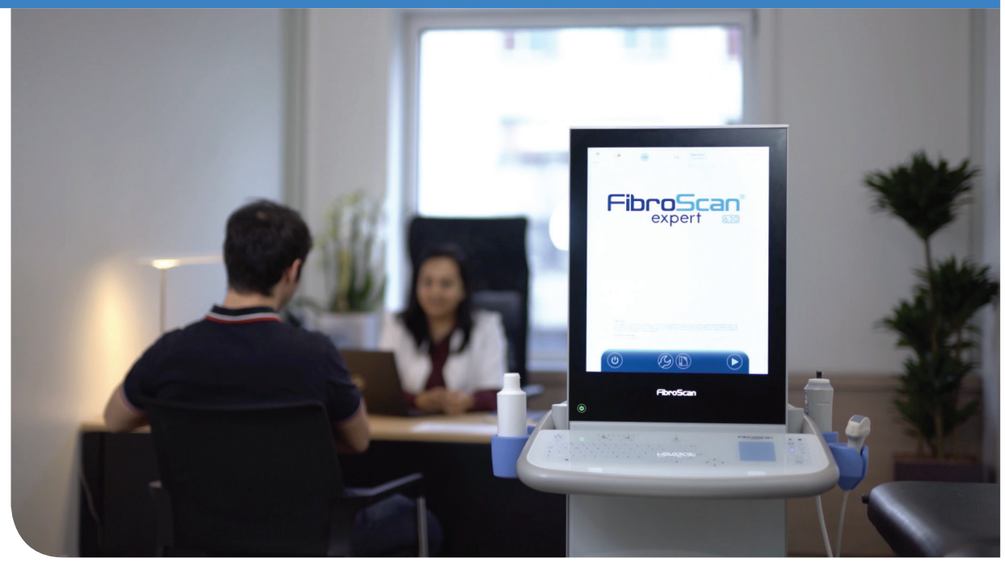
# VCTE™ & SPLEEN STIFFNESS

## Clinical utility of spleen stiffness measurement in the work-up, risk stratification and follow-up of cirrhotic patients

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# Vibration Controlled Transient Elastography VCTE™ and spleen stiffness


## REMINDERS ON VCTE™

First introduced in 2004, VCTE™ is a modality that allows rapid, non-invasive and painless assessment of liver stiffness [1, 2]. Since then, it has been increasingly used and validated to stage fibrosis as an aid for physicians in the management of chronic liver diseases.

VCTE™ measures stiffness by generating low frequency pulses (50 Hz) to create shear waves that travel through liver tissue (between 25 and 65 mm with the FibroScan® M probe). Liver stiffness (kPa) is deduced from the shear wave speed (Vs, in m/s) obtained using a time-of flight algorithm.

## A NEW SPLEEN STIFFNESS DEDICATED ALGORITHM

However, the technical characteristics of VCTE™ tailored for liver stiffness assessment are not adapted for spleen evaluation and required some specific adjustments. Table 1 provides the main technical characteristics of VCTE™ for liver and spleen measurements.

### Adapted range of stiffness values

First, as pointed out by several studies using FibroScan® for spleen stiffness assessment, the main limitation of the technique is the stiffness upper limit of 75.0 kPa, which is reached in many spleen stiffness examination and therefore undermines a good discrimination between grades of oesophageal varices. As a result, the examination of spleen using VCTE™ includes an adjusted stiffness range of values from 5.0 to 100.0 kPa.

### Adapted shear wave frequency

Second, as the shear wave wavelength is larger in stiff organs, the time of flight algorithm would overestimate [3] spleen stiffness. As a result, the acquisition parameters are adapted to reduce the shear wave wavelength. This was obtained by fixing the shear wave frequency at 100 Hz (with 1 mm amplitude peak to peak) for spleen evaluation.

### Adapted measurement depths

Third, in order to better target the organ, which is usually located 1 to 2 cm below the skin surface, with a depth of approximately 4 cm in non-obese healthy subjects, measurement depths also need to be adjusted accordingly, and were fixed between 25 and 55 mm.

Note that all these adjustments were possible by using the same FibroScan® M probe.

**TABLE 1** VCTE™ technical characteristics for liver and spleen stiffness measurement algorithm

| | Liver (VCTE™-50Hz) | Spleen (VCTE™-100Hz) |
|---|---|---|
| Shear Wave Frequency | 50 Hz | 100 Hz |
| Probe Model | M | M |
| Ultrasound center frequency | 3.5 MHz | 3.5 MHz |
| Measurement depths | 25 mm - 65 mm | 25 mm - 55 mm |
| Stiffness range | 1.5 kPa<br>75.0 kPa | 5.0 kPa<br>100.0 kPa |



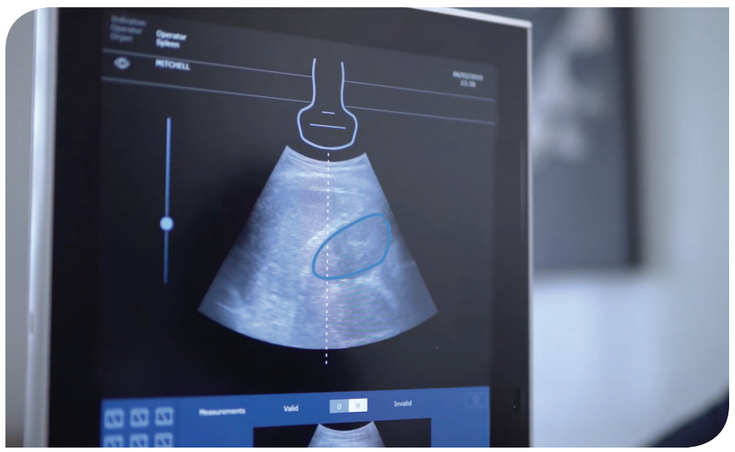
# Relevance of spleen stiffness evaluation

## SPLEEN STIFFNESS AND PORTAL HYPERTENSION

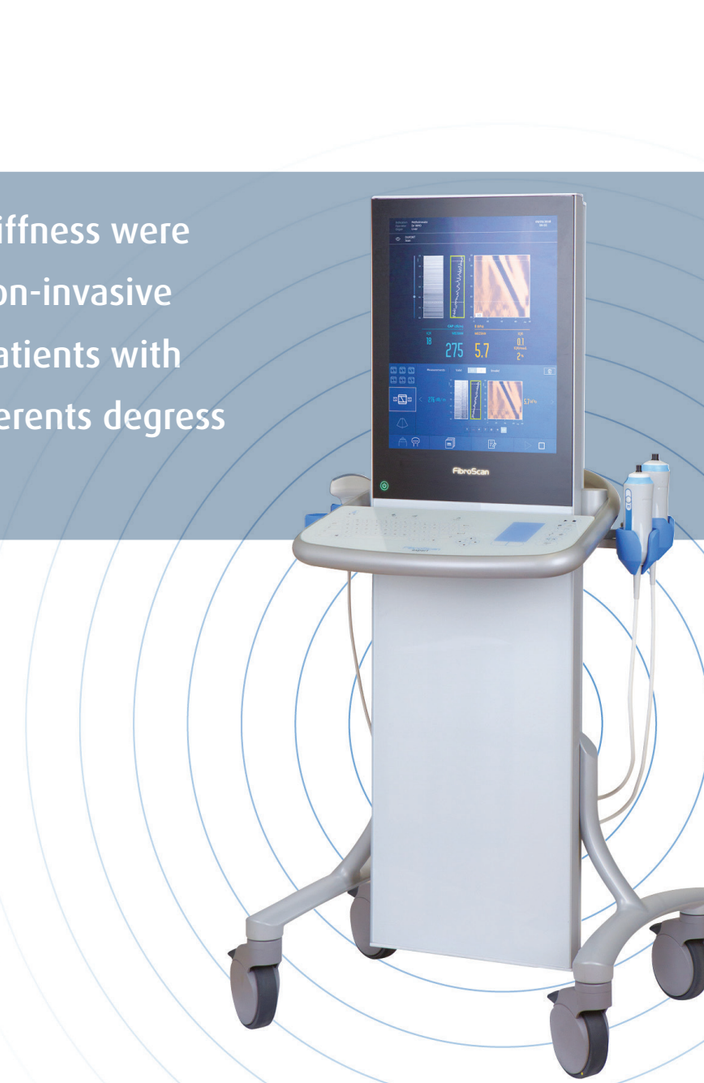
The pathophysiology of splenic involvement in liver cirrhosis is poorly understood, poorly investigated and poorly used for diagnostic purposes. Overall, is not clear whether spleen enlargement, so often detected in cirrhosis, plays a role in the pathogenesis of portal hypertension (PH). Work performed in the past decade, particularly in the area of non-invasive methods for the evaluation of disease progression in chronic liver diseases (CLD), has re-discovered the spleen as a relevant pathophysiological player in this clinical context.

The prevalence of splenomegaly in patients with liver cirrhosis and PH is 60-65% [2] and PH is the most common cause of splenomegaly in Western countries. Splenomegaly developing in patients with liver cirrhosis is commonly attributed to “congestion” as a consequence of portal hypertension. However, if splenomegaly were caused only by the congestion, a relationship between splenomegaly and portal pressure would be expected. On the contrary, no relationship has been reported between spleen size and portal pressure [5-7] or the degree of oesophageal varices [12]. Altogether these data highlight that PH is not the only determinant of splenomegaly in cirrhosis. Accordingly, histopathological studies have demonstrated a clear modification of the splenic architecture in cirrhosis with the presence of diffuse tissue fibrosis and neo-angiogenesis [8-10] often associated with the development of intra-splenic arterial aneurysms [10]. An increase in the white pulp volume has also been highlighted, with an increase in white pulp arterial bed and in peri-arterial lymphatic sheaths [9-12].

The increase in white pulp indicates a possible immunologic involvement in the genesis of splenomegaly. Therefore, splenomegaly in cirrhosis cannot be simply classified as congestive, but rather as congestive-hyperplastic. This interpretation is supported by the analysis of the changes in spleen size after liver transplantation where the dramatic decrease in outflow resistance of the splenic vein is followed by a slight decrease in spleen size likely secondary to the decrease in hemodynamic congestion. This observation tends to support the presence of structural changes occurring during the long clinical course of cirrhosis.




**Spleen stiffness and liver stiffness were more accurate than other non-invasive parameters in identifying patients with esophageal varices and differents degress of portal hypertension.**




Following the demonstration that the anatomical and haemodynamic changes occurring in the spleen could translate in changes in spleen tissue stiffness, the pioneer study by Colecchia and co-workers [13] measured spleen stiffness (SS) and liver stiffness (LS) by VCTE™ using the FibroScan® 502 device in 100 consecutive patients with hepatitis C virus–induced cirrhosis. The ability of both SS and LS to predict clinically significant PH and the presence of esophageal varices (EV) was compared to that of the previously proposed methods, i.e. the LS–spleen diameter to platelet ratio score (LSPS) and platelet count to spleen diameter [14-16].

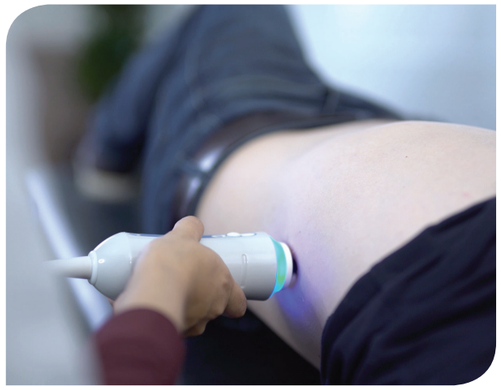
SS and LS were more accurate than other non-invasive parameters in identifying patients with EV and different degrees of PH. Importantly, this study demonstrated a strong direct correlation between SS and the whole range of HVPG values >5 mm Hg indicating that the increase in SS progresses closely with the progression of PH from the early to the late stages of cirrhosis. These results suggest that, in patients with cirrhosis, SS is possibly characterized by a wider range of application when compared with LS, likely because of a progressively higher relevance of extra-hepatic factors conditioning the increase of portal pressure [17].

Indeed, although LS is related to the increase in intra-hepatic vascular resistance consequent to tissue fibrosis, it cannot reflect the complex hemodynamic changes characteristic of late PH and particularly the so-called “hyperdynamic syndrome” and the opening of porto-systemic shunts. Colecchia and coworkers [18] also reported on the predictive value of SS for decompensation in a cohort of patients with HCV-related compensated cirrhosis followed-up for two years.

## CLINICAL VALIDATION OF THE NEW VCTE™ SPLEEN STIFFNESS ALGORITHM

Overall, these studies and later studies introduced SS as a possible non-invasive method for the prediction of clinically significant/severe PH and the presence of EV in patients with compensated cirrhosis. However, as stated earlier, the data obtained were limited by the upper limit of detection (i.e. 75.0 kPa) of the FibroScan® device calibrated for the assessment of LS (50 Hz), with a significant proportion of cirrhotic patients presenting SS values abundantly over this detection limit, and also with an overestimation of the stiffness measured when using the 50 Hz fixed shear wave frequency adapted to liver [1]. Applicability is also limited since a significant proportion of examinations were either unsuccessful or unreliable, [19] likely due to non-adapted measurement depth.

Recently Bastard et al. [3] reported the results of a FibroScan® "Spleen Stiffness" European multicenter study conducted on 196 patients which was specifically designed to evaluate the novel VCTE™ spleen stiffness acquisition parameters (SSM-100Hz) for the measurement of SS and evaluate its ability to detect high risk EV (HREV) in comparison with the standard examination (SSM-50 Hz).



Results reveal that this novel spleen dedicated VCTE™ examination (SSM-100Hz) with FibroScan® device is significantly superior ($p<0.01$) to the standard FibroScan® (SSM-50Hz) to detect presence of large EV (grade≥2), with an AUC of 0.79 [0.71-0.86] vs 0.70 [0.62-0.79] (Table 2), with an optimal cut-off of 55.3 kPa. SS values obtained with SSM-100 Hz were also lower than those obtained with SSM-50 Hz, correcting the stiffness overestimations mentioned earlier.

TABLE 2 **Diagnostic performance of two FibroScan® spleen stiffness measurement algorithms to detect large EV (grades 2 and 3)**

| Parameter | SSM-50 Hz | SSM-100 Hz |
|---|---|---|
| AUROC [95% CI] | 0.70 [0.62-0.79] | 0.79 [0.71-0.86] |
| Optimal cut-off | 71.2 | 55.3 |
| Sensitivity (%) | 70.9 | 74.2 |
| Specificity (%) | 69.0 | 76.2 |
| PPV (%) | 39.7 | 45.1 |
| NPV (%) | 89.2 | 91.8 |
| Diagnostic accuracy (%) | 70.5 | 74.6 |

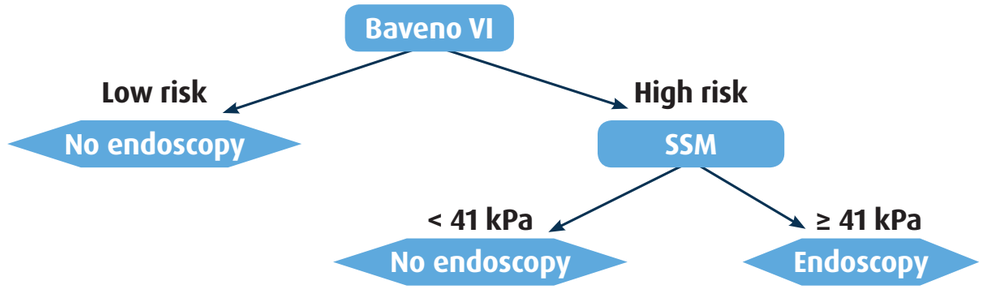
On the same set of data, Stefanescu et al. [20] reported an excellent applicability rate of the new spleen stiffness examination SSM-100 Hz (88%), as well as its non-inferiority versus HVPG for detection of large oesophageal varices (see Table 2).

TABLE 3 **Diagnostic performances of SSM-100 Hz by FibroScan®, versus HVPG, for detection of large EVs with grades ≥2 (n=88)**

| | SSM-100 Hz | HVPG | P value |
|---|---|---|---|
| AUROC [95% CI] | 0.83 [0.74 - 0.92] | 0.78 [0.67 - 0.92] | Difference: 0.623 |
| | | | Non inferiority: 0.028 |

Finally, when evaluating the utility of SSM-100 Hz to identify patients with low risk for HRV for whom EGD can be safely avoided, it was demonstrated that a combination of SSM-100 Hz with an optimal cut-off of 41 kPa, used in adjunction with the Baveno VI criteria, spared further 22% of unneeded EGDs, leading to an EGD spared rate of 32%, while maintaining a low missed HRV rate at 0%. Based on these encouraging results, authors suggested a new sequential algorithm detailed in Figure 1. Application of such algorithm would restrict the use of the SSM-100 Hz examination only to patients with high risk of HRV.

FIGURE 1 **Proposed algorithm to reduce the need for endoscopies based on the combination of Baveno VI criteria used in adjunction with spleen stiffness measurement**




## CONCLUSION

The novel FibroScan® VCTE™ spleen stiffness examination presents a high applicability rate. It is also a more accurate to detect high risk varices when compared to liver or spleen stiffness measurements performed with a standard FibroScan®. Spleen stiffness, when combined with the current BAVENO VI clinical criteria based on liver stiffness and platelets, also allows to better detect patients with high risk EVs, potentially having some clinical and economical utility by allowing to spare a significant number of endoscopies.

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