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● *Original Contribution*

A NOVEL FIBROSCAN EXAMINATION DEDICATED TO SPLEEN STIFFNESS MEASUREMENT

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Abstract—Esophageal varices (EVs) are among the most severe complications of cirrhosis, with a prevalence of 50% to 60% among cirrhotic patients. International guidelines therefore recommend that cirrhotic patients should be screened for the presence of EVs. The main objective of this study was to introduce a new spleen-dedicated FibroScan (Echosens, Paris, France) examination and to assess its performance in detecting large EVs (grade 2 and 3). This novel examination has been validated in simulation and phantom studies and has been used in a population of patients with chronic liver disease. The study described here suggests that the novel spleen-dedicated FibroScan examination performs better than the standard FibroScan for the detection of large EVs (area under the curve = 0.70 for the standard examination and 0.79 [$p < 0.01$] for the spleen examination), but further clinical studies are needed to investigate the role of spleen stiffness in the management of cirrhotic patients.
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Key Words: **Transient elastography (TE), Vibration-controlled transient elastography (VCTE), FibroScan, Spleen, Spleen stiffness, Esophageal varices, Portal hypertension, Cirrhosis, Chronic liver disease.**

INTRODUCTION

Cirrhosis is the end stage of all chronic liver diseases and is characterized by abnormal liver structure and function. Portal hypertension (PH) is an important complication of cirrhosis leading to variceal bleeding (Pagliaro et al. 1994). PH is defined as high pressure in the portal vein caused by increased vascular resistance in the cirrhotic liver.

The gold standard for the assessment of PH is measurement of the hepatic venous pressure gradient (HVPG). HVPG is defined as the difference between wedged (WHVP) and free (FHVP) hepatic vein pressure, at hepatic vein catheterization using a balloon occluding catheter, as described by Bosch et al. (2009). Therefore, HVPG is measured inside either the right or middle hepatic vein, with the balloon inflated (WHVP) or deflated (FHVP). HVPG values >10 mm Hg characterize patients with clinically significant portal hypertension (CSPH), who are at risk of developing esophageal varices (EVs); patients with severe PH (≥12 mm Hg) are at risk for variceal bleeding (Garcia-Tsao et al. 2017). However, the HVPG procedure is invasive, operator dependent and costly.

In clinical practice, the presence of EVs at upper gastrointestinal endoscopy (EGD) is a clinical criterion to diagnose CSPH. Indeed, rupture of EVs represents one of the most severe and life-threatening complications of cirrhosis. The prevalence of EVs among cirrhotic patients is between 50% and 60% (D'Amico et al. 2001). The natural prevalence of EV bleeding is around 30%, and mortality within 6 wk after a bleeding episode reaches 15% to 20% with current treatment (Garcia-Tsao et al. 1985). International consensus therefore recommends that cirrhotic patients with a liver stiffness (LS) > 20 kPa or platelet count <150 g/L should be screened for the presence of EVs using EGD (de Franchis and Baveno 2015). Like HVPG, EGD is invasive and is rather poorly accepted by patients especially because it must be repeated at 1- or 2-y intervals depending on the presence or absence of small EVs.

In the past year, several non-invasive tests (NITs) have been proposed for evaluation of the development of PH

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and its complications. Biomechanical markers such as liver stiffness (LS) and spleen stiffness (SS) have recently been studied as accurate surrogate NITs for estimating the presence of EVs or CSPH (Colecchia et al. 2015; Elkrief et al. 2015; Giunta et al. 2016; Kim et al. 2015, 2016; Park et al. 2016; Procopet et al. 2015; Singh et al. 2014; Sirli et al. 2015; Takuma et al. 2016; Zykus et al. 2015). Different elastographic techniques such as vibration-controlled transient elastography (VCTE or TE), acoustic radiation force impulse (ARFI) imaging (Bota et al. 2012), real-time tissue elastography (RTE) and shear wave elastography (SWE) (Kim et al. 2016) have also been investigated. The overall results of these studies are promising (Ma et al. 2016), although technical limitations, especially for SS measurement, need to be considered for EV diagnosis (Singh et al. 2014). Moreover, other non-invasive scores including blood tests (Lok score) and platelet count/spleen diameter ratio (PSR) have been investigated but have exhibited moderate performance (Cho et al. 2015; Pateu et al. 2018; Stefanescu et al. 2015).

FibroScan (Echosens, Paris, France) is a device based on VCTE and dedicated to LS measurement (Sandrin et al. 2003). It is widely used in the management of chronic liver diseases and has been clinically validated in a large number of studies to stage liver fibrosis (de Ledinghen et al. 2006; Ganne-Carrie et al. 2006; Ziol et al. 2005). LS measurement using FibroScan has also been correlated with portal hypertension and EV degree (Castera et al. 2008, 2009). More recently, SS measurement using the FibroScan has been investigated to assess EVs in cirrhotic patients (Calvaruso et al. 2010, 2013; Stefanescu et al. 2011). In these studies, SS measured by the FibroScan performed well in detecting EVs or large EVs, but was limited by the technical settings of the FibroScan, which are optimized for LS measurement, especially the stiffness range (1.5–75 kPa) (Berzigotti 2017; Castera and Garcia-Tsao 2013). In their study, Calvaruso et al. (2013) pointed out that the normal spleen was reported to be stiffer than the normal liver; the acquisition parameters of the FibroScan (low-frequency excitation for shear wave, ultrasound pulse repetition frequency) should therefore be adapted to accurately assess SS.

The aims of the present study were (i) to describe a novel FibroScan examination specifically designed for SS measurement and (ii) to assess its performance in detecting large EVs in a population with chronic liver disease.

METHODS

Spleen anatomy and function

The spleen is the largest lymphoid organ of the body. It is located in the upper left part of the abdomen and is adjacent to the stomach and to the left kidney. It is organized in two distinct regions. The red pulp represents most of the splenic parenchyma and plays a role in the filtration of blood cells; the white pulp plays a role in the immune system. Spleen maximum size is approximately 12 cm × 8 cm × 4 cm in healthy patients. In non-obese people, the distance between the spleen and skin surface is approximately between 1 and 2 cm. Spleen enlargement is a well-known consequence of liver cirrhosis (Li et al. 2017). It is due mainly to tissue hyperplasia, but also to portal congestion/hypertension and splenic fibrosis (Bolognesi et al. 2002). Splenomegaly linked to cirrhosis seems less pronounced in alcoholic etiology than in chronic hepatitis C or non-alcoholic steatohepatitis (Kashani et al. 2015).

Spleen stiffness range

As pointed out by several studies using the FibroScan for SS measurement (Calvaruso et al. 2013; Stefanescu et al. 2011), the main drawback of the standard FibroScan examination, when used on the spleen, is the upper stiffness limit (75 kPa), which is reached for many patients and prevents good discrimination between patients with and those without large EVs.

In a study using SWE (Procopet et al. 2015), normal median SS was reported to be 21.9 kPa for control patients and reached 41.8 kPa in patients with decompensated cirrhosis. In another study (Cassinotto et al. 2015), SS measured using SWE ranged from 11.8 to 68.1 kPa in cirrhotic patients. With ARFI imaging, mean SS in a group of 35 healthy volunteers was reported to be 2.44 m/s (17.9 kPa) (Gallotti et al. 2010). SS values measured by magnetic resonance elastography (MRE) (Mannelli et al. 2010; Talwalkar et al. 2009) were in the same range: The shear modulus was between 2.7 and 19.2 kPa in patients with chronic liver disease (Young's modulus E being related to shear modulus μ by the relation $E = 3\mu$, it was equivalent to an SS between 8.1 and 57.6 kPa). Overall, most studies reported that the normal SS range was higher than the normal LS range, suggesting that the lower and upper thresholds of the FibroScan should be modified to fit SS.

FibroScan principle

FibroScan is a diagnostic device based on VCTE (Sandrin et al. 2003). It measures a mean tissue stiffness (between 25 and 65 mm in the liver of non-obese patients) in a medium considered homogeneous and isotropic. FibroScan is equipped with a probe composed of an ultrasonic transducer (3.5 MHz for non-obese patients) mounted on the axis of a vibrator. This vibrator generates a low-frequency pulse (50 Hz and 2-mm peak-to-peak amplitude for LS measurement in non-obese patients) that induces a shear wave that propagates through the tissue. Shear wave propagation is followed by pulse-echo ultrasound, and the strains induced in the tissue are computed as a function of time and depth. Tissue stiffness E is