New technologies in liver fibrosis assessment, with special consideration of dynamic elastography

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Abstract

Liver diseases leading to cirrhosis and liver failure pose a frequent problem encountered in clinical practice by various specialists. The insidious and latent progress of liver diseases, including especially those of infectious origin, is a source of major diagnostic and therapeutic challenges. The period between the emergence of the initial unspecific symptoms to an accurate diagnosis is frequently too long. Therefore, there has been a wide search for new methods of assessing the degree of fibrosis advancement. Until recently core-needle biopsy was the only method of assessing liver fibrosis [1]. Currently use is made of plasma biomarkers, such as APRI, GAPRI and the Fibrotest, along with imaging examinations, including magnetic resonance elastography (MRE), supersonic shear wave imaging (SSWI), acoustic radiation force imaging (ARFI) and transient elastography (TE). Liver biopsy is a gold standard for staging of fibrosis and diagnosis of cirrhosis. Under local anesthesia, a core of liver tissue is obtained for pathologic analysis. The intervention has many contraindications and is subject to risk of complications and reduction in quality of life.

Currently transient elastography enjoys great popularity. The measurement of transient elastography is performed by a FibroScan®. To evaluate the stiffness of the liver using both ultrasonic waves 3,5 MHz and low frequency waves 50 Hz. The speed of waves propagation is directly related to the flexibility (stiffness) of the hepatic parenchyma. The examination is non-invasive, painless, repeatable, short, without side effects. In many scientific articles it has been confirmed high consistency of results compared to liver biopsy.

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Liver biopsy is the traditional gold standard for staging of fibrosis and diagnosis of cirrhosis [1,2]. Under local anesthesia, a core of liver tissue is obtained for pathologic analysis. Several scoring systems exist to stage the degree of fibrosis in the biopsy specimens. The METAVIR and Ishak scores are used most commonly. The METAVIR system scores fibrosis on a 5-point scale, with F0 equating to no fibrosis, and F4 equating to cirrhosis [1,3] Indications for percutaneous liver biopsy are: chronic hepatitis B and C, Co-infection HCV/HBV, liver cirrhosis other than viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, abnormal liver tests, alcoholic liver disease, non-alcohoilc fatty liver disease NAFLD, toxic liver injury, hyperbilirubinemia [4]. The intervention has many contraindications e.g.: the uncooperative patient, extrahepatic biliary obstruction, bacterial cholangitis, abnormal coagulation indexes, ascites, cystic lesions, amyloidosis [5]. Blind liver biopsy is subject to risk of complications such as: haemorrhage to the peritoneal cavity, hemothorax of the right pleural cavity, biliary peritonitis following puncture of the gall bladder or large bile duct. Laparotomy is require in some cases. Pain at the site of puncture and/or right shoulder is the most common complication. Other complications included the following: vasovagal reaction (syncope, reflex hypotension, transient bradycardia), bile duct puncture (without resulting in bile leak and biliary peritonitis), leukocytosis after biopsy [3,4]. Age did not influence the risk of complications and a reduction in quality of life [6]. Biopsy under ultrasound control minimizes complications. Looking algorithms composed of several plasma ratios for example in the Enhanced Liver Fibrosis algorithm which takes into account the concentration of hyaluronic acid, N-terminal propeptide of type III collagen and the tissue inhibitors of metalloproteinases. APRI is a ratio of alanine aminotransferase to platelet counts. GAPRI is a ratio GGT activity to platelets, AAR is the ratio of aspartate aminotransferase to alanine aminotransferase, HAPRI is relationship of the hyaluronic acid to the rate of prothrombin. Fibrotest is calculated on the basis of 6 parameters: α2-macroglobulin, alpha 2 globulin, gamma globulin, apolipoprotein A1, total bilirubin, and GGT levels.

MR elastography (MRE) involves the use of a transducer placed under the rib cage of patients that transmits mechanical waves into the liver [7,8,9].

Acoustic radiation force imaging

In this technique is used conventional ultrasounds US to generate a shear wave directly within the liver tissues. The researcher depends on use US images and also specify a region of interest (ROI) for estimation of liver elasticity. The propagation velocity of the shear wave is reported in meters per second, and correlates with the liver stiffness [3]. The latest studies show the advantages MRE over ARFI for the diagnosis of fibrosis in patients with biopsy-proven non-alcoholic fatty liver disease.

Shear wave elasticity imaging (SWEI) is a new approach to imaging and characterizing tissue structures based on the use of shear acoustic waves remotely induced by the radiation force of a focused ultrasonic beam it is performed at relatively low frequencies (<20 MHz) [10,11].

Transient elastography due to fibroscan® device

FibroScan®, a device used in transient elastography, was marketed in 2003 by the French company Echosens. The examination is non-invasive, as the measurements are performed using a head touching the right intercostal space at the level of the xiphoid process. The patient undergoing the examination feels slight impulses sent by the head (Fig. 1). FibroScan®, being the first device of with reliability proven clinically, provides accurate, detailed and repeatable data regarding liver stiffness (fibrosis). It employs a patented technology VCTe™ (Vibration-controlled Transient elastography) which comprises testing three parameters that are crucial to elastography, i.e. wave quality, energy stability and a result calculation algorithm.

On touching the patient's skin, the device probe generates a mechanical impulse – an elastic wave at a frequency of 50 Hz (Fig. 1).

The wave goes through the patient's subcutaneous tissues and reaches the liver. This device is based on one-dimensional (1-Due) transient elastography, a technique, that uses both ultrasound 3,5 MHz and low-frequency (50Hz) elastic waves, whose propagation velocity is directly related to elasticity. [12]. The speed of wave propagation [V] depends on the liver hardness/stiffness degree [E kPa] [13].The staff at our centre uses an M-sized probe that covers a skin-to--liver distance of 6 cm. When the distance is longer, the computer notifies the examiner that an XL-sized probe needs to be used. In one examination we charge of 10 measurements. The technique measures the stiffness in a cylindrical volume 1 cm in diameter and 4 cm in length, amounting to about 1/500 of the entire liver volume – 100 times larger than the volume of the liver biopsy specimen [14,15,16] (Fig. 2).

Fig. 1.
The probe's view. www.fibroscan502touch.com

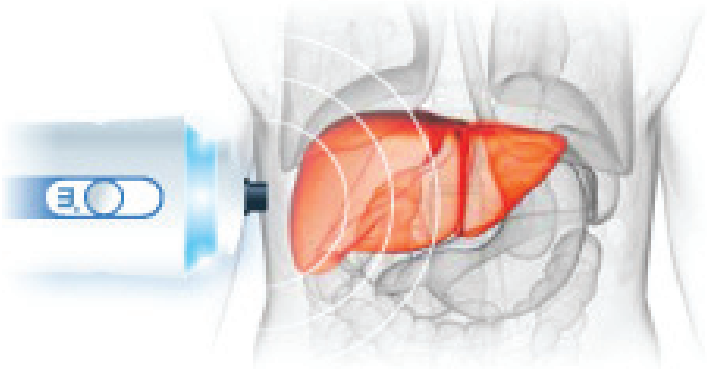

Fig. 2.
The point of probe's application. www.echosens.com

Application of the transient elastography

The counter indications to perform the examination include water belly, pregnancy and significant obesity. A body mass index BMI > 30 kg/m^2 had the strongest association with both test failure and unreliable results. A special probe (XL probe) with a measurement depth of 35-75 mm was developed for morbidly obese patients [17,18,19]. Technical differences between the M and XL probes include their central ultrasound frequency (3.5 versus 2.5 MHz), vibration amplitude (2 versus 3 mm), and the diameter of their tips (9 versus 12 mm). In addition, measures from XL probe are deeper compared to those performed by M probe [15]. The "normal" values of TE were defined in healthy individuals as around 5.5 kPa with the M probe, showing that liver stiffness was higher in males compared to females and in obese individuals compared to those with normal weight [16.17.18]. The examination is painless, repeatable, as it is non-invasive has no potential complications, is rapid (<10 min), and can be performed at the patient's bedside [15,17] . The probe size S intended for children.

Factors that can impact on liver fibrosis: the high level of alanine transaminases (ALT), extrahepatic cholestasis and liver congestion, non-fasting status, liver steatosis, operator effect, interobserver variability. There is no evidence that presence of hepatocellular carcinoma might impact on liver stiffness [17]. What is more, TE has a prognostic value to predict the development of liver neoplasm [22].

Three reliability categories are therefore defined, with significantly different diagnostic accuracy: "very reliable" (IQR/M ≤ 0.10), "reliable" (0.10 < IQR/M ≤ 0.30 or IQR/M > 0.30 with a median of LS < 7.1 kPa), and "poorly reliable" (IQR/M > 0.30 with a median of LS ≥ 7.1 kPa) [23]. IQR it is inter quartile range of all valid measurements within the current examination. IQR/M indicates the IQR/median ratio. A number of scientific studies have confirmed the compatibility of the FibroScan® and the biopsy [24,25]. Moreover, there are many studies assessing the comparability of non-invasive methods to assess liver fibrosis: Trovato et al. showed that transient elastography has a better performance than ARFI, which has a lower sensitivity, in the diagnosis of severe stages of fibrosis [26]. Sarvazyan AP et al investigated, that SSI, FibroScan®, and ARFI correlated significantly with histological fibrosis score (r=0.79, p<0.00001; r=0.70, p<0.00001; r=0.64, p<0.00001, respectively) [27]. The application of the FibroScan® in liver disease diagnostics is recommended by the leading hepatology organisations, including the Polish Group of HCV Experts, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. It is used to assess the degree of fibrosis and steatosis occurring in the following diseases: hepatitis B and C virus infection, also in HIV co-infection, primary biliary cirrhosis, non-alcoholic steatohepatitis, alcoholic liver disease, primary sclerosing cholangitis and autoimmune hepatitis, as well as to monitor liver fibrosis in post-transplant patients [28]. Another advantage of elastography stems from its lack of impact on living comfort, contrary to the negative effect exerted by a biopsy [16]. Furthermore, patients more likely to opt for the method of invasive non-invasive. The fibrosis level indicated in kPa is converted into Metavir values. The examination results should be interpreted by an examiner trained to properly use the device, taking into account the results of laboratory tests, the disease history, and the aetiology and clinical condition of the patient [14,15,16]. In the event of the results obtained being inconsistent with the patient's clinical condition, or the simultaneous occurrence of several liver diseases being suspected, the elastography result cannot be relied on and a biopsy should be performed.

Conclusions

TE is an alternative for percutaneous liver biopsy (Fig 3). It is necessary to remember to prepare the patient before the examination. Moreover, the result of TE should interpret an experienced researcher who made more than 100 examinations. This is an objective test. The evaluation of the result

lies in the interpretation of the figures, which the computer provides. The interpretation of the results considering the clinical condition of the patient. Transient elastography is accurate for staging liver fibrosis and can be used for prediction of mortality and severe outcome in patients with chronic liver diseases. The examination is rapid, about 10 min, and can easily be performed at the patient's bedside. The test is painless, repeatable and accepted by the patients.

Fig. 3.
General view of FibroScan. www.echosens.com

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