Hepatology Snapshot:

Different techniques for ultrasound liver elastography

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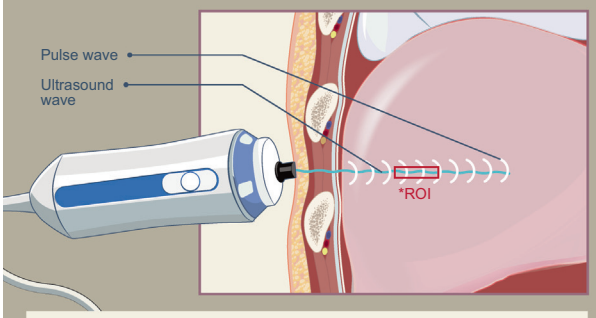
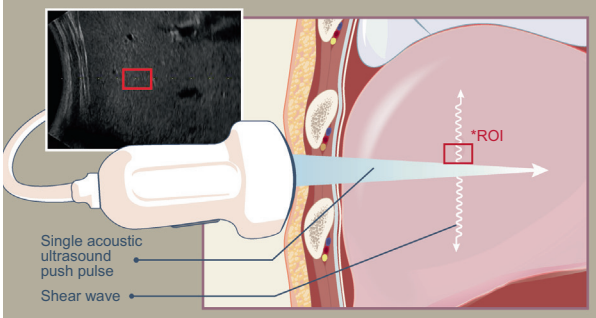
TRANSIENT ELASTOGRAPHY



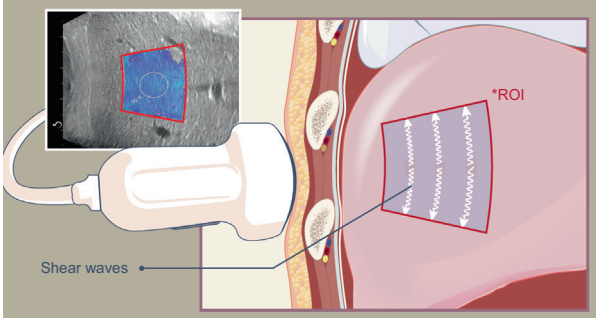
Compression push deformation (hemispherical waves) travels longitudinally through the liver.
Ultrasound measures (~~~~) its travelling speed.

pSWE



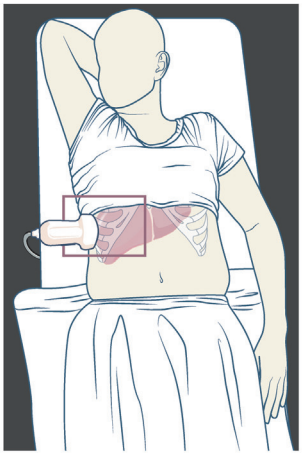
*Selected small (10x5 mm) region of interest (ROI).
ROI can be freely moved anywhere in the scanning plane up to 8 cm in depth to capture shear wave speed.

2D SWE



Geometrical box as ROI (1-4 cm) to measure tissue stiffness by assessing shear waves speeds generated by multiple stimulating ultrasound beams (specific method depending on the proprietary technology).

They can work as one time emitted push pulse or in real time based on the proprietary technology.

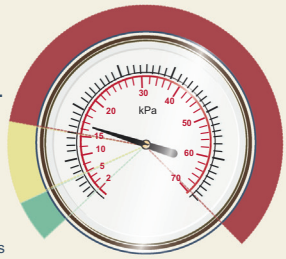


SWE MEASUREMENTS

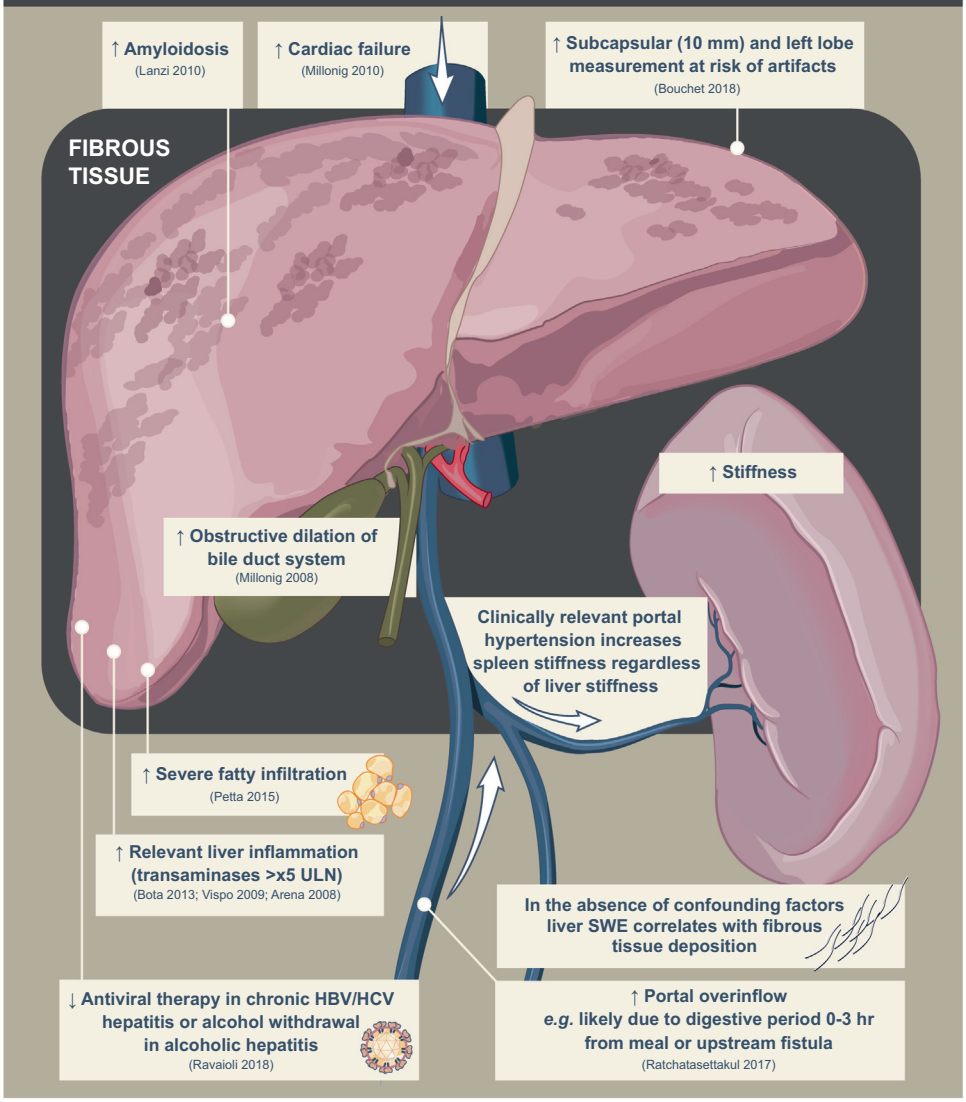
0-5 kPa no significant fibrosis
(regardless of the machine).

Range from 5-6 to 13-17 kPa includes thresholds to distinguish different fibrosis stages (F2-F3-F4).
Precise threshold depends on specific technologies/manufacturers and liver disease etiology.

>13-17 kPa suggests established cirrhosis, with progressive higher values associated to higher risk of more significant prognostic events. Please note that cirrhosis might already be present also at lower stiffness thresholds, depending on the specific machine model.



CONFOUNDING FACTORS IN THE ASSESSMENT OF LIVER FIBROSIS BY ELASTOGRAPHY (↑↓ INCREASE/DECREASE IN LIVER STIFFNESS)



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The advent of vibration controlled transient elastography (VCTE or simply TE) with Fibroscan in 2003 the first tool able to non-invasively quantify liver stiffness using ultrasound, thereby providing evidence of liver disease stage can be considered a milestone in hepatology given the limitations of biopsy in terms of sampling and invasiveness. Thresholds for the differentiation of no/mild fibrosis from significant fibrosis, or severe fibrosis or cirrhosis have been provided with TE on the basis of many original works using histology as the reference standard.[1,2] From 2009 onwards other new quantitative elastography technologies started to arrive on the market, this time embedded in conventional ultrasound (US) devices. At present almost all ultrasound manufacturers have developed their own liver stiffness quantification modality.[2] All share the capacity to assess tissue deformation and measure the speed of shearwaves travelling perpendicular to the axis of an applied force (consisting of ultrasound energy, unlike the Fibroscan which uses the push of a piston). These technologies are collectively called shearwave elastography (SWE), with the two main categories being point SWE (pSWE), which samples a tiny linear portion of tissue (few mm), and bidimensional SWE (2D-SWE), which samples large square areas 14cm^2. A more detailed illustration of the various technologies is reported in the EFSUMB guidelines[2] and is graphically summarized. Strain elastography is another technology that evaluates tissue stiffness and it is provided by the large majority of manufacturers, since before the advent of SWE. However, it does not provide quantitative measurements of stiffness and did not prove to be as effective as SWE for liver disease: consequently, it has no current role in hepatology.

SWE, which is easy to learn and perform has substantially empowered the working armamentarium of the modern hepatologist. It is sufficient to have a good view of the liver at ultrasound, push a button and read the liver stiffness value on the screen (valid measurements are in general obtained in 80%95% of patients, the rates depending on the patients characteristics, hardware of the machines and elastography technique). However, in order to properly use the stiffness value in the clinical practice a number of factors have to be kept in mind (the main ones are graphically illustrated and summarized in the figure). Theoretically, most of them are expected to stand true for all the different elastography techniques and must therefore be carefully considered, even though the risk of confounding has only been demonstrated in a few pieces of equipment so far (mainly because most techniques are too recent).

The main application of SWE in hepatology is the fibrosis staging of liver disease. The assessment of tissue stiffness for characterization of focal liver lesions or to verify the outcome of percutaneous ablation are among the hot topics of research, but such applications are not ready or validated yet. Hopefully, technological advancement like 3D (volumetric) or 4D-SWE,[3] made theoretically possible thanks to more powerful calculators, could further expand the number of clinical applications in the future. Importantly, machines from different manufacturers are based on proprietary technologies, resulting in different calibration and stiffness ranges among each other and in comparison to TE (traditionally held as reference technique).[4,5] This is of relevance for the fibrosis staging of liver disease. Any possible difference in stiffness values with different machines become more evident in patients with significant fibrosis. In particular, some machines show smaller increases in stiffness values than TE for increasing degree of liver fibrosis. Unfortunately the extent of divergence from TE is variable between different pieces of equipment.[47] Thus, specific thresholds to distinguish different fibrosis stages would be needed for each specific piece of equipment based on scientific studies; furthermore new technical releases should be tested *vs.* a reference standard (especially when a new hardware is adopted, for instance new device platforms or new transducers, even though from the same manufacturer).[8] This is a critical and challenging issue, since today it is almost impossible to run new studies with histology as a reference standard considering the drop in indications for biopsy,[7,8] making the validation of new technologies difficult, if not impossible. Accordingly, the majority of SWE machines which arrived on the market after around 2014 lack large enough scientific validation. Unfortunately, none can completely represent the heterogeneously diseased liver in a living body.

To date, the only general firm conclusion we can draw is that low levels of stiffness (on personal experience <5kPa) firmly indicate the absence of any significant fibrosis, irrespective of the machine, and are obtained with high interequipment reproducibility.[5] Conversely, thresholds for higher fibrosis stages are strictly related to each technology. Therefore, any elastography report should indicate the equipment and technology utilized, even in a short form (*e.g.* 2D-SWE-SSI or bidimensional SWE with Supersonic or pSWE-SIE for pSWE with Siemens, and so on).

If a report wants to suggest a fibrosis stage, then the pertinent specific reference literature is to be reported as the known thresholds of TE cannot be directly adopted for other machines.[6] Notably, different etiologies imply different structural changes of liver histology and this impacts on stiffness thresholds for defining liver stages. Hence studies focused on the specific etiology under investigation should be preferred, rather than mixed etiologies studies.

On practical grounds pSWE techniques tend to require a higher number of valid measurements to achieve an accurate median stiffness value (recommendation is 6 measurements or even more if reliability criteria are not fully met).[9,10] This is expected to be related to the fact that they sample a smaller portion of tissue and are therefore more prone to suffer the heterogenous involvement of the liver in case of significant fibrosis (since the sampled portion may fall in a regenerative nodule as well as in a large scar). On the other hand, bidimensional SWE, is often accurate after only 35 measurements, but may be more prone to subjective judgement in all those technologies in which the location of the Region of Interest (ROI) within the stiffness box is freely chosen by the operator. However, some of them offer a quality measurement to identify the most reliable regions for quantification.

In conclusion, SWE technologies are ready to be used in clinical practice, but require an adequate level of awareness of the appropriate measurement modalities and clinical meaning of the results based on the literature.

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Conflict of interest

Dr. Cantisani reports personal fees from Bracco, Samsung and Toshiba outside the submitted work. Dr. Piscaglia reports personal fees from Esaote, Bayer, Bracco, Meda Pharma and Eisai outside the submitted work. Dr. Mulazzani has nothing to disclose. GE, LaForce, Astrazeneca, Tiziana Life Sciences and Eisai outside the submitted work. Dr. Mulazzani has nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.012.

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