters (right interlobar renal artery resistance index, intraparenchymal splenic artery resistance index, and superior mesenteric artery pulsatility index) was found to be weak, especially in subjects with severe portal hypertension (i.e. ≥12 mmHg). On the other hand, this study suggested that the proposed USD measurement may be useful, together with other non-invasive tools (i.e. TE) for the evaluation of the degree of portal hypertension in stages preceding the development of clinically evident/severe portal hypertension (i.e. HVPG ≥10-12 mmHg). Therefore, studies aimed at further assessing this possibility are also encouraged.

A poor diagnostic accuracy has been reported concerning the usefulness of USD variables for the prediction of the hemodynamic response to vasoactive agents [58, 60]. Finally, it should be further stressed that the USD technique is equipment- and operator-dependent [61].

### Table 2.

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Available non-invasive methodologies for the assessment of portal hypertension are less accurate, unreliable, and/or not truly non-invasive.

* in the presence of varices, especially large ones.

# modest underestimation of portal pressure values due to resistance opposed by collateral vessel to blood flow.

* minimally invasive.

USD : Ultrasound colour duplex Doppler; HVPG : Hepatic Venous Pressure Gradient; TE : Transient Elastography; UGE : Upper Gastrointestinal Endoscopy; VP : Variceal Pressure; CT : Computer Tomographic scan; MR : Magnetic Resonance Imaging; LAB : Laboratory
Other imaging techniques

Computed tomographic scan (CT) and magnetic resonance (MR) allow an accurate visualization of portal venous system. Dynamic contrast-enhanced single-section CT scans and MR and phase contrast MR angiography have been shown to provide an observer-independent quantitative measurement of portal [62] and azygos [63] blood flow. In particular azygos blood flow has been found to correlate with the presence and the risk of bleeding from esophageal varices. A good correlation with HVPG was also found for the portal fraction of liver perfusion and mean transit time evaluated by MR [64]. At present, no data concerning the usefulness of these techniques for monitoring drug therapy in portal hypertensive patients are available.

Transient elastography

TE (FibroScan®) is a novel, rapid, non-invasive, and reproducible method developed for assessing liver stiffness as an indicator of liver fibrosis [65-66]. Pioneer studies showed that TE accurately predicted advanced fibrosis and cirrhosis in patients with hepatitis C [65-66]. These results were confirmed in a recent study performed in a cohort of HCV related CLD patients by employing more stringent methodological and statistical criteria [67]. Indeed, this study confirms that TE accurately predict the presence of advanced fibrosis stages (i.e. ≥F3 according to METAVIR scoring system). Accordingly, since hepatic tissue scarring is the major determinant for the development of portal hypertension, liver stiffness measurement has theoretical potential for the evaluation of portal hypertension. Kazemi et al. [68] suggested that TE may predict the presence of big varices in patients with liver cirrhosis and could, therefore, be used to select those patients to be referred for upper gastrointestinal endoscopy. In this study, however, endoscopic assessment was retrospective, and the performance of TE was not superior to than of other easily available clinical parameters. Additionally, TE was not discriminative towards the presence of small varices, since the best cut-off for detecting all types of varices overlapped with that for detecting cirrhosis [69]. In a study performed by Carrion et al. [70] in a cohort of subjects with HCV recurrence after liver transplantation, TE showed an excellent correlation with HVPG. In this study, a liver stiffness value ≥8.74 kPa had a sensitivity and specificity of 90% and 81% for the diagnosis of portal hypertension (i.e. HVPG ≥10 mmHg). A study performed in a cohort of consecutive HCV-chronic liver disease related subjects [71] showed an excellent correlation between liver stiffness and HVPG < 10 mmHg. The results of these studies may have important implications for the clinical assessment of patients at stages of evolution of CLD preceding the development of clinically significant portal hypertension. Interestingly, the HVPG value of 10 mmHg appears to be a key determinant in the relationship between HVPG and liver stiffness in the study of Vizzutti et al. [71]. Indeed, the correlation between the two parameters seems optimal for HVPG values ≤10-12 mmHg, whereas hardly reaches statistical significance for values ≥12 mmHg (Fig 1). This important observation could suggest that beyond a certain degree of portal pressure, i.e. ≥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 tissue stiffness. Indeed, it is well established that in advanced cirrhosis several extrahepatic factors such as the hyperdynamic circulation, the splanchic vasodilatation and the resistance opposed to portal blood flow by the porto-systemic collaterals contribute to the rise in portal pressure [1]. It is also likely that, beyond a certain degree of cirrhotic transformation of liver tissue, the measure of liver stiffness does not reflect the changes in liver angio-architecture and the active contraction of scar tissue secondary to the unbalanced predominance of vasoconstrictors. All together these factors constitute important mechanistic variables that can independently affect portal pressure with a different impact in different patients (Fig 2). Further larger and blinded studies, preferably on a multicenter basis, in unselected consecutive patients are needed to definitively assess the usefulness of TE in the management of portal hypertension.

Capsule endoscopy

Capsule endoscopy represents an alternative to upper gastrointestinal endoscopy and may be considered as an alternative non-invasive methodology for indirectly assess
the presence of clinically significant/severe portal hypertension. A negative predictive value of 57-100% for detection of esophageal varices was reported in a series of pilot studies [72-74]. Preliminary results from a multicenter study [75] comparing upper endoscopy and capsule endoscopy, showed a good agreement in detecting both the presence (86%) and size (77%) of esophageal varices. However, the incidence of false negative cases and varices underestimation by capsule endoscopy was remarkable. Further study aimed at better defining reproducibility, reliability, accuracy, and cost-effectiveness of capsule endoscopy are needed. Regardless, this tool may be a reasonable alternative to upper endoscopy in subjects unable or unwilling to undergo upper endoscopy.

**Conflict of interest:** Francesco Vizzutti, Umberto Arena, Luigi Rega and Massimo Pinzani have no conflict of interest.

**Références**


