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# Myths and mysteries about staging hepatic fibrosis by Fibroscan

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The staging of hepatic fibrosis is a cornerstone of prognosis and assessment of disease progression in those with chronic liver diseases including nonalcoholic steatohepatitis (NASH). This is so because a histological assessment of fibrosis has been the only clinically applicable readout of such progression over the last century. The last ten years have, however, seen numerous changes that have challenged classical paradigms and are creating new norms for the evaluation of progression and regression of chronic liver diseases.

Much of the impetus for the development of newer ways to assess disease progression comes from the inadequacies of liver biopsies as the gold standard for evaluating hepatic fibrosis.[1] Liver biopsies often yield a core of 1–2 mm diameter and a length varying 1 to 2 cm.[2] While there has been tacit acceptance that this reflects what is happening in the entire liver, it is now well established that there is substantial sampling variability associated with biopsies in routine settings.[2] Specifically, in those with NASH, it has been shown that two biopsies performed at the same location can be associated with a one-stage variability in fibrosis in 36%, and a two-stage variation is assessment of fibrosis in 35%.[3] Also, the biopsy length is a critical determinant of the risk of under- or over-assessment of hepatic fibrosis with cores less than 1 cm length often providing uninterpretable information.[2, 3] On the other hand, when the core approaches 4 cm length and an asymptote in error rates is reached, there remains substantial baseline variability in fibrosis assessment.[4] Liver biopsies are also uncomfortable and occasionally accompanied by severe morbidity and rare mortality. These have hindered widespread use of this technique for evaluation of abnormal liver enzymes in the general population. With the growing epidemic of NASH which is estimated to affect 3–5% of the general population,[5] there is also a lack of trained workforce that can perform and evaluate biopsies even when they are done.

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From a clinician's perspective, the key question is whether a given patient is progressing towards cirrhosis and how close they are to having a liver related adverse event. Answering the question drives management of the patient to prevent complications of advanced liver disease. Vibration-controlled transient elastography (VCTE) by Fibroscan is one such promising technology that has been available for use over the last decade.[6] It was, however, only recently approved by the regulatory authorities for use through a 510(k) clearance by the U.S. Food and Drug Administration (FDA). In order to overcome the learning curve effect, the FDA-manufacturer agreement requires that an operator undergo course training and perform a minimum of 10 cases under supervision of a proctor before being able to use the device independently. The Fibroscan device works on the simple concept of transmitting a vibration of mild amplitude at low frequency to induce an elastic shear wave and measure the speed of propagation using a pulse-echo ultrasonic acquisition.[6] In simple terms, the velocity of the wave propagation directly relates to the tissue stiffness. The device also acquires information from approximately 100 times more sample tissue than a liver biopsy, potentially minimizing the risk of sampling error.[6] It is also rapid, noninvasive, and can easily be performed at bedside. The availability of the results for immediate discussion with the patient during the visit is very convenient and offers an opportunity for the patient to be involved in the decision process.

Liver stiffness measurement (LSM) by VCTE using Fibroscan serves as a surrogate for degree of fibrosis.[6] It is generally considered to be reproducible,[7] and several cross-sectional studies have reported good correlation with underlying liver fibrosis with disease-specific cut-offs.[8–11] A recent study not only showed good correlation with severity of primary sclerosing cholangitis at baseline but also showed that the incremental change in the LSM ($\Delta LSM/\partial t$) was predictive of disease progression and clinical outcomes.[10] Serial measurements of LSM may thus become an integral part of management of chronic liver disease, both for assessment of severity and monitoring of response. It is in this context that the current study by Nascimbeni et al. finds critical relevance.[12] In this retrospective analysis of an existing database of VCTEs performed using Fibroscan at the investigator's institution over several years, the authors examined the short-term variability (>1 day and <1 year) in LSM in 531 pairs of LSMs obtained in 432 untreated, clinically stable, immunocompetent patients with various chronic liver diseases. The two measurements i.e., first LSM (LSM1) and second LSM (LSM2) were not statistically significantly different to raise concern about the variability in the LSM measurement not related to disease progression. Although reassuring at the study population level, a variability of >20% was seen in almost half, >30% in one-third and >50% in up to 12% in the paired measurements. This variability was constant across the spectrum of LSM1 values. This variability resulted in fibrosis classification change by one stage in 30% and two or more stages in up to 10%. Predictors of variability were: two different operators, at least one non-senior operator, the interquartile range/median ratio, first LSM (LSM1) showing ≥7 kPa, baseline BMI, and doubling of LAT between paired measurements. The authors conclude that monitoring of fibrosis by VCTE using Fibroscan could be altered by clinically significant variability unrelated to the natural course of the disease and associated with operator and patient-related factors. The lowest variability was seen in patients with no/early fibrosis and when VCTE was performed by a single experienced operator.

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There could be several potential causes of the reported intra-individual variability in the VCTE results reported in this study.[12] There is both intra- and inter-reporter variability in the assessment of fibrosis.[12] This may be due in part to varying periods of fasting prior to the studies, variability in positioning both the subject and the probe. Also, in the context of NASH, the impact of changing hepatic fat content on the fibrosis readout by VCTE is not well characterized and may have contributed to the observed variability. There are also other conditions that can affect the VCTE results including hepatic congestion due to heart disease, infiltrative disorders etc.[13] An in depth review of these factors was recently published.[14] Finally, the study was performed only with the medium probe in a variety of liver disorders and no disease-specific cut-offs were implemented in staging of the fibrosis.

These factors highlight the need to develop standardized protocols for performance of VCTE and the reporting of metrics associated with the quality of the study procedure.[14] Normally, VCTE should be performed with the patient in a fasting condition for two hours before the procedure, lying in supine position with normal breathing, with right arm in maximum abduction to allow optimal exposure of right lateral abdomen. It is also important to maximize the amount of liver tissue interrogated and to avoid the lower edge of the liver. It is possible that for those where multiple studies are anticipated, the location of where the probe was placed is noted in the report to help the next operator perform the study optimally. Furthermore, the median and interquartile range of results must be reported; every attempt should be made to keep the variance in VCTE measurements to a minimum and ideally under 10%.[14]

There is increasing use of VCTE in the everyday management of patients with chronic liver disease from varied etiology.[9, 15, 16] The variability reported in the current study should be of concern to clinicians who are using LSM to make decisions with meaningful impact.[12] The current study highlights the short term variability in LSM measurements but does not account for many of the variables related to 4Ts (Table 1). With this study, the assumption (myth) of reproducibility of VCTE has been challenged, bringing attention to the gaps in knowledge (mystery) that need to be resolved to establish the use of VCTE in clinical practice. Until such time, we recommend that a good clinical and medication history followed by an imaging study, hepatic panel, and etiology specific serologic work-up, be available to pursue a context-related interpretation of LSM (wand) and the selective use of liver biopsies to maximize their diagnostic yield in a manner that will guide management.

## Abbreviations

| | |
|---|---|
| **AST** | Aspartate aminotransferase |
| **LSM** | Liver Stiffness Measurement |
| **NAFLD** | Non-alcoholic fatty liver disease |
| **NASH** | Non-alcoholic steatohepatitis |
| **PSC** | Primary Sclerosing Cholangitis |
| **VCTE** | Vibration Controlled Transient Elastography |

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## Table 1

The 4Ts: List of variables that could affect the liver stiffness measurement or its interpretation when using vibration-controlled transient elastography.

| Technology | Technician/Technique | Tissue | Tablets/Tonics |
|---|---|---|---|
| Shear wave propagation | Operator experience | Probe to liver distance | Medication usage |
| TM mode | Variability[17] | -Ascites | -Beta Blockers[18] |
| A mode | -Intra-operator | -Adiposity | Etiology specific therapy |
| Algorithm | -Inter-operator | -Altered anatomy | Significant weight loss |
| Software | | Acute hepatitis[19] | -Bariatric surgery |
| Probe size[20] | | Cholestasis[21] | Excessive alcohol use[22] |
| -Medium | | Portal flow | |
| -Extra-large | | -Postprandial state[23] | |
| | | TIPSS | |
| | | Tumor | |
| | | Cysts | |
| | | Infiltrative liver disease | |
| | | Hemangioma[24] | |
| | | Congestive hepatopathy[13] | |
| | | ?Hepatic steatosis | |

TIPSS: Transjugular intrahepatic portosystemic shunt, HCV: Hepatitis C virus