Research Article

Real-time shear-wave elastography: Applicability, reliability and accuracy for clinically significant portal hypertension

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Background & Aims: Real-time shear wave elastography (RT-SWE) might be useful to assess the severity of portal hypertension; reliability criteria for measurement are needed.

Methods: We prospectively included 88 consecutive patients undergoing hepatic venous pressure gradient measurement (HVPG, reference standard) for portal hypertension. Liver stiffness (LS) was measured by RT-SWE and by transient elastography (TE). Spleen stiffness (SS) was measured by RT-SWE. Reliability criteria for RT-SWE were searched, and the accuracy of these techniques to identify HVPG $\geqslant$10 mmHg (clinically significant portal hypertension, CSPH) was tested and internally validated by bootstrapping analysis.

Results: LS and SS by RT-SWE were feasible respectively in 87 (99%) and 58 (66%) patients. Both correlated with HVPG (LS: R = 0.611, p <0.0001 and SS: R = 0.514, p <0.0001). LS performed well for diagnosing CSPH (optimism corrected AUROC = 0.858). Reliability of measurements was influenced by standard deviation (SD)/median ratio and depth. SD/median $\leqslant$0.10 and depth of measurement <5.6 cm were associated to 96.3% well classified for CSPH, while when one or none of the criteria were fulfilled the rates were 76.4% and 44.4%, respectively. Measurements fulfilling at least one criterion were considered acceptable; in these patients, RT-SWE performance to detect CSPH was excellent (AUROC = 0.939; 95% CI: 0.865–1.000; p <0.0001; best cut-off: 15.4 kPa). LS by RT-SWE and by TE were strongly correlated (R = 0.795, p <0.0001) and performed similarly both in "per protocol" and in "intention-to-diagnose" analysis after applying reliability criteria.

Conclusions: LS by RT-SWE is an accurate method to diagnose CSPH if reliability criteria (SD/median $\leqslant$0.10 and/or depth <5.6 cm) are fulfilled.

Keywords: HVPG; Sonoelastography; Cirrhosis; Liver disease; Ultrasound.
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Abbreviations: RT-SWE, real-time shear wave elastography; TE, transient elastography; HVPG, hepatic venous pressure gradient measurement; LS, liver stiffness; SS, spleen stiffness; CSPH, clinically significant portal hypertension; SD, standard deviation; CLD, chronic liver disease; PH, portal hypertension; ROI, region of interest; ICC, intraclass correlation coefficient; AUROC, area under the receiver operating characteristic curve.

Introduction

In the natural history of chronic liver disease (CLD) the occurrence of liver-related complications is mainly due to the development of portal hypertension (PH). The best way to evaluate the presence of PH is the measurement of hepatic venous pressure gradient (HVPG), which represents the strongest prognostic marker in patients with advanced CLD [1]. In particular, it is important to detect development of clinically significant portal hypertension (CSPH) (HVPG $\geqslant$10 mmHg) in patients with compensated CLD, since it identifies a clinical stage with an increased risk of complications and death [1]. HVPG has also prognostic value in other clinical settings, such as liver transplantation, alcoholic hepatitis and decompensated cirrhosis [1]. However, the main drawback of HVPG measurement is that it is an invasive technique and is not widely available. Therefore, development of non-invasive simple, objective, reproducible and accurate alternatives to assess the presence of CSPH and to estimate HVPG has become a research priority.

Up to now only liver stiffness measurement (LS) by transient elastography (TE) (alone or combined to platelet count and spleen size measurement by ultrasound) proved sufficient accuracy to be used for this aim [2,3]. LS correlates with HVPG and is an accurate tool to diagnose CSPH in patients with compensated CLD. Spleen stiffness measurement (SS) by TE has also been recently reported to be promising to diagnose CSPH [4,5]. However, LS is not suited to assess the exact value of HVPG, since the correlation is not close enough, especially at HVPG values $\geqslant$10 mmHg [6]. Furthermore, applicability of LS and SS by TE are suboptimal due to technical limitations (e.g., obesity, narrow intercostal spaces, ascites, small spleen size).

Real-time shear wave elastography (RT-SWE) is a new elastographic method that can evaluate the stiffness of a given tissue by measuring the speed propagation of shear waves generated by ultrasound-pushes across it. Even if the principle of LS by

RT-SWE is similar to that of TE, RT-SWE has several theoretical advantages: (1) the shear waves are generated directly within the tissue, allowing measuring stiffness also in patients with ascites; (2) it is implemented on a last-generation ultrasound equipment, which provides the advantage of guiding the area where the measurement is to be performed by a high frame-rate B-mode image; and (3) it allows imaging liver stiffness on a color-coded box in real time, so controlling for major measurement bias. A drawback when compared to TE is the lack of criteria to judge when a LS measurement by this technique should be considered valid. Despite this, initial studies of LS by RT-SWE suggest that it is as accurate as TE to assess liver fibrosis [7–9]. However, there is very limited data about the performance of LS and SS by RT-SWE for the evaluation of portal hypertension [10], and it is currently uncertain whether it can be considered a valid alternative to TE.

Given all this, the aims of the present prospective study were: (1) to investigate the applicability of LS and SS by RT-SWE in patients undergoing clinically indicated measurement of HVPG; (2) to assess if LS and SS by RT-SWE correlate with HVPG and are accurate for the diagnosis of CSPH; (3) to identify reliability criteria for LS by RT-SWE for the assessment of CSPH and (4) to compare the feasibility and the accuracy of LS by RT-SWE and by TE in an "intention-to-diagnose" approach in patients undergoing LS measurements by both techniques.

Patients and methods

This prospective study was approved by the Ethics Committee of our Center (ref. HCB/2014/0501). The nature of the study was explained to the patients, and informed consent was obtained according to the principles of the Declaration of Helsinki (revision of Edinburgh 2000).

Population

One hundred twelve consecutive patients referred to Hepatic Hemodynamic Lab in Barcelona for HVPG measurement (alone or combined with transjugular liver biopsy) from February 20th to June 20th 2014, were screened. Patients in whom HVPG measurement for the assessment of portal hypertension was not the primary aim of the hemodynamic study were excluded. This occurred in 24 patients that had the hemodynamic study in order to perform a transjugular liver biopsy for the histological evaluation of acute hepatitis (n = 8), suspected rejection of the graft in previous liver transplantation (n = 5), throughout assessment of non-cirrhotic ascites (n = 5), suspected post-chemotherapy sinusoidal obstruction syndrome (n = 4), suspected hepatic infiltrative lymphoma (n = 1) and HIV associated portal hypertension (n = 1). Fig. 1 summarizes the inclusion algorithm.

The included population (n = 88) was composed by patients within the following clinical scenarios: – Compensated long-lasting chronic hepatitis (CLD) or cirrhosis (n = 55; 4 with severe liver fibrosis, 51 with cirrhosis), in whom HVPG was required to assess the presence/absence of CSPH; – decompensated cirrhosis (n = 24; 20 with ascites), in whom HVPG was indicated before starting NSBB (n = 6) or before TIPS insertion (n = 4), or within the evaluation of newly appeared ascites (n = 14; post-transplantation recurrence of cirrhosis in one case); – control group to check for normality range (n = 9): patients without any chronic liver disease but having one or two liver metastases from extrahepatic cancer, in whom HVPG and liver biopsy were performed to rule-out PH due to previous chemotherapy. In all these patients liver resection surgery for the metastases was performed and pathological examination of the hepatic parenchyma excluded any liver disease.

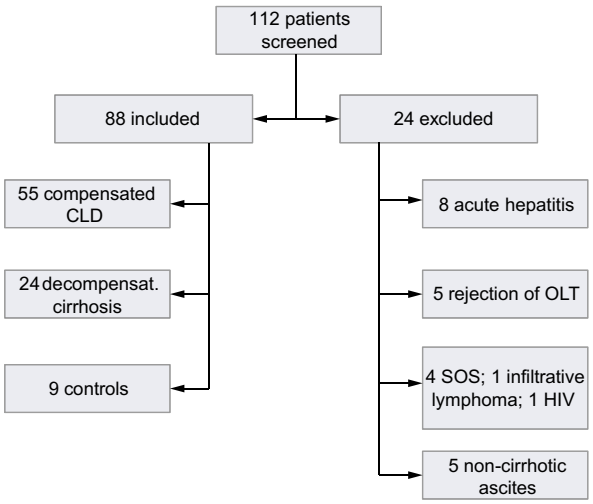

Fig. 1. Flow chart of patients included in the study.

Hepatic venous pressure gradient measurement

HVPG was measured in fasting conditions as previously described [1] using a 7F balloon-tipped catheter (Fogarty® catheter, Edwards Lifesciences™, Irvine, CA, USA) and data were registered using a pre-calibrated electromechanical transducer and polygraph (Mac-Lab; GE Healthcare, Freiburg, Germany). The HVPG was calculated as the difference of wedged hepatic venous pressure and free hepatic venous pressure, and was expressed in mmHg. All measurements were performed in triplicate, and permanent tracings were recorded [1]. The final HVPG value was the mean of 3 repeated measurements. CSPH was defined as an HVPG $\geqslant$10 mmHg.

LS and SS by RT-SWE

All RT-SWE measurements were done in the Hepatic Hemodynamic Laboratory in fasting state few minutes before HVPG measurement by two physicians experienced in abdominal ultrasound; in all cases, operators were blinded to the results of HVPG measurement. The Aixplorer US system (SuperSonic Imagine S.A., Aix-en-Provence, France) with a convex broadband probe (SC6-1) was used. The detailed principles of RT-SWE elastography are described elsewhere [11]. Patients were placed in supine position with the right arm (LS) or left arm (SS) in maximal abduction. The transducer was placed in the right intercostal spaces that allowed a good visualization of the right hepatic lobe parenchyma in B mode for LS, and in the left intercostal space allowing a good visualization of the spleen for SS. All RT-SWE acquisitions were performed using a 3.5 $\times$ 2.5 cm box, placed at more than 2 cm under the Glisson capsule, avoiding the big vascular structures. During the acquisition the patient was requested to hold his/her breath for about 5 seconds. After obtaining a stable and homogenous elastographic image inside the box, a region of interest (ROI) was selected using the Q-box tool and placed in the most homogeneous blue area (normally in the center of the acquisition box), and the median values of LS within the ROI was displayed and registered. The diameter of the Q-box was set >15 mm. Three different elastographic images [9,12] were obtained in all patients both in the liver and in the spleen, and the median value was used. In a subgroup of 61 patients, a higher number of measurements (4 in 38 patients and 5 in 23 patients) was obtained in order to evaluate whether this increased the reliability of the results in this specific clinical scenario. Failure to obtain a stable elastogram within the acquisition time was considered as technical failure.

Transient elastography

LS by TE was performed using FibroScan® (Echosens, Paris, France) in fasting condition right after obtaining LS by RT-SWE. Due to technical reasons (physical absence of TE equipment in 3 cases; lack of time in the remaining), the TE was not attempted in 15 patients. LS by TE was performed as previously described [13] by two experienced operators, both with an experience of over 500 LS examinations. Ten measurements were obtained, and a minimum success rate of 60% was required. According to Boursier *et al.* [14], measurements were considered unreliable when they showed a >0.30 interquartile (IQR)/median (M) ratio, reliable when they showed 0.11-0.30 IQR/M and very reliable if IQR/M $\leqslant$0.10. We defined "technical failure" the impossibility to obtain any value. Finally, in the present study SS by TE was not measured.