Chapter

Noninvasive Assessment of Diffuse Liver Diseases Using Vibration-Controlled Transient Elastography (VCTE)

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Abstract

Because of the limitations and invasive nature of liver biopsy, other noninvasive means are being tested for the evaluation of diffuse liver diseases. One of these methods is vibration-controlled transient elastography (VCTE). This chapter reviews the principle of VCTE, the examination technique, the normal range for liver stiffness values, the pathological changes that may influence liver stiffness, as well as the diagnostic performance in several diffuse liver diseases, especially chronic hepatitis C, chronic hepatitis B, nonalcoholic steatohepatitis, and alcoholic liver disease. Apart from the assessment of fibrosis stages, we will also discuss the diagnosis of cirrhosis and its complications as well as other applications of VCTE, reviewing its advantages and limitations.

Keywords: diffuse liver disease, fibrosis, noninvasive, vibration-controlled transient elastography, Fibroscan

1. Introduction

Chronic liver diseases are an important public health issue. Extensive research has been made lately on the development of noninvasive diagnostic methods, able to accurately assess fibrosis and steatosis. Among these, an important place is reserved for elastographic techniques and especially vibration-controlled transient elastography (Fibroscan).

2. Principle

Vibration-controlled transient elastography is performed with the Fibroscan® equipment (Echosens, Paris) [1]. The transducer of the device is placed in an intercostal space above the right liver lobe, in a point of maximal hepatic dullness. A mechanical vibrator is mounted on the axis of the device; the vibrator generates a painless vibration, inducing a train of elastic waves, which propagate through the skin and subcutaneous tissue to the liver. In parallel to the vibration, the transducer performs ultrasound acquisitions, at a frequency of 4 kHz [1–3] By comparing the ultrasonographic signals thus obtained, tissue deformation records, induced by the propagation of the elastic wave, can be drawn. The time necessary for the train of waves to propagate along the interest

area, as well as the velocity of propagation, is recorded. The liver stiffness can afterwards be calculated using the formula: E = 3ρVs2 (E, the elasticity module; ρ, density; Vs, the elastic wave velocity in the liver parenchyma). The stiffer the tissue, the higher the velocity of the wave train [1–3].

On the other hand, knowing that fat impairs ultrasound propagation and induces attenuation, the producers of the Fibroscan equipment have developed a software able to precisely quantify the ultrasound attenuation. This controlled attenuation parameter (CAP) is expressed in dB/m and is calculated using the same radio-frequency data, and the same region of interest, as the region used to assess the liver stiffness [4, 5].

3. Examination technique

The patient is placed in a dorsal decubitus position, with the right arm in maximum abduction above the head, in order to best expose the right abdominal quadrant, perpendicularly to the intercostal space, in an area of maximal dullness, free of any large vascular structure [1, 3]. When pressing the transducer button, the vibration is generated and transmitted to the liver. The software of the equipment analyzes the tissue deformation records and measures the stiffness of the parenchyma. The results are expressed in kilopascals (kPa) and represent the median value of 10 valid measurements. The equipment can measure values ranging between 2.5 and 75 kPa [1, 3]. At the same time, the software can measure both the liver stiffness (for the assessment of fibrosis) and the controlled attenuation parameter, CAP (for the assessment of steatosis).

It is important to choose the correct transducer for the examinations (S, M, or XL). The choice is made according to the circumference of the thorax: if below 75 cm, the S probe is chosen (either S1 < 45 cm or S2 for 45–75 cm and the M probe for a thoracic circumference above 75 cm). The XL transducer will be chosen if the distance between the skin and the liver capsule exceeds 25 mm. It is worth mentioning that, when measured with the XL probe, the median liver stiffness is significantly lower than that measured with the M probe [6].

The examination should be performed after an overnight fast, or at least 2 hours after a meal, because a postprandial examination would raise the stiffness value due to increased hepatic blood flow [7, 8]. In addition, the patient should remain at rest for 10 minutes before the examination [9] and hold his or her breath during the examination [10].

A proper measurement can be performed even by a technician after a training period (approximately 100 cases) [6, 10], but the clinical interpretation of results must always be issued by an expert taking into account the demographic data, disease etiology, and biochemical profile at the moment of the examination [3, 11].

Following the manufacturer's recommendation, the assessment is reliable only when 10 valid readings and an IQR ≤ 30% of the median (IQR/M ≤ 30%) are obtained [9].

4. Normal range of liver stiffness

The mean value of liver stiffness in healthy subjects, without any known liver disease and with normal biochemistry and hematology tests, is 5.5 ± 1.6 kPa according to some authors [12] and 4.8 ± 1.3 kPa according to others [13]. Age does not appear to influence this value, but stiffness is higher in men than in women (5.8 ± 1.6 kPa vs. 5.2 ± 1.6 kPa) as well as in subjects with a BMI > 30 kg/m^2

(6.3 ± 1.9 kPa vs. 5.4 ± 1.5 kPa) [14]. It is very difficult to establish the normal range of liver stiffness without biopsy, but the reverse is not feasible. In a group of HCV patients, without pathological changes on the biopsy sample, the liver stiffness was 4.84 ± 1.49 kPa [15]. In our unit, values of or above 5.3 kPa have a positive predictive value of 90% for the prediction of a fibrosis stage of at least F1.

5. Pathological changes influencing liver stiffness

Although liver stiffness correlates very well with fibrosis, just a single physical parameter (stiffness) cannot be used to completely describe a complex biological system, in which fibrosis is just a part [2]. Liver stiffness is increased by hepatic inflammation (often but not exclusively revealed by an elevated transaminase level) [16–18], obstructive cholestasis [19], hepatic congestion [20], amyloidosis, lymphomas, and extramedullary hematopoiesis [9]. These error factors must be taken into consideration when interpreting the liver stiffness values.

Necroinflammatory activity leads to an increase in liver stiffness alongside the degree of histologic activity [21–23]. For instance, the tissue changes occurring during an acute hepatitis can associate a rise in liver stiffness reaching sometimes cirrhotic values, due to cellular intumescence and sometimes to severe cholestasis [24]. The contribution of these non-fibrotic alterations on stiffness has been demonstrated by recording the progressive decrease in stiffness alongside the decrease in transaminase levels [17, 18]. On the other hand, in patients with relapsed chronic hepatitis, the higher stiffness values are caused not only by pre-existing fibrosis but also to the superimposed cellular intumescence [16]. Therefore, caution is advised when interpreting the liver stiffness values in patients with increased ALT: if the ALT values exceed a 2.5-fold increase, there is a risk of overestimating the fibrosis stage which should be specified in the written report [15].

Extrahepatic cholestasis can increase the stiffness independently from fibrosis [19], and after biliary drainage, the liver stiffness values decrease at a mean rate of 1.2 ± 0.56 kPa for every 1 g/dL decrease in bilirubin levels. It would therefore be prudent to exclude a possible cholestasis through imaging and lab tests before interpreting liver stiffness values in order to avoid overestimating the fibrosis stage.

Congestive heart failure may lead to increased liver stiffness reaching even cirrhotic levels, due to a higher liver blood volume, in up to 60% of patients [25–27].

Liver steatosis influence on liver stiffness values remains controversial. In some studies, steatosis did not significantly affect stiffness values, even after adjusting for fibrosis stage, but the proportion of patients with severe steatosis was too low to allow accurate quantification of a potential influence [1, 21, 28]. Other studies, however, have proven that, for the same fibrosis stage and the same necroinflammation grade, the presence of steatosis leads to a significant increase in liver stiffness [29]; furthermore, the morphometric analysis of biopsy samples has proven that steatosis does change liver stiffness independently from fibrosis. This influence is negligible in cirrhotic patients, but significant in non-cirrhotic patients. Further studies are however required to clarify this issue [28].

6. Diagnostic performance of VCTE

6.1 Chronic hepatitis C (CHC)

The first patients to have benefited from vibration-controlled transient elastography were those diagnosed with chronic C viral hepatitis (HCV). Studies performed

on large groups of HCV patients indicate that the liver stiffness values are strongly correlated with fibrosis stage, but there is some degree of overlap between adjacent stages. The practical utility of the method is based on establishing certain threshold stiffness values for each fibrosis stage. The diagnosis of stages F ≥ 2, F ≥ 3, and cirrhosis is based on the following stiffness values: 5.2–9.5 kPa, 9.5–9.6 kPa, and 11–15 kPa, respectively, as proposed by certain studies [15, 21, 30–34]. As suggested by studies assessing other noninvasive methods [35], the difference between these values can be explained by the varying prevalence of each fibrosis stage in the analyzed groups as well as by the different aims of the investigation (screening strategy vs. exclusion strategy). Therefore, although the already-defined cutoffs may be relevant to a certain population, they may not be applicable in another population with different prevalence of fibrosis stage and with another diagnostic aim for performing VCTE. In any case, according to the EFSUMB guidelines, "TE can be used as the first-line assessment for the severity of liver fibrosis in patients with chronic viral hepatitis C. It performs best with regard to the ruling out of cirrhosis" [9].

6.2 Chronic hepatitis B (CHB)

In patients with CHB, VCTE has a similar performance as in CHC patients [9]. For this type of patients, Marcellin and collaborators [36], considering the METAVIR scoring system, have suggested as early as 2009 the 7.2 kPa stiffness value as the cutoff for the prediction of F ≥ 2 (Se 70%, Sp 83%, PPV 80%, NPV 73%, AUROC 0.81), 8.1 kPa for F ≥ 3 (Se 86%, Sp 85%, PPV 65%, NPV 95%, AUROC 0.93), and 11 kPa for the prediction of cirrhosis (Se 93%, Sp 87%, PPV 38%, NPV 99%, AUROC 0.93).

Other articles [37–42] have confirmed the performance of the method, yielding AUROC values raging between 0.80 and 0.90 (for the prediction of significant fibrosis) and liver stiffness cutoffs varying between 6.6 and 8.8 kPa [9, 43–47]. With regard to the prediction of cirrhosis, AUROCs vary between 0.81 and 0.97 and the cutoffs between 9.4 and 13.4 kPa [44, 45]. The meta-analyses have suggested that a liver stiffness above 11.7 kPa should raise the suspicion of cirrhosis in patients with CHB [9, 45].

Generally, the cutoff value used for the cirrhosis prediction is lower in CHB than in CHC patients. One explanation could be the fact that HBV infection is one of the causes of macronodular cirrhosis, so that the predominant macronodular regeneration and the fine fibrous septa surrounding the nodules mean a smaller quantity of fibrosis than in micronodular cirrhosis with thick fibrous septa. It follows that, generally, liver stiffness is lower in macronodular than in micronodular cirrhosis.

On the other hand, liver stiffness values below 5 kPa in patients with normal ALT and low serum HBV DNA levels (<2000 IU/ml) are characteristic for inactive HBV carriers [9, 48, 49]. VCTE can be used to rule out significant fibrosis and cirrhosis in HBV inactive carriers, which is the best indication for VCTE in HBV.

According to the EFSUMB guidelines, "TE is useful in patients with CHB to identify those with cirrhosis, but concomitant assessment of transaminases is required to exclude flare-ups (elevation > 5 times upper limit of normal)". In addition, TE is useful in inactive HBV carriers to rule out fibrosis, in case the liver stiffness is below 5 kPa [9].

6.3 Nonalcoholic steatohepatitis (NASH)

In NASH patients, the correlation between stiffness and fibrosis is weaker than in patients with chronic viral hepatitis, because of a different fibrosis distribution

pattern (in chronic viral hepatitis, fibrosis appears early in the periportal areas and gives rise to a dense, stellate, and regularly distributed portal fibrosis; in steatohepatitis, however, the fibrosis is located in the perisinusoidal space of the centrilobular area and in the walls of the centrilobular vein) [28, 50]. There is a direct proportion between the amount of dense, stellate portal fibrosis and liver stiffness, whereas perisinusoidal fibrosis distributed preferentially in the centrilobular areas does not proportionally increase the liver stiffness values, as was proven by morphometric studies [28].

A meta-analysis including 854 NASH patients examined with the M probe [51] has proven the very good performance of VCTE in diagnosing stages F ≥ 3 (Se 82%, Sp 82%) and F4 (Se 92%, Sp 92%) and its moderate performance in diagnosing significant fibrosis F ≥ 2 (Se 79%, Sp 75%). The cutoff yielded by various studies varies between 6.6 and 7.7 kPa (for F ≥ 2), 8–10.4 kPa (for F ≥ 3), and 10.3–17.5 kPa (for the prediction of cirrhosis) [50, 52–57].

The available data indicate that, in patients with NAFLD, VCTE is a highly accurate, noninvasive method for the exclusion of advanced fibrosis and a moderately accurate method for the exclusion of significant fibrosis. According to the EFSUMB and EASL Guidelines and Recommendations on the clinical use of liver ultrasound elastography, "TE can be used in NAFLD patients to confidently exclude severe fibrosis and especially cirrhosis," with a high negative predictive value (around 90%) [9, 34].

6.4 Alcoholic liver disease (ALD)

There is no consensus regarding the optimal cutoffs for the prediction of fibrosis stages in ALD patients [9, 58]. In various studies, the cutoffs range between 7.8 and 9.6 kPa for significant fibrosis, 8.0–17.0 kPa for severe fibrosis, and 7.15–34.9 kPa for cirrhosis prediction; the explanation for this variation lies in the difference in prevalence of fibrosis stages in the analyzed groups, as well as in the different patient selection methods (with or without exclusion of acute alcoholic hepatitis or of patients with decompensated disease) [59–62].

In a meta-analysis by Pavlov, the cutoffs used for the prediction of fibrosis stages were the following: 5.9 kPa for ≥F1 (Se 83%, Sp 86%, PPV 97.6%, NPV 35.3%, and AUROC 0.84), 7.5 kPa for ≥F2 (Se 94%, Sp 89%, positive likelihood ratio 8.2, negative likelihood ratio 0.07), and 9.5 kPa for ≥F3 (Se 92%, Sp 68%, positive likelihood ratio 2.9, negative likelihood ratio 0.11) [63]. For the prediction of cirrhosis, the proposed 12.5 kPa cutoff had a 95% sensitivity and 71% specificity, a 3.3 positive likelihood ratio, and a 0.07 negative likelihood ratio [63].

The proposed cutoff values for the different stages of hepatic fibrosis may be used in clinical practice, but with caution, since those reported values were simply the most common cutoff values used by the study authors and are insufficiently validated while, additionally, there is always the risk of overestimation of LS values in patients who are not abstinent from alcohol consumption.

It is also important to consider the AST levels when using VCTE to assess fibrosis in ALD patients. For AST levels above 100 U/L, the liver stiffness may increase independently from fibrosis, as a result of steatohepatitis, leading to interpretation errors [59]. On the other hand, liver stiffness decreased significantly after alcohol cessation over a long period of follow-up. It follows that liver stiffness measurements in alcoholic liver disease should be interpreted with caution and assessed in regard to the current alcohol consumption. Large-scale prospective studies should be performed to determine the different optimal cutoff values according to alcohol consumption, and more data are required to determine the best delay after alcohol cessation prior to VCTE evaluation.

VCTE is more suited to rule out than to rule in cirrhosis. At a Young's modulus of 12.5 kPa, VCTE may rule out cirrhosis with a negative likelihood ratio of 0.07 if the disease prevalence is 50% or lower.

In conclusion, according to the EFSUMB guidelines, "TE can be used to exclude cirrhosis in patients with alcoholic liver disease, provided that acute alcoholic hepatitis is not present" [9]. The current alcohol drinking status is also relevant.

6.5 Other chronic liver diseases

The performance of VCTE in identifying significant fibrosis was also assessed in other chronic liver diseases, such as HCV-HIV coinfection [64, 65], post liver transplantation status [66–69], cholestatic liver diseases (primitive biliary cirrhosis or primary sclerosing cholangitis) [70], and hemochromatosis [71]: the results yielded AUROC values between 0.74 and 0.93 for the prediction of significant fibrosis, at cutoffs ranging between 4 and 10.1 kPa.

6.6 The diagnosis of cirrhosis and its complications

One of the most important applications of VCTE is the noninvasive diagnosis of liver cirrhosis. The diagnostic accuracy of VCTE is far better in the prediction of cirrhosis than that of other stages of fibrosis, with areas under the ROC curve (AUROCs) ranging between 0.90 and 0.99 at cutoffs between 9 and 26.6 kPa. In a meta-analysis performed by Friedrich-Rust [72], the mean AUROC for the diagnosis of cirrhosis was 0.94, and the optimal cutoff for cirrhosis prediction proved to be 13.01 kPa. In Stebbing's meta-analysis [73], the 15.08 kPa cutoff had 84.45% sensitivity and 94.69% specificity for the prediction of cirrhosis. Tsochatzis [74] assessed the diagnostic accuracy of VCTE in the prediction of cirrhosis in a meta-analysis of 30 studies, which yielded a LS optimal cutoff of 15 ± 4.1 kPa (median, 14.5 kPa, ranging between 9 and 26.5 kPa in the various studies analyzed), with 83% sensitivity and 89% specificity. It is however important to keep in mind that the cutoffs proposed by the various studies were chosen based on the AUROCs providing the maximal sum between sensitivity and specificity. As was suggested in certain studies performed for the assessment of other noninvasive methods, the difference between these values can, however, be explained by the difference in prevalence of cirrhosis in the analyzed groups [35].

On the other hand, interpreting the LS value as compatible with the diagnosis of cirrhosis can only be made after excluding some other conditions: significant cytolysis, significant cholestasis, right heart failure, or performing the examination after a meal. Nevertheless, even if the liver stiffness values are not typical for cirrhosis, cirrhosis may however be present in 3% of cases. This is the case of macronodular cirrhosis (more frequent in HBV infection, but also in other liver diseases) where the nodules are surrounded by fine fibrous septa, which do not increase the liver stiffness to "cirrhotic" levels.

6.6.1 Portal hypertension screening

Various studies have reported on the correlation between the LS value and portal hypertension (PHT), identified either through the presence of esophageal varices (EV) during upper digestive endoscopy [75–77] or by measuring the hepatic venous pressure gradient (HVPG), considered the gold standard in the assessment of portal hypertension [66, 77–79].

Despite an excellent correlation at HVPG values below 10 or 12 mm Hg, the comparison did not yield valuable results at HVPG values > 10 mm Hg (which is

the HVPG threshold for the prediction of varices) or > 12 mm Hg (threshold for the prediction of other complications, such as variceal effraction or ascites).

When analyzing the relationship between liver stiffness and the presence of esophageal varices, the area under the ROC curve for the prediction of varices varied between 0.74 and 0.85. When using the 13.9 kPa, 17.6 kPa, and 21.3 kPa cutoff values, the authors found high sensitivity for the prediction of varices (95%, 90%, and 79%, respectively) but relatively low specificity (43, 43, and 70%, respectively) [3, 75–77].

Some authors claim that there is a correlation between liver stiffness values and variceal size [75, 76, 78], while others could find no proof of this correlation [77]. For the prediction of grade 2 and 3 varices, TE had a high sensitivity (91% and 76%) at the 19 kPa and 30.5 kPa cutoffs, respectively, but with low specificity (60% and 80%, respectively) and positive predictive value (48% and 54%, respectively) [75, 76].

According to the Baveno VI criteria [80], in patients with compensated chronic liver diseases of viral etiology, the noninvasive methods may predict the clinically significant portal hypertension, identifying the proportion of patients at risk of having endoscopic markers of PHT. For that purpose, liver stiffness measurements above 20–25 kPa can be used alone or in combination with platelet levels and spleen size. Liver stiffness below 20 kPa and platelet levels above 150,000 indicate a very low risk of esophageal varices requiring treatment, and therefore endoscopic screening can be avoided. These patients must be followed-up annually (VCTE and platelet levels), and an endoscopy must be performed in case of increasing stiffness or decreasing platelets.

The assessment of spleen stiffness has emerged as a new technique in hepatology, which may provide useful information on the presence and degree of portal hypertension and the prediction of its complications.

6.6.2 Prognostic significance of LS in patients with liver cirrhosis

Some studies suggested that VCTE could be used as a risk marker for the development of a hepatocarcinoma in patients with hepatitis C [81, 82], who have a fivefold increase in risk at liver stiffness values above 25 kPa. On the other hand, in our experience, in patients with hepatitis C-related cirrhosis, a liver stiffness value > 38 kPa and an IQR > 30% of the median value (after previous exclusion of gross technical errors) are important markers which suggest the need for further imaging investigations in search of a possible hepatocarcinoma (HCC) [83]. Some authors have found that an increase in LS of more than 1 kPa at 3 years is correlated with a worse prognosis and with an increase in mortality rate in the next 2 years; for every 1 kPa increase over the median LS found in any given patient, the relative risk for a severe clinical event in that particular patient increases: 1.07 for hepatic decompensation, 1.11 for HCC, and 1.22 for death [84]. Nevertheless, these results require confirmation through prospective studies performed on large groups of patients, in order to confirm whether liver stiffness can indeed predict complications in decompensated cirrhosis [11]. In case it does, elastography may serve as a method of fast noninvasive screening, in order to classify each patient in a risk category [85].

6.7 Other applications of VCTE

The assessment of liver stiffness using VCTE is useful in the monitoring of adverse effects of hepatotoxic medication [86] as well as that of the effect of

antiviral therapy. Of course, in the latter situation, it is difficult to establish with certainty to what extent the decrease in liver stiffness is caused by a regression in fibrosis, a stabilization of necroinflammation, or both: however, a decrease in LS values in parallel with antiviral treatment exhibited favorable short- and long-term outcomes in patients with chronic viral hepatitis.

7. Advantages of VCTE

The technique is easy to use, painless, noninvasive and does not require hospitalization. It can measure at the same time liver stiffness (for the prediction of fibrosis) and the controlled attenuation parameter (CAP) for the prediction of steatosis, in a volume 100 times larger than that examined during a liver biopsy.

8. Limitations of VCTE

Liver fibrosis cannot be evaluated by VCTE in 5–8% of the cases [3], especially in the case of obesity, ascites, or narrow intercostal spaces. In the case of obesity, using the XL probe helps to lower the measurement failure. The measurement failure is significantly less frequent when using the XL probe than the standard M probe [54]. The XL probe can still yield unreliable results, but only in 25%, as opposed to 50% of cases with the M probe [87]. The main limiting factors for the XL probe are a skin-to-liver capsule distance > 3.4 cm and extreme obesity (BMI > 40 kg/m^2) [54].

9. Conclusions

In conclusion, vibration-controlled transient elastography (VCTE) is a useful method in the assessment and monitoring of diffuse liver diseases. It is important to perform the technique correctly and to interpret the results considering the clinical context, disease etiology, and laboratory results.

Conflict of interest

Nothing to declare.

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