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Review Article

Novel ultrasound-based methods to assess liver disease: The game has just begun

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ABSTRACT

In the last 10 years the availability of ultrasound elastography allowed to diagnose and stage liver fibrosis in a non-invasive way and changed the clinical practice of hepatology. Newer ultrasound-based techniques to evaluate properties of the liver tissue other than fibrosis are emerging and will lead to a more complete characterization of the full spectrum of diffuse and focal liver disease. Since these methods are currently undergoing validation and go beyond elastography for liver tissue evaluation, they were not included in the recent guidelines regarding elastography issued by the European Federation of Societies in Ultrasound in Medicine and Biology.

In this review paper, we outline the major advances in the field of ultrasound for liver applications, with special emphasis on techniques that could soon be part of the future armamentarium of ultrasound specialists devoted to the assessment of liver disease. Specifically, we discuss current and future ultrasound assessment of steatosis, spleen stiffness for portal hypertension, and elastography for the evaluation of focal liver lesions; we also provide a short glimpse into the next generation of ultrasound diagnostic methods.

1. Introduction

The availability of ultrasound-based diagnostic methods to assess liver fibrosis changed the clinical practice of hepatology in the last 10 years, leading to a substantial reduction of liver biopsies performed to stage chronic liver disease. The field of non-invasive assessment of liver disease by ultrasound-based, real-time techniques is moving fast, and ultrasound elastography methods are getting more numerous and available in different ultrasound machines. As for the current available methods, besides transient elastography, which is implemented in the FibroScan device, all the elastographic methods implemented in ultrasound systems are based on the acoustic radiation force impulse technique (ARFI), i.e. the force of the ultrasound beam. The stiffness of tissue may be assessed at a single location, as in point shear wave elastography (pSWE), or in a larger area inside a sample box, as in 2D-SWE. Each manufacturer has developed a proprietary software for pSWE or 2D-SWE, however all of them rely on the ARFI technique. Normal values for the different techniques have been recently summarised [1] [Fig. 1], and quality parameters [2–4] have been proposed for many systems; however, clinical users knowledge of the advantages and disadvantages of the different techniques is often still incomplete. In addition, newer ultrasound-based techniques and indications are emerging. These methods go beyond liver elastography, and aim at evaluating other properties of the liver tissue, and to achieve a better characterization of the full spectrum of severity of liver disease. Some of these technqiues or parameters are currently undergoing extensive validation. Despite some of them are close to being routinely used in clinical practice, they were considered too preliminary to be included in recent guidelines, such as

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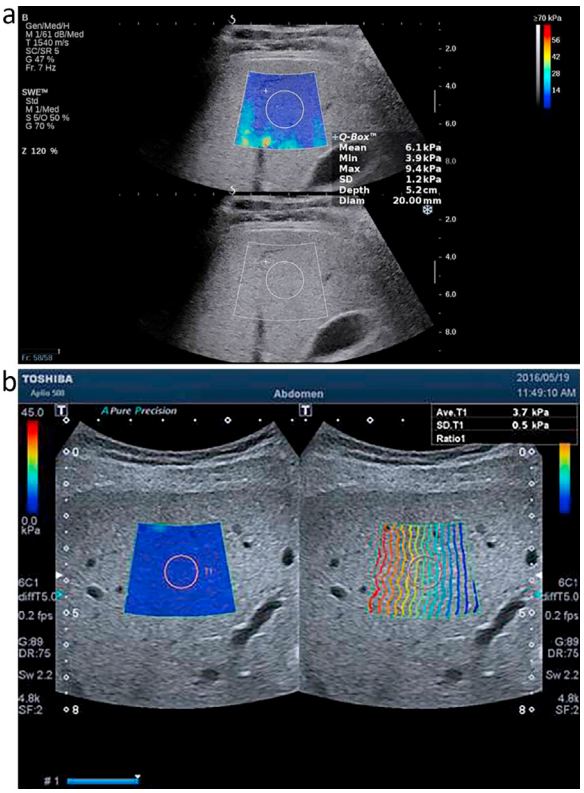

Fig. 1. Normal liver parenchyma evaluated using 2D shear wave elastography with different ultrasound systems. Aixplorer (Supersonic Imagine) (a), Aplio 500 (Toshiba Medical Systems) (b).

those regarding elastography issued by the European Federation of Societies in Ultrasound in Medicine and Biology (EFSUMB) [5–7], or in other guidelines published in this field [3,4,8–12].

In this review paper, we outline the major advances in the field of ultrasound for liver applications, which could soon be part of the armamentarium of ultrasound specialists devoted to the assessment of liver disease. This review paper discusses current and future ultrasound assessment of steatosis, the value of the assessment of liver stiffness in patients with portal hypertension, the use of elastography for the evaluation of focal liver lesions and some other future methods (outlook).

2. Ultrasound assessment of steatosis

The assessment of steatosis (liver fat content) is relevant in patients suspected of, or diagnosed with, chronic liver diseases. Steatosis is usually a diffuse process within the liver tissue, but a non-uniform distribution can be sometimes observed (focal fatty changes or zonal/regional steatosis; focal or segmental sparing) [13–20]. On standard grey scale ultrasound, a semi-quantitative scale partially reflecting the histological grade can be used [21–24]. New methods quantitatively assessing steatosis have been recently proposed and are summarised below.

2.1. Ultrasound echo amplitude quantification: Acoustic Structure Quantification (ASQ)

Fat droplets within the liver behave as small ultrasound interfaces, which differ from the normal liver parenchyma in terms of ultrasound echo amplitude distribution. Therefore, with appropriate statistical modelling the difference between theoretical and real echo amplitude distribution can be measured. The Acoustic Structure Quantification (ASQ) software is based on this concept [25,26].

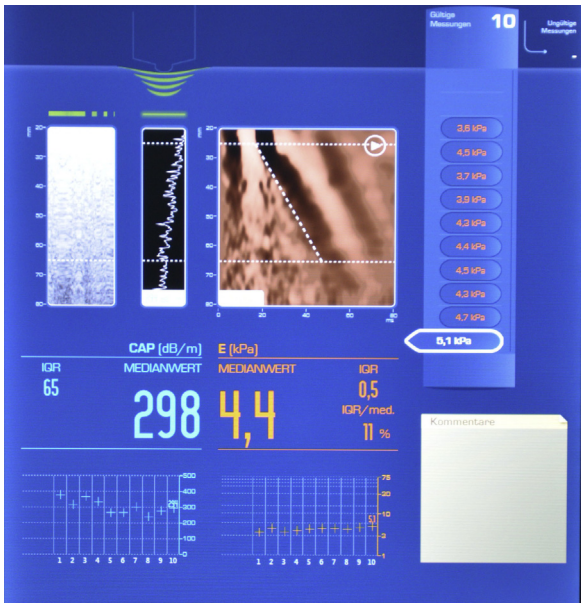

Fig. 2. Controlled Attenuation Parameter using fibroscan indicated in blue. The interquartile range (IQR), which is a quality parameter, is displayed as well.

A parameter calculated by using ASQ, namely focal disturbance ratio, showed a significant correlation with fat droplet area and size in a murine model of liver steatosis [25]. This parameter was used in a human study using ^{1}H MR spectroscopy as the reference standard method for liver steatosis quantification [27]. Fifty three consecutive potential living donors for liver transplantation and 40 healthy subjects were studied. Focal disturbance ratio showed a strong inverse linear correlation with hepatic fat fraction measured by ^{1}H MR spectroscopy, and an excellent discriminative ability for steatosis ≥ 10% (AUROC 0.96) [27]. Despite this preliminary data is interesting, further studies in less selected populations are needed before using this method in clinical practice.

2.2. Controlled Attenuation Parameter

Recently, the Controlled Attenuation Parameter (CAP) [28] has been proposed as a new technology in this field. CAP assesses steatosis according to the degree of ultrasound echoes attenuation through the liver and results are therefore expressed in acoustic energy attenuation in decibel/meter (dB/m) [Fig. 2]. CAP software is embedded into the transient elastography device (FibroScan, Echosens, France), and CAP is measured simultaneously to liver stiffness (Table 1).

2.2.1. Grading of steatosis in patients with chronic liver disease

CAP values differ between patients with and without steatosis both in the adult [29–31] and in the paediatric population [32]. The results of nine studies comprising 1171 patients with chronic liver diseases of different aetiologies from different countries with paired CAP measurement and liver biopsy has been object of a recent meta-analysis [33]. The meta-analysis confirmed that liver tissue attenuation measured by CAP correlates with the amount of steatosis assessed by liver biopsy. CAP has a good to very good discriminative accuracy for steatosis >10% (any steatosis, ≥S1; AUROC 0.85; 95% CI 0.81–0.88); >33% (significant steatosis, ≥S2; AUROC 0.88; 95% CI 0.85–0.91) and >66% (severe steatosis, S3; AUROC 0.87; 95% CI 0.84–0.90). Fagan plot analysis to evaluate the clinical utility of CAP for the detection of S1 hepatic steatosis showed that with a pretest probability of S1 of 25%, the post-test probability, given positive and negative CAP results, were 55% and 9% [33].

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