Ultrasound-based elastography: "hard" to implement in the pleural effusion work-up?

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Ultrasound elastography may have emerged as an adjunctive tool in combination with conventional ultrasound for pleural effusion differentiation http://bit.ly/303bYg0

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Thoracic ultrasound (TUS) has been incorporated as a routine bedside tool for the diagnosis of pleural diseases and the performance of safe pleural procedures [1]. It is generally accepted that TUS can provide valuable information on the possible malignant nature of a pleural effusion. Ultrasound appearances suggestive of malignancy include parietal or visceral pleural thickening of more than 1 cm, diaphragmatic thickness greater than 7 mm, pleural or diaphragmatic nodules and liver metastases, but the sonographic fluid characteristics themselves are nonspecific [2, 3]. These imaging criteria, also applicable to computed tomography [4], are highly specific and moderately sensitive when considered in combination. Accuracy data may be influenced by the overrepresentation of certain aetiologies, such as mesotheliomas (increases sensitivity) and tuberculosis (decreases specificity), in the study population. While conventional TUS reports morphological findings, ultrasound elastography provides stiffness information, which can also be potentially used for diagnostic purposes as the study by Jiang *et al.* [5] demonstrates in this issue of the *European Respiratory Journal*.

The Israeli engineer Jonathan Ophir, who died in 2017, invented ultrasound elastography during his time at the University of Texas Medical School [6]. Elastography allows noninvasive assessment of tissue elasticity, that is, the resistance to tissue deformation following an applied stress. The stress can be applied *via* compression stimuli or shear wave propagation. According to these mechanical excitation methods, current techniques are divided into strain elastography and shear wave elastography (SWE), respectively [7, 8]. In the former, the operator exerts external manual compression on the tissue using the transducer or a mechanical vibrating device. In the latter, a dynamic stress in the form of an acoustic radiation force impulse (ARFI) generates low amplitude shear waves that displace the tissue. In two-dimensional (2D) SWE, ARFI is used to displace the tissue at multiple points. As a general rule, a faster shear wave propagation is seen in stiffer tissue as compared with healthy tissue. 2D-SWE systems report "stiffness" values of a particular region of interest (ROI) as shear wave propagation speed (in $m \cdot s^{-1}$), the algebraically derived Young's modulus (in kPa), or both. The operator has a real-time visualisation of a colour coded quantitative elastogram superimposed on a B-mode image. In order to obtain accurate pleural stiffness values there are a set of mandatory rules: 1) the conventional (linear) transducer should be held in place with minimal pressure on the chest wall, and placed parallel to the intercostal window to avoid rib

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shadowing; 2) measurements should be performed during the holding of breath in the mid-respiratory phase, while avoiding breath suspension in deep inspiration; 3) optimal B-mode images are required; and 4) an imaging confidence map, used along with the stiffness map (elastogram), should display whether measurements are being obtained on tissue areas with adequate shear wave propagation (figure 1).

Thus far, SWE has been substantially explored in several organs, including the liver, breast, thyroid, lymph nodes and prostate, where it can be used to detect malignant tumours [9]. The pleura can now be added to the growing list of SWE applications, according to a few preliminary studies. In one investigation, the mean shear wave velocity of 20 malignant pleural-based lung lesions (3.50±0.69 $m \cdot s^{-1}$) was significantly higher than that of 13 benign subpleural consolidations (2.18±0.49 $m \cdot s^{-1}$) [10]. The same research group further explored the utility of SWE for differentiating transudative and exudative pleural effusions [11]. They found that the mean shear wave velocity of 43 exudates was 3.29±0.63 $m \cdot s^{-1}$, whereas that of 17 transudates was 2.29±0.41 $m \cdot s^{-1}$ ($p<0.001$). Using a cut-off value of 2.52 $m \cdot s^{-1}$, SWE identified pleural exudates with a sensitivity of 91% and a specificity of 76.5%. Measurements were performed within effusion areas, which is surprising because shear waves do not propagate in pure liquid environments and, thus, mapping of a fluid is usually null. In any case, the transudate–exudate differentiation does not represent a relevant clinical application of SWE, in contrast to the discrimination between malignant and benign pleural effusions. The study by JIANG *et al.* [5] addresses this latter point, for the first time. A total of 244 patients with pleural effusions, who were separated into development and validation sets, were explored through 2D-SWE applied to the parietal pleural surfaces. Mesothelioma cases represented 8.3% of 108 malignant effusions, while one-third of the benign fluids had a tuberculous origin. In the validation cohort, the finding of a pleural mean elasticity index greater than 47.25 kPa increased the pre-test probability of malignancy by nearly 50% (positive likelihood ratio=9), whereas lower values decreased it by around 30% (negative likelihood ratio =0.18). For instance, in a hypothetical patient with pleural effusion,

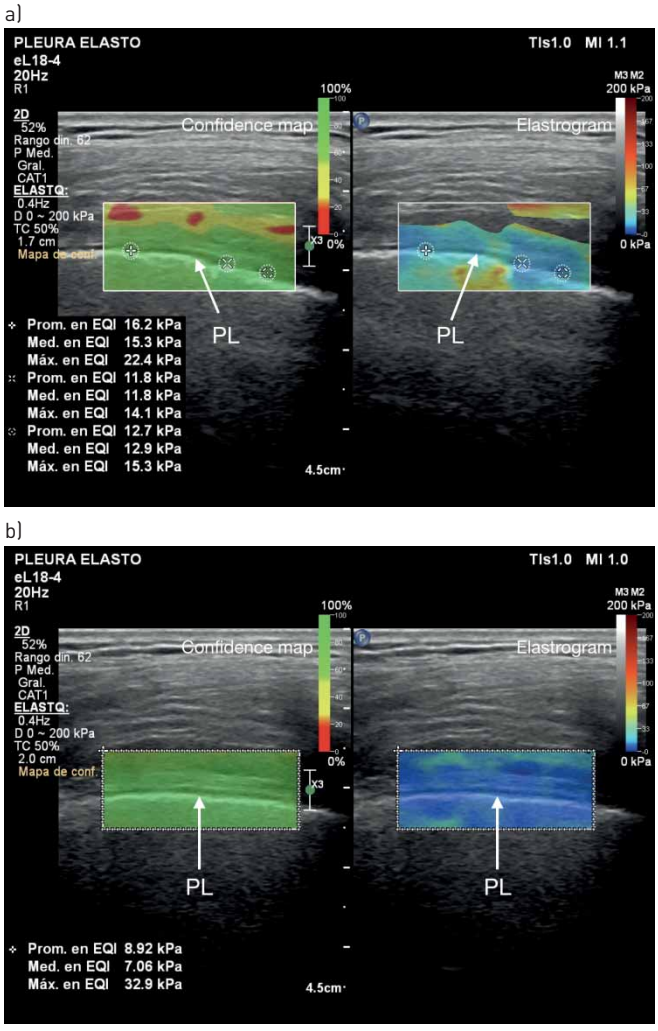

FIGURE 1 Pleural shear wave elastrography in a patient with a cardiac effusion. Stiffness values (kPa) can be obtained from a) specific regions of interest (circles) or b) selected areas (boxes). A confidence map (left hand panel in a and b) indicates trusted values (green colour), which are visually displayed according to a colour map or elastogram scale (right hand panel in a and b) and numerically quantified (bottom left in a and b). PL: pleural line.

the presence of an elasticity index above the preceding cut-off value would increase the probability of malignancy from 30% (*i.e.*, the pre-test calculation, based on the prevalence of the disease [12]) to 80%. Furthermore, the absence of TUS morphological features of malignancy shifted the probability very little (negative likelihood ratio=0.43). The results of this study were in favour of the use of pleural SWE, since it offers noninvasive complementary information to conventional TUS and only requires a few extra minutes. In truth, a negative SWE and TUS virtually ruled out malignancy.

Interpretation and generalisation of these results, however, should consider potential pitfalls and technical limitations. Although SWE is less operator dependent than strain elastography, it still has a moderately steep learning curve and should be performed by experienced personnel. System settings and parameters (*e.g.* type of transducer, gain, sampling rate and selection of the ROI) can introduce variability. Various commercial devices are available and, thus, technical variations make comparing or extrapolating measurements from one manufacturer to another a difficult task. In addition, a wide range of artefacts in 2D-SWE can alter the acquired information [13]. Finally and more importantly, elastographic methods are not available on most clinical ultrasound machines and their application on pleural membranes needs standardisation. This technology is still under development and additional mechanical properties of the medium other than stiffness, such as nonlinearity, anisotropy and viscoelasticity are being explored to improve the diagnosis and monitoring of patients who undergo therapeutic interventions. Currently, costs and limited availability represent a "hard" barrier for the spread of ultrasound-based elastography in pleural medicine clinics.

In conclusion, ultrasound elastography may have emerged as an adjunctive tool in combination with conventional TUS for pleural effusion differentiation. Although a promising technique, the research data are still too limited to establish its definitive role in the work-up of undiagnosed pleural effusions.

Conflict of interest: J.M. Porcel has nothing to disclose.

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