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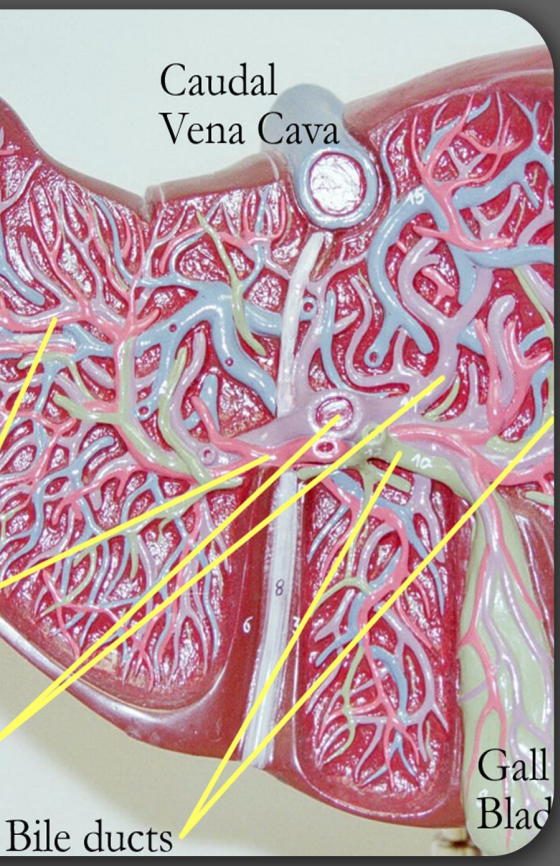
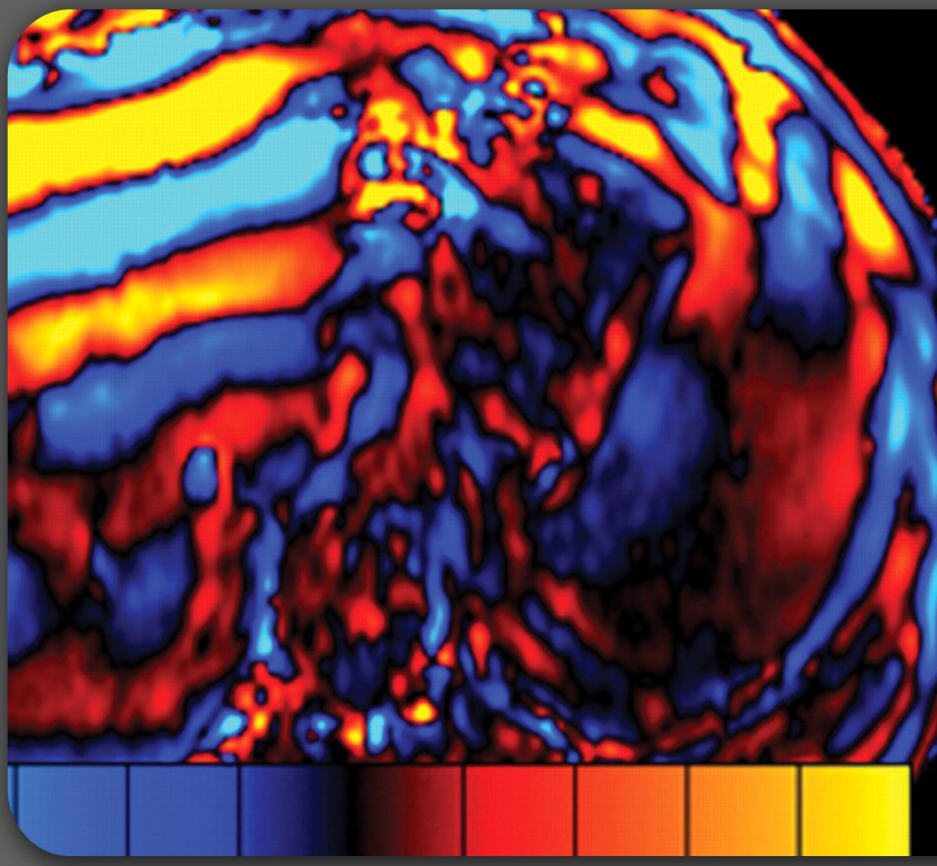
Hepatic Elastography Using Ultrasound Waves

Revised Edition of Volume 1





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FOREWORD

Chronic liver diseases are common worldwide, including chronic viral hepatitis B and C, alcohol related and non-alcoholic fatty liver disease (NAFLD) and many others. The use of ultrasound has significantly contributed to the evolution of hepatology.

B mode ultrasound is the most frequently used initial imaging modality to examine patients with acute and chronic liver diseases. Doppler ultrasound techniques provide morphological and functional information of the liver vascularity which is most important for the evaluation of portal hypertension and its complications. Contrast enhanced ultrasound has revolutionized liver imaging. More recently the ultrasound based elastography technology has introduced a new dimension of imaging. The introduction and widespread use of non-invasive elastography techniques have reduced the need for invasive liver biopsies (LB) in patients with chronic liver disease.

The revised edition of the eBook edited by Prof. Dr. Ioan Sporea and Dr. Roxana Şirli on liver elastography summarizes the current and up to date knowledge on the use of elastography in the evaluation of liver diseases. The ebook introduces an understanding of this novel technique through the lens of important clinical background information which is also discussed. The well-known Roumanian authors around Prof. Ioan Sporea have published not only this book but also evidence based National Guidelines and Practical Recommendations on liver elastography. This book and the “practical recommendations” are helpful for all doctors starting to use these methods.

The book describes the physical principles of elastography, referring to the elastography guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and World Federation on Ultrasound in Medicine and Biology (WFUMB).

Various elastography modalities are available, requiring different examination techniques and providing slightly different clinical information. The techniques described include transient elastography and acoustic radiation force impulse (ARFI) elastography, 2D shear Waves elastography and strain elastography amongst others. Importantly, examination technique, reproducibility and confounding factors are explained in detail.

A link to this book is available on the EFSUMB website (www.efsumb.org).

Congratulations to the authors who write with the benefit of their long standing clinical and research expertise in this field. I commend their valuable contributions to elastography.

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PREFACE

The incidence and prevalence of chronic liver diseases increases in everyday practice. The main etiologies are chronic hepatitis C or B, ethanol abuse (alcoholic steatohepatitis - ASH) or nonalcoholic steatohepatitis (NASH), while autoimmune hepatitis or primary biliary cirrhosis (PBC) are encountered more rarely, but are not negligible.

Staging liver fibrosis severity is essential in chronic liver diseases work-out for prognosis and for decision regarding treatment. Until a few years ago, fibrosis evaluation was made only by means of a liver biopsy (LB) - the "gold standard" technique for staging, but also for grading liver diseases [1].

After percutaneous LB was introduced in daily practice in hepatology (some decades ago), it became an indispensable tool for liver disease assessment. It evaluates the fibrosis stage and activity grade, but it also reveals fatty infiltration or specific markers for some hepatic diseases (such as the Mallory bodies in alcoholic steatohepatitis). The morphologic examination is considered the "gold standard" method for assessing lesions' severity in chronic hepatopathies and, until some years ago, was also considered mandatory for prognosis assessment.

An old problem of LB is that the specimen obtained is very small, only approximately 1/50,000 of the liver. Another issue is the uneven distribution of fibrosis in the liver. Also, an important problem is the specimen size. To be relevant, liver samples must be at least 2 to 4 cm long [2]. Other authors state that a specimen adequate for pathological examination should be longer than 25 mm and including more than 8 portal tracts [3] or, including at least 11 portal tracts [4]. Colloredo *et al.* [5] showed that the chance of underestimating fibrosis severity and necroinflammatory activity increases in parallel with the shortness of the liver sample. Bedossa *et al.* [6] imagined a mathematical model that predicted a 25% diagnostic error rate if the biopsy specimen was only 25 mm long. This model estimated that the optimal specimen hould be at least 40 mm long.

In daily practice, in many cases the liver specimen is suboptimal and can underestimate the fibrosis severity and necroinflammatory lesions. According to two multicentre studies performed in France, in up to 10-15% of cases the LB is uninterpretable due to the small size of the specimen [7]. In a previous multicentre Romanian study concerning the quality of liver sample obtained by percutaneous LB [8], only in half of the cases, the LB fragments were optimum for pathological interpretation, including more than 11 portal tracts, while in approximately two thirds of cases the fragments were only satisfactory (more than 8 portal tracts). In approximately 1/3 of cases, the tissue specimen was not good enough for a correct

staging of liver disease (less than 8 portal tracts).

In a systematic review on the quality of LB specimens [9], it was demonstrated that major and minor complications occur during the procedure in up to 6% of cases, while 0.04 to 0.11% of them can be life threatening. In this review including more than 8,700 patients, in more than half of cases the mean length and mean number of portal tracts of LB specimens was much lower than the published minimum sample size requirements [5, 6] (only 42% of liver samples included at least 10 more) [9].

Our group evaluated a cohort of more than 1000 percutaneous echo assisted LB performed with 1.4 mm and 1.6 mm Menghini modified needles, with 2 liver passages [10] in which the quality of liver specimen was evaluated. We divided the LBs into 4 groups (< 15 mm; 15- 24 mm; 25-39 mm; > 40 mm). We calculated the mean lengths for every group and using Bedossa's study [6] we analyzed the percentage of expected correctly classified biopsies. The overall mean length of liver specimen obtained in our cohort was 33±9 mm, with a mean number of portal tracts of 20±10 (indicative of a good quality specimen). 1% (10) of the LBS were included in the first group (< 15 mm) with a mean length of 9.8±2 mm, 13% (135) LBS were included in the second group (15- 24 mm) obtaining a mean length of 20±1.8 mm, 41% (418) of the LBs had between 25 and 39 mm with a mean length of 30±3 mm, 45% (449) of the LBs obtained specimens larger than 40 mm with mean length of 42±5 mm [10]. Using Bedossa's study and diagram referring to the sensitivity of LB for staging liver fibrosis according to the length of biopsy specimen, we obtained the following sensitivities: Group 1 (< 15 mm) 55%; Group 2 (15-24 mm) 70%; Group 3 (25-39 mm) 75%; Group 4 (> 40 mm) 83% and an overall sensitivity of LB of 80%. Thus, despite the fact that good liver specimens were obtained in our study using Menghini needles with 2 passages technique (mean length of liver specimen 33±9 mm, with a mean number of portal tracts of 20±10) the overall sensitivity of liver biopsy was only approximately 80% using Bedossa's criteria. The conclusion of the study was that the “gold standard’ method (LB) is not actually a very good “gold standard” [10]. This paper raised the question if similar (or better) results could not be obtained with other (non-invasive) methods?

Another problem when evaluating the LB results is the inter- and intraobserver concordance. A study on the interobserver agreement in assessing LBs from patients with chronic hepatitis C showed concordant opinion in assessing fibrosis of 0.78 and for necroinflammatory activity of 0.48 if Knodell score was used. For the Metavir score, the concordance for fibrosis assessment was 0.80, and 0.56 for necroinflammatory activity [7].

With regard to the patients’ perspective, we must ask ourselves why patients are afraid of LB. The first reason is pain and discomfort, but also the risk of complications, which is low, but not zero. A paper published in 2010 presented the results of a study regarding elective

percutaneous LBs performed using data collected by the National Health Service in England from 1998 to 2005 from 61,187 subjects [11]. Seven day mortality directly related to LB and bleeding episodes up to 7 days after biopsy were evaluated. The study revealed that death within 7 days, directly related to LB occurred, at most, in 1/10,000 biopsies, and that 6 episodes of major bleeding occurred per 1000 biopsies.

This risk of complications increases in patients with advanced fibrosis, as shown by the results of the HALT-C study [12]. In this study, from 2,740 liver biopsies, approximately 0.5% of patients with hepatitis C and advanced fibrosis experienced potentially serious bleeding after LB and the risk significantly increased in patients with a platelet count of 60,000/mm or less.

Thus, considering these limitations of LB in daily practice, maybe other methods can be used to evaluate the severity of liver lesions. Some years ago, hepatologists focused on non-invasive methods for the evaluation of liver diseases severity which could represent an alternative to LB. Some authors favor biological markers [13], some are in favor of elastographic methods [14, 15], while others consider that the combination of these methods can reduce the number of LBs [16, 17].

Indeed, the number of LBs performed across the world has decreased in the last years. In France, liver fibrosis in chronic hepatitis C patients can be assessed by means of LB or by non-invasive methods such as FibroTest or FibroScan®. In an American study from Beth Israel Medical Center New York which evaluated the last 15 years' experience regarding LB, the number of LBs performed for chronic hepatitis C peaked in 2003, followed by an annual decrease, while the number of annual biopsies for chronic hepatitis B increased during the same period [18]. On the other hand, nowadays, when very potent drugs are available for HCV chronic infection, with a cure rate of more than 90-95%, the patients can be treated to cure the infection and to stop disease progression, without much interest regarding the disease severity. Fibrosis severity evaluation is used (or can be used) only to prioritize treatment, considering its current high cost.

Schiano [19] wrote an interesting editorial in Clinical Gastroenterology and Hepatology, concerning the LB (in autoimmune hepatitis). The title is a very provocative one: "To B(iopsy) or Not to B(iopsy)...".

Thus, we can open the discussion concerning the future of LB — "Quo vadis" liver biopsy? The question is if there still is a place for LB in the evaluation of chronic hepatopathies? This is a very provocative question and long debates have been known to develop regarding this topic. If LB can be avoided (at least in the majority of cases), is this strategy applicable only for chronic hepatitis C, or is it also possible in chronic hepatitis B? But what should we do

regarding other chronic liver diseases, such as non-alcoholic steato-hepatitis (NASH), alcoholic liver disease (ALD), autoimmune hepatitis, cholestatic liver diseases, overlap syndrome or drug-induced liver injury (DILI) ?

The number of ***non-invasive methods for liver fibrosis assessment*** has increased in the last decade [20]. They can be: ***serum based tests*** (direct and indirect, the most frequently used in clinical practice being FibroTest) or ***imaging tests***. The latter, becoming more popular every day, based either on ultrasound (Ultrasound based liver Elastography) or on magnetic resonance imaging (MR Elastography-MRE), are used for liver stiffness (LS) assessment, as a marker of fibrosis. Serologic tests evaluate both the necroinflammatory activity (ActiTest) and fibrosis (FibroTest) and can give information concerning fat infiltration or alcohol abuse (Fibro Max) [20].

The first method used for LS evaluation using ultrasound waves was Transient Elastography (FibroScan®, Echosens® France). Other techniques have been latterly developed, such as Real Time Elastography (by Hitachi) or Acoustic Radiation Force Impulse (ARFI) Elastography. They are used more and more, in daily practice and many papers have been published, proving their value. 2D Shear Waves Elastography (2D SWE) has been developed more recently.

This book intends to be an overview regarding the value of different elastographic methods using ultrasound waves for LS assessment, in patients with chronic liver diseases. Our team's experience, together with published data from the latter years, offers the reader a perspective of the role that these methods play in the liver evaluation algorithm. Many papers concerning the value of different elastographic methods for LS evaluation have continued to be published, some considering LB as the reference method and others trying to demonstrate the non-inferiority of new elastographic methods, as compared to a validated method, such as Transient Elastography (FibroScan®).

At the end of this book, there is some information regarding the new development directions of elastography for the evaluation of focal liver lesions (FLL). The role of elastographic methods for FLL assessment has not yet been established, but some results have already been evidenced.

This e-book is the revised edition of Vol.1 of Hepatic Elastography Using Ultrasound Waves, presenting the most recent papers looking at the value of ultrasound based elastography for liver stiffness assessment. Rapid development in liver elastography, with new machines appearing in the market, made it imperative to produce this second edition, in which new guidelines and clinical recommendation have been included. We hope that readers of this book will gain enough practical information regarding all types of ultrasound based

liver elastography, that will permit them to work with these methods in clinical practice.

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CHAPTER 1

Transient Elastography (TE)

Ioan Sporea and **Roxana Şirli***

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Abstract: Transient Elastography (TE) is the first ultrasound-based method for fibrosis assessment, developed by Echosens®(France). In order to obtain reliable liver stiffness (LS) measurements by means of TE, the manufacturer recommended that at least 10 valid shots should be obtained. They should have a success rate (SR: the ratio of valid shots to the total number of shots) of at least 60% and an interquartile range (IQR, the difference between the 75th percentile and the 25th percentile, essentially the range of the middle 50% of the data) less than 30% of the median LS value. New quality criteria were proposed by Boursier in which only IQR is taken into consideration. TE fails if no valid shots can be obtained, and is unreliable if fewer than 10 valid shots are obtained. TE failure is correlated with the body mass index, increasing in obese patients. By using the XL probe, the success rate of TE measurements significantly improves. Also, unreliable results are obtained during aminotransferases flares that can lead to an overestimation of fibrosis. The LS upper limit in healthy subjects was estimated to be 5.3 kPa. Several meta-analyses assessed LS measurements by TE as a predictor of fibrosis, cut-offs for F≥2 ranging from 7.2-7.6 kPa and for F=4 from 12.5-17.3 kPa, according to the etiology of chronic liver disease. Several studies have been published regarding the value of TE for predicting the occurrence of cirrhosis complications. The AUROC's for predicting clinically significant portal hypertension were 0.945 - 0.99, for cut-off values between 13.6 - 21 kPa, while for predicting esophageal bleeding the best cut-offs ranged between 50.7 – 62.7kPa, with AUROC's 0.73-0.75. European Guidelines recognize TE as a reliable method to evaluate fibrosis.

Keywords: Cirrhosis, Esophageal varices, Liver fibrosis, Liver stiffness, Transient elastography.

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1. TE TECHNIQUE

Transient Elastography (TE) is a shear wave and ultrasound-based method, developed by Echosens® (France), initiating from the principles of Hooke's law, which characterizes a material's strain response to external stress [1]. A FibroScan® device is used (Fig. **1**), whose ultrasound transducer probe (Fig. **2**), mounted on the axis of a vibrator, transmits low-frequency vibrations into the liver. The transducer is placed in a right intercostal space and generates an elastic shear wave that propagates into the liver. A pulse-echo ultrasound acquisition is then used to detect shear waves propagation velocity, which is proportional to tissue stiffness; faster shear waves progression occurs through stiffer material. LS measurement is then performed and measured in kiloPascals (kPa) (values between 1.5kPa and 75 kPa are expected).

Fig. (1). The FibroScan® device.

Fig. (2). Pediatric (S), standard (M) and obese (XL) FibroScan® probes.

Using TE, liver stiffness measurements (LSMs) are performed in the right liver lobe through the intercostal spaces, while the patient lies in a dorsal decubitus position with the right arm in maximal abduction. The tip of the transducer is covered with coupling gel and placed in the 9th to 11th intercostal space, at the level where a liver biopsy would be performed. The operator, assisted by ultrasound A-mode images provided by the system, locates a portion of the liver at least 6 cm thick and free of large vascular structures. Once the area of measurement had been located, the operator presses the probe button to begin an acquisition. TE measures LS in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 mm and 65 mm below the skin surface. Acquisitions that do not have a correct vibration shape or a correct follow-up of the vibration propagation are automatically rejected by the software [2 - 5]. Following each measurement, the measured value of LS is displayed (CS). Following 10 valid measurements, the median value of these values is displayed, as well as the IQR and the SR (Figs. **3**, **4**)

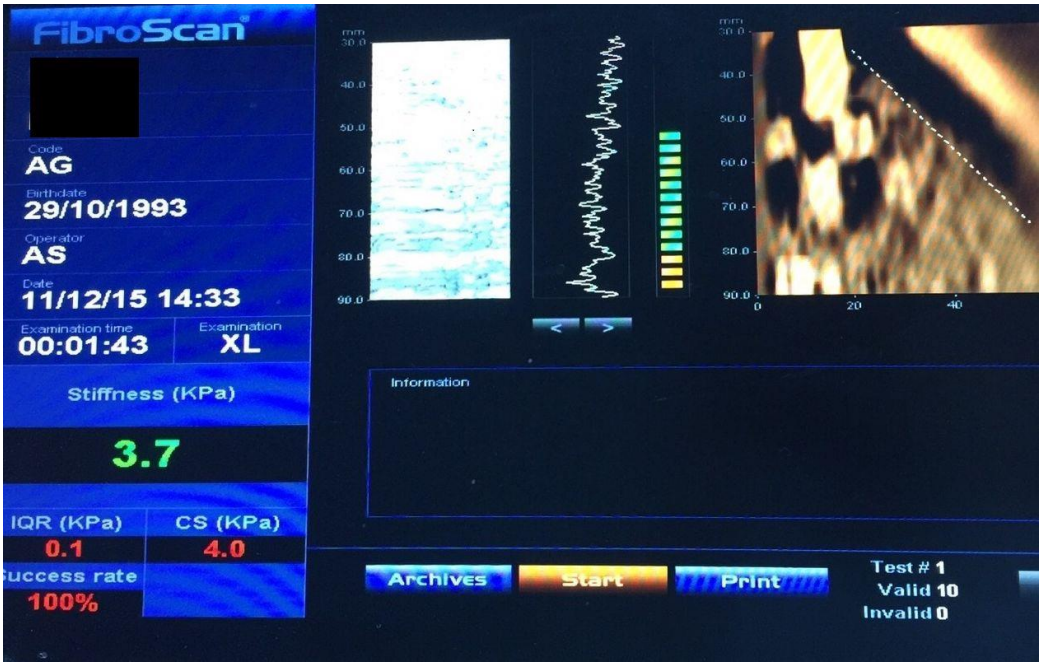

Fig. (3). Transient elastography measurement in a normal individual (median value of 10 measurements).

CHAPTER 2

Point Shear Wave Elastography

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Abstract: VTQ **(**ARFI) elastography is a new method developed in the last 5-6 years for the non-invasive evaluation of liver fibrosis, integrated into a Siemens Acuson ultrasound system. Ten valid measurements are performed in the right liver lobe, a median value is calculated and the result is expressed in meters/second. The AUROC's range between 0.75-0.85 for predicting significant fibrosis and for predicting cirrhosis between 0.85-0.95. To increase the accuracy of liver cirrhosis diagnosis, the spleen stiffness (SS) assessed by VTQ (ARFI) can be used. VTQ (ARFI) it is a reproducible method (intraclass correlation coefficient ranging from 0.81-0.87), especially in patients with severe fibrosis and cirrhosis. Similar with Transient Elastography (TE), elevated levels of aminotransferases are associated with the increase of liver stiffness (LS) values assessed by VTQ (ARFI). Even if the manufacturer did not recommend the use of technical parameters IQR (interquartile range interval) and SR (success rate) well-known from TE, published data proved that the accuracy of the method significantly increased with the use of these quality parameters. Regarding the prediction of liver cirrhosis complications, especially portal-hypertension, data regarding the usefulness of LS and/or SS are not so solid, but VTQ (ARFI) accuracy can be increased by combining different parameters.

ElastPQ is a newly developed point Shear Waves elastographic method. Only few data, but with promising results, were published until now regarding this technique.

Keywords: ARFI elastography, Chronic hepatitis, ElastPQ, Liver cirrhosis, Liver stiffness, Portal hypertension, VTQ.

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Ioan Sporea & Roxana Șirli (Eds.)

II.A. ACOUSTIC RADIATION FORCE IMPULSE (ARFI) ELASTOGRAPHY

1. VTQ (ARFI) Elastography Technique

Virtual Touch™ Quantification (VTQ) uses Acoustic Radiation Force Impulse (ARFI) technology in a Siemens Acuson S2000TM ultrasound system (Siemens AG, Erlangen, Germany) with 4C1 and 4V1 transducers to evaluate the elastic properties of a targeted anatomical region with the use of a region of interest (ROI) cursor, while performing real-time B-mode imaging.

The principle of VTQ (ARFI) elastography is that compression of the examined tissue induces a strain into the tissues. The ultrasound probe automatically produces an acoustic "push" pulse that generates shear-waves which propagate into the tissue, perpendicular to the "push" axis. The speed of the shear-waves, measured in meters/second (m/s), is displayed on the screen. The highest theoretically reachable velocity in the hardest medium corresponds to approximately 6 m/s. The propagation speed increases with tissue stiffness, thus with fibrosis severity. Shear wave speed may be quantified, in a precise anatomical region, focused on a region of interest, with a predefined size, provided by the system. Speed measurement value and depth are reported and the results of the elasticity are given in meters/second (m/s) [1, 2].

The operator can select the depth at which liver elasticity is evaluated, by placing a "measuring box" (10/5 mm) in the desired place (Fig. **1**). Scanning is performed between the ribs in the right liver lobe (*e.g.* segment 8 or 5) (in order to avoid cardiac motion), approximately in the place where a liver biopsy is usually performed, 1-2 cm under the capsule, with minimal scanning pressure applied by the operator, while the patient is asked to stop breathing for a moment, in order to minimize breathing motion. Usually, 10 valid measurements are performed and a median value is calculated (expressed in m/s). If the measurement is not reliable "X-X-X" is displayed on the screen.

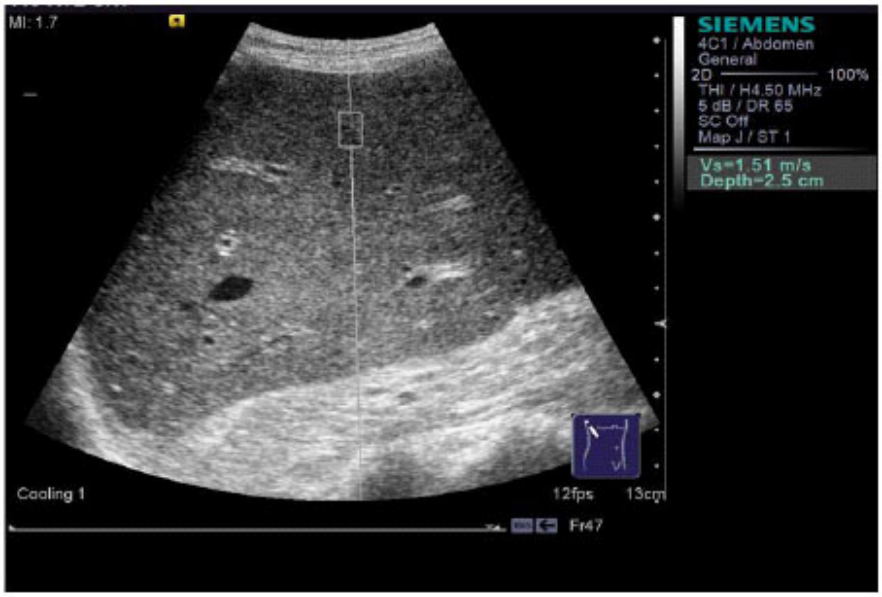

Fig. (1). VTQ (ARFI measurement).

Our study published in 2011 [3] showed that the best correlation with histological fibrosis was observed for measurements made 1-2 cm and 2-3 cm under the liver capsule (0.675 and 0.714, respectively), but in up to 15% of cases, valid measurements could not be obtained for profound measurements (2-3 cm). Another study [4] showed that VTQ (ARFI) assessments with the lowest rate of invalid measurements are obtained by an intercostal approach to segments VII/VIII of the liver, while our study [5] demonstrated that similar VTQ (ARFI) values are obtained in segments VIII and V of the liver.

The device's manufacturer did not made specific recommendations regarding the technique that should be used for liver fibrosis evaluation in children.

2. Reproducibility of VTQ (ARFI) and Factors which Influence the Correlation of Liver Stiffness with Fibrosis

Non-invasive methods for liver fibrosis evaluation should have a good diagnostic accuracy and must be reproducible in order to be used in clinical practice. Also, it is imperative to know which factors influence the correlation of liver stiffness (LS) assessed by VTQ (ARFI) with fibrosis.

CHAPTER 3

2D-ShearWaves Elastography (2D-SWE)

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Abstract: Shear waves elastography is a technique designed to overcome some of the disadvantages of other elastographic techniques. It is based on supersonic share imaging, an ultrasound-based technique used for real-time visualization of soft tissue viscoelastic properties. This technique is based on the combination of a radiation force induced into the tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence able to capture in real time the transient propagation of the resulting shear waves. Shear waves' propagation induces small tissue displacements which are recorded by the imaging system, and measured using tissue Doppler techniques. 2D-SWE offers as major innovations the ability to measure area and distance ratios, a high spatial resolution and real-time capabilities. The technique produces an image where true local tissue elasticity is displayed in a color map in "real time". Elasticity is displayed using a color coded image superimposed on a B-mode image. The true elasticity is assessed based on Shear Waves propagation speed into the tissue. Thus the technique permits a quantitative mapping of liver tissue viscoelasticity. The technique was first available on the Aixplorer® system (SuperSonic Imagine, France) and initially was used for the evaluation of breast nodules, of prostate elasticity, for the evaluation of muscle and tendon stiffness and for thyroid disease diagnosis. Published data showed a real value of this method for liver stiffness estimation in patients with chronic hepatitis. It has the advantage that it can be also used in patients with ascites. A similar technique is now available on the Logiq E9 system (General Electric) with promising results.

Keywords: Liver stiffness, Shear waves elastography, Viscoelasticity.

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Ioan Sporea & Roxana Şirli (Eds.)

1. 2D-SHEARWAVES ELASTOGRAPHY TECHNIQUE

2D-Shear Waves Elastography (2D-SWE) is a new technique designed to overcome some of the disadvantages of other elastographic techniques. It is based on supersonic share imaging, an ultrasound-based technique, used for real-time visualization of soft tissue viscoelastic properties. The technique is based on the combination of a radiation force induced into the tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence, able to capture in real time the transient propagation of resulting shear waves [1].

Thus, 2D-SWE uses transient pulses to generate shear waves into the body [2 - 4], the only approach able to provide measureable and local elastic information in "real time" [5] - a major advantage. Fully automatic generated acoustic radiation force impulses induced by ultrasound beams perturb the underlying tissues, generating mechanical waves and shear waves, which propagate transversely into the tissue. Using SonicTouch™ technology, ultrasound beams are successively focused at different depths into tissues, all resulting shear waves interfering constructively along a "Mach cone", creating two quasi-plane shear Waves fronts propagating in opposite directions through the tissue. The shear waves generated using the SonicTouch™ excitation are captured by the ultrasound system. In order to capture shear waves in sufficient detail, frame rates of a few thousand of images per second are needed, 100 times faster than the frame rates offered by current state-of-the-art ultrasound technology. This ultrafast imaging mode acquires raw radiofrequency data at a very high frame rate, up to 5000 frames/s.

Shear waves' propagation induces small tissue displacements, which are recorded by the Ultrafast™ imaging system and measured using tissue Doppler techniques. 2D-SWE offers as major innovations, the ability to measure area and distance ratios, a high spatial resolution and real-time capabilities. Fully automated shear waves generation from the ultrasound transducer also allows user-skill independent and reproducible imaging.

2D-ShearWaves™ Elastography (2D-SWE) produces an image where true local tissue elasticity is displayed in a color map in "real time". Elasticity is displayed using a color coded image superimposed on a B-mode image. Stiffer tissues are

coded in red and softer tissues in blue, with an image resolution of approximately 1 mm. The true elasticity is assessed based on shear Waves propagation speed into the tissue. Thus the technique permits a quantitative mapping of liver tissue viscoelasticity [1].

The 2D-SWE method was used for the evaluation of breast nodules, of prostate elasticity, for the evaluation of muscle and tendon stiffness and for thyroid disease diagnosis. Preliminary results have shown the value of this method for liver stiffness (LS) estimation in patients with chronic hepatitis.

The technique has several advantages. The elasticity estimation is performed over a large area (10 cm^2) and probably reduces sampling errors; it also allows a mapping of local stiffness heterogeneities, thus allowing a precise location of hepatic lesions. Another interesting aspect of the supersonic share imaging technique relies on its ultrafast imaging characteristics, the high frame rates up to 5000 frames/s removing the influence of low-frequency displacement artifacts, such as respiratory motion or cardiac vibrations, which are error factors for the other elastographic techniques [1]. Thus the method is proven to be rapid, easy to perform, repeatable and reproducible [1].

On the other hand, the frequency bandwidth of the generated shear Waves is large, typically ranging from 60 to 600 Hz, different from transient elastography (FibroScan®) for example. By averaging shear Waves speed over a large bandwidth, supersonic share imaging seems to provide a more discriminator parameter for fibrosis evaluation [6] increasing the diagnosis accuracy.

The technique was first available on the ***Aixplorer® system*** (SuperSonic Imagine, France), integrated in an ultrasound system. The evaluation protocol requires placing the patient in supine position with the right arm in maximum abduction. The patient has to be fasted and the evaluation is recommended to be performed in normal breathing. The convex probe is placed in an intercostal space, using the best acoustic window available for liver evaluation. It is recommended to perform the acquisition on the right liver lobe and slow or no movement of the probe is preferable in order to avoid motion artifacts and to allow map stabilization. The 2D-SWE box has to be placed in vessel free parenchyma, in a uniform zone, not

CHAPTER 4

Real-Time Strain Elastography (HI-RTE)

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Abstract: Real-Time Strain Elastography performed by the Hitachi System (HI-RTE) uses a conventional ultrasound probe to compare and analyze echo signals before and under slight compression. Initially, HI-RTE offers only qualitative results. To overcome this limitation several quantitative methods in RTE have been developed, such as Elastic Ratio, Elastic Index, Elasticity Score and Liver Fibrosis Index (LFI). Despite being the first ultrasound-based elastography technique, HI-RTE has not yet yielded the desired results in the evaluation of liver fibrosis. This lack of performance is a consequence of inconsistency between the ultrasound-systems, methods and data analysis among different research teams. In the past few years, it seems that the technique has become more standardized and the elastographic assessment parameters are already established. The overall results of a meta-analysis suggested that LFI was excellent in diagnosing F≥3 and has moderate accuracy for F≥2 and F=4. However, LFI could not be applied to accurately differentiate F2 *versus* F0-1 and F=4 *versus* F0-3. HI-RTE is readily available with the ultrasound machine, is feasible in patients with ascites and inflammation and has promising results for non-invasive liver fibrosis evaluation in patients with chronic viral hepatitis and fatty liver diseases. In the future, a large, prospective, international multicenter study is essential to obtain a further evaluation of the potential diagnostic value of HI-RTE.

Keywords: Elasticity index, Liver stiffness, Real Time Elastography.

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As mentioned in the previous chapters, there is a current trend towards replacing liver biopsy with ultrasound-based elastography in the evaluation of liver fibrosis in chronic diffuse liver diseases. In all elastographic methods mechanical stress acted upon the liver induces a tissue displacement. Measuring tissue displacement offers an estimation of the elastic properties of the liver, which in turn allows a reliable assessment of liver fibrosis severity.

1. REAL-TIME STRAIN ELASTOGRAPHY TECHNIQUE

Real-Time Strain Elastography (RTE) is an add-on module that can be incorporated, similar to acoustic radiation force impulse (ARFI) technology, in standard ultrasound devices; this represents an advantage when compared with transient elastography (TE), for example, where a new unit must be purchased. On the other hand, both Real-Time Elastography and ARFI use conventional ultrasound transducers for the examination, allowing a direct visualization of liver parenchyma while performing a liver stiffness (LS) evaluation. Thus, the examiner is able to avoid the liver capsule, to adjust the transducer's position, and thus to obtain the best acoustic window, even in difficult patients, such as overweight ones. The method is also reliable and reproducible in patients with ascites [1].

Real-Time Strain Elastography was performed for the first time with Hitachi systems (EUB-8500 and EUB-900) [2]. It uses a conventional ultrasound probe to compare and analyze echo signals before and under slight compression [3]. To perform free-hand HI-RTE, usually with the patient in supine position, the transducer is placed in the intercostal space and the examiner must apply stress by moving the transducer [4]. The examination is usually performed in the right liver lobe. The Hitachi Real-Time Elastography (HI-RTE) module uses an extended combined autocorrelation method to produce a real-time elasticity image, by using a freehand approach and compressing the tissues with the ultrasound transducer. The relative tissue elasticity is calculated and displayed as a color overlay on the conventional B-mode image. Stiffer structures are displayed in blue, while the more easily deformed tissues are displayed in red.

Initially, HI-RTE offered only qualitative results. To overcome this limitation

several quantitative methods in RTE have been developed, such as **Elastic Ratio, Elastic Index, Elasticity Score and Liver Fibrosis Index (LFI).**

Despite being the first ultrasound-based elastography technique, HI-RTE has not yet yielded the desired results in the evaluation of liver fibrosis. This lack of performance is a consequence of inconsistency between the ultrasound-systems, methods and data analysis among different research teams. In the past few years, though, along with the development of the new HI-RTE systems (HI VISION Avius, Preirus, Ascendus systems - Hitachi Medical Systems Europe Holding AG), it seems that the technique has become more standardized and the elastographic assessment parameters are already established. The examination is performed using a linear probe (3.5-7 MHz), positioned in the intercostal space, without compressing, seeing that the device already uses the internal pressure generated by the heart beats on the liver parenchyma. In this fashion, the sampling errors produced by the examiner compression are avoided. A well trained examiner with sufficient experience is needed in order to keep clear of any artifacts related to obesity, ROI setting, avoidance of large vessels and costal shades, as well as adjustment of the probe position in order to obtain a reliable image of the liver parenchyma, where compression/relaxation is homogeneous and axial to the probe.

1. Feasibility and Reproducibility

Ultrasound examinations are operator-dependent techniques and different levels of training and experience could influence the results of the HI-RTE as well. A prospective study in which patients were examined by two doctors with different levels of experience in ultrasound obtained good intra- and inter-observer variability values [5]. The authors did not find significant differences between the two physicians, regardless of the patients' real status (cirrhosis, chronic hepatitis, steatosis, or healthy subjects). In a study published by Koizumi *et al.*, elastography was performed at four liver locations by two independent observers. The authors found no difference in reproducibility for the four measurement positions, while the interobserver agreement was very good (k=95%) [6].

CHAPTER 5

Combined Methods for Liver Fibrosis Evaluation

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Abstract: Biological tests, elastographic methods alone or in combination can be used for the non-invasive evaluation of chronic liver diseases, in order to increase their value.

Combinations of non-invasive tests were searched for in order to improve the diagnostic performance of significant fibrosis (F≥2) and severe fibrosis/cirrhosis (F3–F4) the most promising being *TE and serologic tests*. In chronic hepatitis C a clinical management algorithm was proposed, using the combination of TE (FibroScan®) and FibroTest as the first-line tests in the work-up strategy, thus avoiding liver biopsy in most patients (77%). In HBV inactive carriers, the combination of TE and FibroTest allowed the exclusion of significant fibrosis (F≥2) in nearly 80% of cases.

Another useful combination is of *two elastographic methods [TE and VTQ (ARFI)]*, which proved to be highly specific for predicting significant fibrosis (F≥2 Metavir). When both TE and VTQ (ARFI) values were higher than the proposed cut-offs, their combination had 93.3% Sp and 96.8% PPV for predicting F≥2, so that liver biopsy could be avoided in 60.5% of cases. For predicting cirrhosis (F4), the results were also very good, with 94.4% Sp, 94.4% NPV and 91.8% accuracy, so that the combination of TE and VTQ was able to confirm, and also to exclude the presence of liver cirrhosis.

Keywords: Combination methods, Elastography, Liver fibrosis, Serological tests.

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Since both serological tests and elastographic techniques are available for the non-invasive assessment of fibrosis severity in chronic liver diseases, many authors have tried to combine them to increase their diagnostic accuracy.

1. COMBINATION OF ELASTOGRAPHIC METHODS WITH SEROLOGICAL TESTS

FibroTest (a serological test that combines six biologic parameters) has been proved to be an accurate test to predict the presence of significant fibrosis (F≥2) as well as of severe fibrosis/cirrhosis (F3–F4) [1 - 3]. If TE and FibroTest results agreed (70 - 80% of cases), there was also a great similarity with liver biopsy results: 84% concordance in patients with significant fibrosis (F≥2); 95% concordance in patients with severe fibrosis (F≥3); and 94% concordance in cirrhotics (F=4).

Castera *et al.* evaluated the accuracy of two algorithms using non-invasive tests to predict liver fibrosis severity using liver biopsy (LB) as the gold standard: one including TE and FibroTest and the other including APRI and FibroTest (SAFE biopsy) [2]. The combination of TE and FibroTest saved 23% more liver biopsies than SAFE biopsy for predicting F≥2 Metavir (71.9% *vs.* 48.3%, $p<0.0001$), but its accuracy was significantly lower (87.7% *vs.* 97.0%, $p<0.0001$). The situation was reversed for predicting liver cirrhosis, where the accuracy of TE + FibroScan was significantly better than of SAFE biopsy (95.7% *vs.* 88.7% $p<0.0001$), while the number of saved biopsies was similar (78.8% *vs.* 74.8%; $p>0.05$).

Cross *et al.* performed a study that evaluated by TE and King score 187 patients with chronic hepatitis C, with LB considered as the reference method (Ishak score was used for staging liver fibrosis) [4]. The AUROCs for TE, King score and the combination of King score and TE for the diagnosis of significant fibrosis (F≥3 Ishak) were 0.83, 0.82 and 0.85, respectively, while for the diagnosis of cirrhosis (F≥5 Ishak) they were 0.96, 0.89 and 0.93, respectively. NPVs higher than 90% were obtained for the diagnosis of cirrhosis for the following cut-off values: 10 kPa for TE (NPV 98%); 24.3 for King score (NPV 91%); and 26.1 for the two combined (NPV 94%).

The combination of TE with FibroTest showed promising results in chronic

hepatitis C patients [5, 6] and also in HBV inactive carriers, in whom it allowed exclusion of at least significant fibrosis (F≥2) in approximately 80% of cases [7].

A number of 212 patients with chronic hepatitis C were evaluated in our department by means of LB, TE and serological tests (APRI score, Lok score, Forns score, FIB-4 score, Fibrosis Index score, King score, Bonacini score) [8]. The strongest correlation with liver fibrosis severity was observed for TE (r=0.62), King score (r=0.57) and APRI score (r=0.56). By multiple regression analysis, the following formula was obtained:

Prediction liver fibrosis score (PLF score) = 0.956 + 0.084 x TE – 0.004 x King score + 0.124 x Forns score + 0.202 x APRI score

The AUROCs of PLF score for predicting F≥1, F≥2, F≥3 and F=4 were 0.76, 0.78, 0.86, and 0.97 respectively. The PLF score had a better predictive value than TE for F≥2 Metavir (AUROCs 0.78 *vs.* 0.74, p=0.02); also for F≥3 Metavir (AUROCs 0.86 *vs.* 0.81, p=0.003), while for diagnosing cirrhosis the performance was similar (AUROCs 0.97 *vs.*0.97, p=0.28).

Liu *et al.* evaluated 111 subjects (95 with chronic hepatitis B and 16 healthy volunteers), by means of VTQ (ARFI), TE and APRI score [9]. Strong correlations were observed between fibrosis stage and ARFI (r=0.85, p <0.001), between fibrosis stage and TE (r=0.81, p <0.001) while only a moderate correlation was found between fibrosis stage and APRI (r=0.63, p <0.001). An optimal linear combination (LC) of the three methods was developed, and its diagnostic performance was evaluated by a 10-fold cross-validation:

LC: For F≥2: ARFI + 0.034 TE – 0.084 APRI

For F4: ARFI + 0.044 TE – 0.135 APRI

The calculated accuracies of LC for significant fibrosis (≥F2 Metavir) and cirrhosis (F4) were 83.86% and 91.88%, respectively, better than those of VTQ (ARFI) (83.50% and 88.76%, respectively); of TE (75.27% and 87.61%, respectively); and also than those of APRI score (73.29% and 81.67%, respectively) [9].

CHAPTER 6

Comparison of Elastographic Techniques

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Abstract: Several elastographic techniques for liver fibrosis assessment are available (on different machines) and practitioners are interested in comparing these techniques with regard to feasibility but also with regard to accuracy in staging fibrosis. Comparative studies including at least three methods are presented in this chapter. Regarding feasibility, the most feasible technique seems to be ElastPQ (approximately 99%), followed by VTQ (approximately 93%) and TE and 2D-SWE (approximately 87%). VTQ, ElastPQ and 2D-SWE had similar accuracies for diagnosing at least significant fibrosis (F≥2) and cirrhosis (F4) considering TE as the reference method.

Keywords: ARFI elastography, Comparative studies, Liver elastography, Transient elastography, 2D-SWE elastography.

At this moment, when many elastographic techniques for liver fibrosis assessment are available (on different machines), practitioners are interested in published data comparing these techniques not only with regard to feasibility but also with regard to accuracy when compared to liver biopsy. Not so many comparative studies have been published to date. We will present in this chapter studies comparing at least three elastographic techniques.

In a study performed in France, 349 consecutive patients with chronic liver diseases underwent liver biopsy and liver stiffness assessment by 2D-SWE (Aixplorer® - Supersonic Imagine), ARFI technology (VTQ - Siemens) and TE

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(FibroScan® - Echosens®) (M probe for patients with BMI < 30kg/m^2 and XL probe for patients with BMI > 30kg/m^2) [1]. AUROCs were calculated and compared for each stage of fibrosis. 2D-SWE, TE, and VTQ correlated significantly with histological fibrosis score (r=0.79, p<.00001; r=0.70, p<.00001; r=0.64, p<.00001, respectively). In this study, AUROCs of 2D-SWE, TE and VTQ were 0.89, 0.86, and 0.84 for mild fibrosis; 0.88, 0.84, and 0.81 for significant fibrosis (F≥2); 0.93, 0.87, and 0.89, for severe fibrosis (F≥3) and 0.93, 0.90, and 0.90 for the diagnosis of cirrhosis, respectively. 2D-SWE had a higher accuracy than FibroScan® for the diagnosis of severe fibrosis (≥F3) (p=0.0016), and a higher accuracy than VTQ for the diagnosis of significant fibrosis (≥F2) (p=0.0003). Finally, no significant differences were observed for the diagnosis of mild fibrosis and cirrhosis using the three elastographic methods.

For daily practice, feasibility of ultrasound based elastography is crucial, so as to be able to evaluate a vast majority of patients that enter an elastography laboratory. In a comparative study performed by our team [2] we aimed to compare the feasibility of four elastographic methods used for liver fibrosis evaluation (Transient Elastography - TE; point Shear Waves Elastography (pSWE) using ARFI technique - VTQ and ElastPQ techniques, respectively; and 2D-SWE).We included in our study 151 consecutive subjects with or without chronic hepatopathies (excluding patients with ascites), in which liver stiffness (LS) was evaluated in the same session by means of 4 elastographic methods: TE (FibroScan®, Echosens®®), VTQ (Siemens Acuson S2000™), ElastPQ (Philips, Affinity) and 2D-SWE (Aixplorer®, SuperSonic Imagine S.A). Reliable LS measurements were defined as follows: for TE and VTQ – the median value of 10 LS measurements with a success rate ≥ 60% and an interquartile range < 30%, for 2D-SWE – the median value of 3 LS measurements acquired in an homogenous area and for ElastPQ - the median value of 10 LS measurements. For TE, M and XL probes were used. LS was expressed in kPa for TE, 2D-SWE, ElastPQ and in m/s for VTQ. All elastographic measurements were performed by experienced operators. In this study, reliable LS measurements were obtained in a significantly higher proportion of patients by means of ElastPQ as compared with TE, 2D-SWE and VTQ: 99.3% *vs.* 87.4% (p<0.0001), 99.3% *vs.* 87.4% (p<0.0001) and 99.3% *vs.* 92.7% (p=0.08). TE and 2D-SWE had similar rates of reliable LS

measurements 87.4% *vs.* 87.4% (p=0.86). Reliable LS measurements by all four shear waves ultrasound elastographic methods were obtained only in 72.2% (109/151) subjects. For TE and VTQ we used technical quality criteria (IQR and SR), but for the other two methods (ElastPQ and 2D-SWE) no quality criteria were used since none were published.

In another comparative study performed by our group [3] we compared the performances of point Shear Waves Elastography using ARFI technique (VTQ and ElastPQ, respectively) and 2D-SWE (SuperSonic Shear Imaging) considering Transient Elastography (TE) as the reference method. We included in this study 151 consecutive subjects (with or without chronic hepatopathies, none with ascites), who were evaluated in the same session by means of 4 elastographic methods: TE (FibroScan®, Echosens®®), VTQ (Siemens, Acuson S2000™), ElastPQ (Philips, Affinity) and 2D-SWE (Aixplorer®, SuperSonic Imagine S.A). For differentiating between stages of liver fibrosis we used the following cut-off values: for TE - significant fibrosis (F≥2) – 7.2 kPa and for liver cirrhosis (F4) - 14.5kPa [4]; for VTQ: F≥2 – 1.35m/s, F4=1.84m/s [5]; for 2D-SWE: F≥2 – 7.1 kPa, and F4=13.5 kPa (HCV,NAFLD) and 11.5 kPa in HBV [6]; and for ElastPQ F≥2-5.9 kPa, F4=12kPa [7]. In this study, considering TE as the reference method, the diagnostic accuracy of VTQ, 2D-SWE and ElastPQ for the diagnosis of absence or mild fibrosis (F<2) was similar: VTQ *vs.* 2D-SWE (86.2% *vs.* 82.5% p=0.57); VTQ *vs.* ElastPQ (86.2% *vs.* 84.4% p=0.85), 2D-SWE *vs.* ElastPQ (82.5% vs. 84.4% p=0.84). For significant fibrosis (F≥2) the values obtained were: VTQ vs. 2D-SWE (84% vs. 76.1% p=0.19); VTQ vs. ElastPQ (84% vs. 80.7% p=0.64), 2D-SWE vs. ElastPQ (76.1% vs. 80.7% p=0.50). For diagnosing cirrhosis we also obtained similar diagnostic accuracies: VTQ *vs.* 2D-SWE (96.3% *vs.* 93.6% p=0.54); VTQ *vs.* ElastPQ (96.3% *vs.* 94.5% p=0.75), 2D-SWE *vs.* ElastPQ (93.6% *vs.* 94.5% p=0.99). In this study, similar to previously published papers, the accuracy of elastographic methods increased with the severity of fibrosis, producing the best results in patients with liver cirrhosis. Finally, the conclusion of this study was VTQ, ElastPQ and 2D-SWE had similar accuracies for diagnosing at least significant fibrosis (F≥2) and cirrhosis (F4).

In another comparative study performed by our group [8] we aimed to compare

CHAPTER 7

Elastography in Focal Liver Lesions

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Abstract: The accurate characterization and the differential diagnosis between different types of focal liver lesions (FLL) are important aims that all imaging modalities available today should satisfy. Elastographic methods aim to exploit the elasticity differences between FLL and liver parenchyma in order to make the differential diagnosis between malignant and benign lesions. Currently, three elastographic methods have been evaluated and showed their applicability in this area: Acoustic Radiation Force Impulse (ARFI) Elastography, Real-time Elastography (RT-E) and Shear Waves Elastography (SWE). Many studies have shown that using one of the elastographic methods, for a chosen cut-off, the differentiation between malignant and benign nodules is possible. Other studies demonstrated that elastographic techniques are helpful to detect recurring hepatocellular carcinomas (HCCs), or to evaluate HCC or liver metastases after local or systemic treatment.

Keywords: Benign or malignant, Elastography, Focal liver lesions.

A focal liver lesion (FLL) refers to an area of damaged tissue identified into the hepatic tissue, with varying significance, depending on the patient's health condition and a variety of other factors. The differential diagnosis of a FLL can be narrowed down by several factors, including age, gender, use of birth control pills or hormone medications, travel history and the presence of cirrhosis, hepatitis or other chronic liver diseases. In many cases, FLLs are detected incidentally, during a routine abdominal ultrasound examination.

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FLLs are classified as ***benign*** or ***malignant***.

Benign (noncancerous) FLLs can be *solid* or *cystic* (meaning that the lesions are fluid filled). Within these types, the subtypes include hemangiomas (the most common), focal nodular hyperplasia (FNH), hepatic adenoma, focal fatty changes, and hydatid cysts and bile duct cysts.

Malignant liver tumors can be *primary* liver cancers or *secondary* liver lesions (metastases).

The most common *primary* malignant liver tumor is hepatocellular carcinoma (HCC) and the second most common type of liver malignancy is cholangio-carcinoma. Other rare liver cancers are: angiosarcomas and hepatoblastomas.

The liver is one of the most often affected organs in advanced cancers and most types of malignant tumors may spread into the liver in the late stages. The most common *secondary* liver tumor is colon cancer metastasis, but other cancers (such as pancreatic, gastric, thyroid, skin and kidney cancer) often spread into the liver.

The accurate characterization and the differential diagnosis between different types of FLLs are important aims, that all imaging modalities available today should satisfy [1].

Conventional ultrasonography (US) is often the first imaging modality performed to screen for, or to study hepatic lesions because of its low cost and wide availability. Color-Doppler, Tissue Harmonic Imaging and more recently, microbubble contrast agents (Contrast Enhanced Ultrasound-CEUS), have significantly improved the characterization of solid FLL. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are second line imaging methods able to accurately characterize previously detected lesions, but they are more expensive and less available. Contrast enhanced imaging modalities, such as contrast-enhanced US, contrast enhanced-CT and contrast-MRI, assess lesion morphology and vascularization, with a high diagnostic accuracy owing to their specific features, well described in the literature. Nevertheless, invasive studies are sometimes required to make a definite diagnosis [1].

Neoplastic and inflammatory diseases can change the tissue's

composition/structure, and thus parenchyma stiffness of an organ. Elastography aims to assess these elasticity differences in order to be able to identify malignant transformation [2].

Many elastographic methods have tried to assess liver tumors' stiffness.

1. POINT SWE USING ACOUSTIC RADIATION FORCE IMPULSE (ARFI) TECHNOLOGY

Point SWE using Acoustic Radiation Force Impulse (ARFI) technology is an elastomeric technique incorporated into a conventional ultrasound (US) system, which permits real-time non-invasive quantification of tissue elasticity during US B-mode examination.

In order to evaluate such a lesion by VTQ (ARFI) technology, the FLL has to be visualized in abdominal US. After that the measurement box is placed in the lesion (Fig. **1**) and VTQ (ARFI) measurements are performed (median value of 10 acquisitions expressed in m/s). VTQ (ARFI) measurements should also be performed in the surrounding tissue.

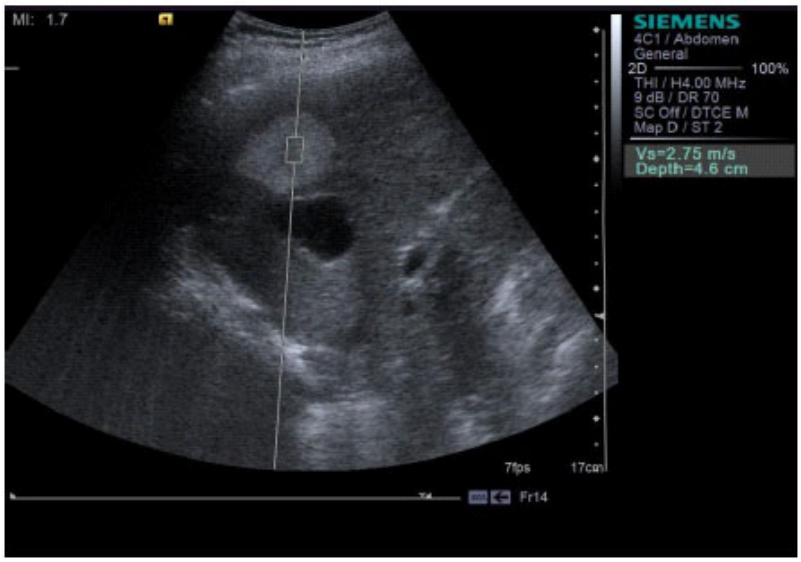

Fig. (1). VTQ (ARFI) measurement in hemangioma.

CHAPTER 8

Guidelines on Liver Elastography

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Abstract: Scientific papers regarding ultrasound based elastographic techniques have been published in great numbers since new elastographic methods are constantly appearing in the market. Thus it is mandatory that professional societies and experts in the field should try to organize the available data in order to assess the clinical usefulness of elastography. In this regard, guidelines were issued by national and international ultrasound societies, as well as by other professional societies. These guidelines are presented in this chapter.

Keywords: EASL guidelines, EFSUMB guidelines, Liver elastography, WFUMB guidelines.

Liver elastography became more and more a clinical procedure. Transient Elastography (TE) was the first method recommended by national or international guidelines (EASL) as an alternative to LB, but the development of other elastographic methods (point or 2D SWE) made guidelines mandatory in order to clarify the value and limits of any elastographic method.

The European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) prepared the first guidelines on ultrasound based elastography, as a proof of this technique's development in Europe. They were elaborated by a group of experts from European countries, based on the most relevant scientific papers

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and on their own experience in this field. These guidelines were divided into two parts, the first covering the basics of elastography (physics and technology) [1] and the second one describing the clinical applications of elastography in some organs [2].

In the first part, the authors classified the ultrasound based elastographic methods into strain elastography and shear waves elastography (SWE). From a practical point of view, strain elastography is used especially for nodules (breast or thyroid) assessment, while SWE for the evaluation of the liver. SWE was further divided into Transient Elastography (TE), point SWE using Acoustic Radiation Force Impulse (ARFI) technology and 2D SWE (or Real Time elastography). This very clear classification of ultrasound based elastographic techniques has attempted to ease the clinicians' approach to a very technical domain.

In the clinical part of EFSUMB guidelines, the authors presented the usefulness of elastography in fields where scientific proof is strong enough to recommend its use in the clinical workflow. According to these guidelines, elastography can be used for the evaluation of the liver, breast, thyroid, lymph nodes, pancreas (by endoscopic ultrasound - EUS), bowel, musculoskeletal. But it must be mentioned that the body of evidence has not the same strength for all the organs presented in the guidelines. Liver and breast are the fields where elastography plays a crucial role in the diagnostic workflow and where this technology is implemented in daily practice.

The EFSUMB guidelines present data available on elastography up to 2012, when they were published. Many papers have been made available regarding TE, but only a few regarding ARFI assessment of the liver, mainly in diffuse liver diseases. The body of evidence was not strong enough to recommend elastographic techniques for focal liver lesions (FLL) assessment. This observation is also valid for the guidelines that appeared later.

Because new data on liver elastography became available at a high rate, national societies made their own guidelines for practitioners, in a field where new technologies and new ultrasound machines constantly arrive in the market. The Japanese Society of Ultrasound issued the first national guidelines on liver

elastography [3]. In these guidelines the authors present data available regarding strain elastography and SWE, giving practical advice and tips for the clinical use of liver elastography. Strain elastography for diffuse liver diseases is presented first, since this is a field where Japanese authors were the pioneers who proved this method's value for liver fibrosis assessment, using the liver fibrosis index (LFI) [4, 5]. The Japanese guidelines also cover SWE, presenting results of Virtual Touch Quantification (VTQ), ElastPQ or 2D SWE, taking into consideration the type of ultrasound machine that was used. Many of the studies included in these guidelines were published by Asian or Japanese groups, so that these recommendations seem to be valid mostly in Asian patients.

The Romanian guidelines and recommendations were published in 2014 [6]. They were the first national European guidelines that tried to combine the large national experience with published papers on this topic from around the world. They also cover only the liver and were written by practitioners with large personal experience in different types of liver elastography. At the end of these guidelines, the authors make practical recommendations regarding the practical approach to liver elastography and its value in clinical practice.

In 2015, the World Federation on Ultrasound in Medicine and Biology (WFUMB) published its own guidelines on ultrasound based elastography. These guidelines were divided into three parts, covering elastography basics [7], as well as clinical application of elastography in the liver [8] and breast [9]. In the part covering the liver, the authors included significant papers published in this field and finally made recommendations regarding the clinical use of different elastographic techniques.

All the guidelines presented above were issued by societies of ultrasound. At the same time, another professional society - the European Society for the Study of the Liver (EASL) issued its own guidelines considering inside information regarding the value of liver elastography using ultrasound waves. In the guidelines concerning the non-invasive tests used for evaluation of liver disease severity, a panel of experts made practical recommendations on the use of biological tests and elastographic methods, summarizing their main advantages and disadvantages (Table **1**) [10].

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