Original papers

Med Ultrason 2013, *Vol. 15, no. 4, 268-272*
DOI:

How many measurements are needed for liver stiffness assessment by 2D-Shear Wave Elastography (2D-SWE) and which value should be used: the mean or median?

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Abstract

Aim: To analyze how many measurements are needed for non-invasive assessment of liver stiffness (LS) by means of 2D-Shear Wave Elastography (2D-SWE) and if the use of mean of median values of 2D-SWE measurements is needed. **Methods:** We evaluated 449 consecutive subjects (with or without chronic liver disease) by means of Transient Elastography (TE) and 2D-SWE. We compared the correlation of LS assessed by TE with 2D-SWE measurements when using either the median of 5 valid 2D-SWE measurements or the mean of 3 or 5 valid 2D-SWE measurements. **Results:** We obtained reliable LS measurements by TE in 330/449 subjects (73.5%). From these, in 281 subjects we obtained 5 valid 2D-SWE measurements. The correlation of LS assessed by TE with 2D-SWE values was similar when we used the median value of 5 valid 2D-SWE measurements, the mean value of 5 valid 2D-SWE measurements or the mean value of 3 valid 2D-SWE measurements: r =0.683, r=0.711 and r=0.691, respectively. There were no significant differences between the median value of 5 valid 2D-SWE measurements; the mean value of 5 valid 2D-SWE measurements; or the mean value of 3 valid 2D-SWE measurements: 7.6 kPa, 7.7 kPa and 7.6 kPa, respectively. **Conclusions:** Our study showed that it is enough to perform 3 valid 2D-SWE measurements and to use the mean value of these measurements.

Keywords: liver stiffness, Shear Wave Elastography, Transient Elastography

Introduction

Chronic liver diseases encountered in daily practice are due to chronic viral infections or to other conditions, such as alcoholic steato-hepatitis (ASH) or non-alcoholic fatty liver disease (NAFLD). The evaluation of chronic liver disease's severity is mandatory, for a decision regarding therapy or to establish prognosis. For many years, liver biopsy (LB) was the only method to evaluate such patients and it is still considered the "gold-standard" method [1,2]. In the last years non-invasive modalities for liver diseases' assessment are being used more and more in daily practice, especially in Europe.

The non-invasive evaluation of the liver disease can be performed either by biological tests or by elastographic methods. From the elastographic methods, those which use ultrasound waves are more developed. Recently, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued Guidelines for the use of ultrasound-based elastographic methods for the evaluation of different organs and pathologies, including liver stiffness (LS) evaluation as a marker of fibrosis. According to these Guidelines [3,4], the elastographic methods are divided into strain/displacement techniques and shear wave speed techniques. The last category includes Transient Elastography (TE), point shear wave elastography (Acoustic Radiation Force Impulse elastography – ARFI and ElastPQ tech-

Received 04.09.2013 Accepted 06.10.2013
Med Ultrason
2013, Vol. 15, No 4, 268-272
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nique), and shear wave elastography (SWE) imaging (including 2D-SWE and 3D-SWE).

Currently, the only validated ultrasound-based elastographic technique is TE [2,4,5]. Recently, a meta-analysis showed that ARFI elastography has a similar value with TE for non-invasive liver fibrosis assessment [6]. Regarding the usefulness of 2D-SWE, until now only relatively few, but promising data were published [7-12].

Unlike TE, for which the manufacturer recommended that 10 valid liver stiffness (LS) measurements should be performed and to calculate the median of these values, the manufacturer of the 2D-SWE device did not recommend a specific protocol for LS measurements. Published studies used different numbers of measurements; in some the median, and in others the mean value of LS measurements was considered as an indicator of fibrosis [7-12].

The aim of this study was to analyze how many LS measurements are required for non-invasive assessment of liver fibrosis by means of 2D-SWE and if we need to use the mean or the median value of the 2D-SWE measurements.

Material and methods

Subjects

Our prospective study included 449 consecutive subjects (with or without chronic liver disease) in which liver stiffness was evaluated in the same session by means of TE and 2D-SWE between May 2012 and April 2013. We included in our study: healthy volunteers (defined as subjects without a history of liver disease, with a normal abdominal ultrasound examination, but in which additional tests, such as aminotransferases, viral markers were not performed), patients with viral or non-viral chronic liver disease without cirrhosis, and patients previously diagnosed with liver cirrhosis by means of clinical, biologic, ultrasonographic, endoscopic, morphological and/or laparoscopic criteria.

All subjects agreed to undergo elastographic measurements; the study was approved by the local Ethics Committee and was performed in accordance with the last revised version of the Helsinki Declaration.

Transient Elastography (TE)

Transient Elastography was performed in all subjects with a FibroScan® device (EchoSens, Paris, France) in fasting condition. In each patient, we aimed for 10 valid TE measurements. The examination was performed in supine position, by intercostal approach, with the right arm in maximum abduction, using a standard M-probe; a median value of 10 valid LS measurements was calculated and the results were expressed in kilopascals (kPa). Reliable measurements were defined as: median value of 10 valid LS measurements with a success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) ≥ 60% and an interquartile range interval (IQR=the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) <30% [13]. The operators who performed TE measurements were blinded to all clinical, biological and 2D-SWE data.

2D –Shear Wave Elastography (2D-SWE)

The evaluation of LS by 2D–SWE was performed with an Aixplorer® ultrasound system (SuperSonic Imagine S.A., Aix-en-Provence, France), using a SC6-1 convex probe. By this technique a quantitative elasticity map of the medium was obtained. This map is required to image the propagation of the shear-wave and to measure its velocity. Because the shear waves generated into the tissue by the acoustic pulse propagate at a few meters per second, a frame rate of several kilohertz is needed to image them. This is not possible using conventional ultrasound scanners (they usually reach a frame rate of approximately 50 Hz). For this reason, an ultrafast, ultrasonic scanner is required, able to remotely generate the mechanical shear wave, by focusing ultrasound at a given location, and image the medium during the wave propagation at a very high-frame rate (up to 6000 images/s). 2D-SWE technique allows the acquisition of echographic images at a pulse repetition that can reach 6000 Hz. The results of LS measurement may be displayed in units of shear wave velocity (meters/second) or converted into units of Young's modulus (kPa), similar with TE [3,14].

In this study, we aimed to achieve in each patient 5 valid LS measurements by 2D-SWE. The examination was performed in fasting condition in supine position, with the right arm in maximum abduction, by intercostal approach, in the right liver lobe, 1.5-2 cm under the liver capsule, in an area of parenchyma free of large vessels, using a box of 3.5 x 2.5 cm in which a 1.5 cm diameter circular region of interest was selected (fig 1). We con-

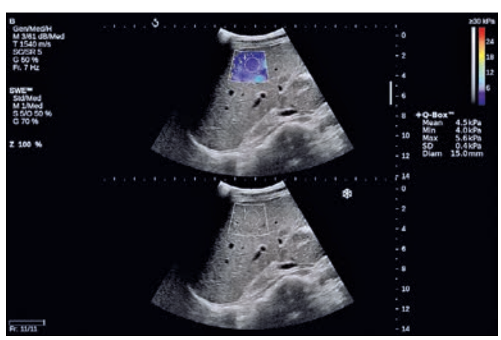

Fig 1. Liver stiffness measurement by means of 2D-SWE technique

Table I. Main characteristics of the subjects.

Parameter	
Age (years)	54 (18-82)
Gender: -male -female	n=215 (47.8%) n=234 (52.2%)
Body mass index (kg/m2)	26.5 ± 5.3
Diagnosis:	
- healthy volunteers	n=56 (12.5%)
- chronic hepatitis B	n=89 (19.8%)
- chronic hepatitis C	n=119 (26.5%)
- coinfection (B+C or B+D)	n=6 (1.3%)
- chronic non-viral hepatitis (most of them NAFLD)	n=124 (27.6%)
- cirrhosis	n=55 (12.3%)

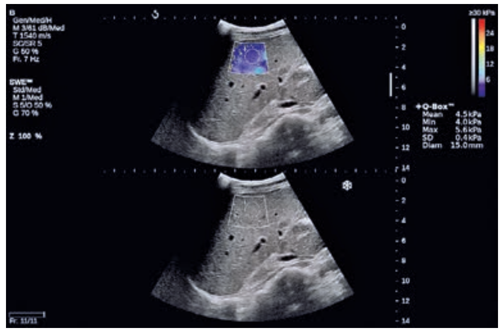

Fig 2. Comparison between LS values by means of 2D-SWE according to the number of measurements performed

sidered a valid 2D-SWE measurement the situation when a homogeneous color map in the box of 3.5 x 2.5 cm was obtained. For each subject we calculated the mean of 3 and 5 valid LS measurements and also the median of 5 valid measurements. We did not use 2D-SWE quality measurements criteria because neither the manufacturer nor other published studies recommend their usage.

The operators who performed 2D-SWE measurements were blinded to all clinical, biological and TE data.

Statistical analysis

The statistical analysis was performed using the MedCalc Software, version 12.7.0 (MedCalc program, Belgium). The Kolmogorov-Smirnov test was used for testing the distribution of numerical variables. Mean value and standard deviation were calculated for numerical variables with normal distribution, while in cases of non-normal distribution, median values and range intervals were used. Qualitative variables were presented as numbers and percentages. For comparing numerical variables with normal distribution, t-test was used; otherwise Mann-Whitney test was performed. Spearman r correlation coefficient was used to assess the correlation between LS measurement and 2D-SWE values. Fisher Z test was used for comparing Spearman r correlation coefficients. For each statistical test 95% confidence intervals were calculated and a p-value < 0.05 was considered as significant for each statistical test.

Results

The main characteristics of the 449 subjects included in the study are presented in Table I.

Reliable LS measurements by TE were obtained in 330/449 subjects (73.5%). From these subjects, in 281 cases we obtained 5 valid 2D-SWE measurements and these subjects were included in the final analysis.

The correlation of LS assessed by TE with 2D-SWE values was similar when we used the median value of 5 valid 2D-SWE measurements, the mean value of 5 valid 2D-SWE measurements or the mean value of 3 valid 2D-SWE measurements (Table II).

There were no significant differences between the median value of 5 valid 2D-SWE measurements; the mean value of 5 valid 2D-SWE measurements; or the mean value of 3 valid 2D-SWE measurements: 7.6 kPa (range 3.8 - 91.6 kPa), 7.7 kPa (range 3.8 - 87.6 kPa) and 7.6 kPa (range 3.7 - 82.4 kPa), respectively (fig 2).

Discussion

In order to be able to use an elastographic technique in daily clinical practice and to compare the results of different studies, it is very important to have a homogeneous examination technique. The technique of LS assessment by 2D-SWE is quite different among published

Table II. The correlation between LS values by means of TE and 2D-SWE

	Median of 5 valid 2D-SWE measurements*	**Mean of 5 valid 2D-SWE measurements≠**	**Mean of 3 valid 2D-SWE measurements¤**	**p value**
Correlation TE-2D- SWE	r=0.683, p<0.0001	r=0.711, p<0.0001	r=0.691, p<0.0001	*≠: p=0.64 *¤: p=0.61 ≠¤: p=0.63

studies [7-12]. Our present study is the first to analyze the number of LS measurements required for an accurate liver fibrosis assessment by means of this technique. Also, we analyzed if the mean or median value of 2D-SWE LS measurements should be used in clinical practice.

The manufacturer recommended a clear protocol for LS measurements only for TE. For ARFI elastography, published studies used 5 [15] or 6 measurements [16]; 10 valid measurements were performed in most studies [17-19]; 12 LS measurements [20] or 20 measurements [21] were also used; but today there is a consensus to use the median value of 10 valid LS measurements, similar with TE.

Regarding 2D-SWE, published studies used three [12], four [8] or five [7,10,11] valid measurements. Also, in some studies the mean value of LS measurements was used [8,12], while in others the median value of 2D-SWE measurements was calculated [10]. The results of our present study showed similar correlations of LS values evaluated by means of TE and 2D-SWE, regardless if mean or median values of 5 valid 2D-SWE measurements were calculated and also if the mean value of 3 LS measurements was used. Thus we can recommend the use of the mean value of 3 valid 2D-SWE measurements in clinical practice, thus shortening the time required to evaluate a patient.

The necessity to use quality criteria for LS measurements by means of 2D-SWE technique is another issue. Some published 2D-SWE studies used measurements quality criteria [10,11], while others did not use any quality parameters [7,8,12]. Similar with the number of LS measurements, only the manufacturer of the TE device clearly specified the quality criteria parameters (IQR <30% and SR ≥ 60%) needed for an accurate assessment, but recently new TE quality criteria were proposed [22]. Published studies in the field of ARFI elastography demonstrated that the accuracy of this technique for the non-invasive assessment of liver fibrosis increase significantly by using quality criteria measurements (especially IQR) [23,24] and subsequently the manufacturer updated the software so that these parameters are automatically displayed. Large 2D-SWE studies using LB as "gold-standard" method are required in order to evaluate the usefulness of technical parameters for this technique.

The strong point of our study is the large number of subjects evaluated, but a limitation is the absence of LB. Lately, many papers no longer use LB as a reference method for liver fibrosis assessment. Instead, an elastographic method - such as TE, or serological tests [7] are used. In a fast moving scientific world, the time needed to perform studies comparing new elastographic methods to LB is usually too long (due to the decreasing number of LBs). Thus, a surrogate can be the comparison with TE, which is a validated ultrasound-based elastographic technique [2,4,5].

Conclusions

Our study demonstrated that it is enough to perform 3 valid 2D-SWE measurements and to use the mean value of these measurements for the non-invasive assessment of liver fibrosis by means of this elastographic technique.

Conflict of interest: none

References

1. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology. 2009; 49: 1017-1044.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011; 55: 245-264.
3. Bamber J, Cosgrove D, Dietrich C.F, et al. EFSUMB Guidelines and recommendations on the clinical use of ultrasound elastography.Part 1: Basic principles and technology. Ultraschall Med. 2013; 34: 169-184.
4. Cosgrove D, Piscaglia F, Bamber J, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall Med. 2013; 34: 238-253.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-185.
6. Bota S, Herkner H, Sporea I, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int. 2013; 33: 1138-1147.
7. Bavu E, Gennisson JL, Couade M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. Ultrasound Med Biol 2011; 37: 1361–1373.
8. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C; Liver Fibrosis Study Group. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012; 56: 2125-2133.
9. Poynard T, Munteanu M, Luckina E, et al. Liver fibrosis evaluation using real-time shear wave elastography: applicability and diagnostic performance using methods without a gold standard. J Hepatol 2013; 58: 928-935.
10. Sporea I, Bota S, Jurchis A, et al. Acoustic radiation force impulse and supersonic shear imaging versus transient elastography for liver fibrosis assessment. Ultrasound Med Biol 2013; 39: 1933-1941.
11. Yoon JH, Lee JM, Woo HS, et al. Staging of hepatic fibrosis: comparison of magnetic resonance elastography and

shear wave elastography in the same individuals. Korean J Radiol 2013; 14: 202-212.
12. Leung VY, Shen J, Wong VW, et al. Quantitative Elastography of Liver Fibrosis and Spleen Stiffness in Chronic Hepatitis B Carriers: Comparison of Shear-Wave Elastography and Transient Elastography with Liver Biopsy Correlation. Radiology 2013 Aug 2. [Epub ahead of print]
13. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010; 51: 828-835.
14. Bercoff J, Tanter M, Muller M, Fink M. The role of viscosity in the impulse diffraction field of elastic waves induced by the acoustic radiation force. IEEE Trans Ultrason Ferroelectr Freq Control 2004; 51: 1523-1536.
15. Sporea I, Sirli RL, Deleanu A, et al. Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. Ultraschall Med 2011; 32 (Suppl 1): S46-S52.
16. Piscaglia F, Salvatore V, Di Donato R, et al. Accuracy of VirtualTouch Acoustic Radiation Force Impulse (ARFI) imaging for the diagnosis of cirrhosis during liver ultrasonography. Ultraschall Med 2011; 32: 167-175.
17. Friedrich-Rust M, Wunder K, Kriener S, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 2009; 252: 595-604.
18. Ebinuma H, Saito H, Komuta M, et al. Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan(®). J Gastroenterol 2011; 46: 1238-1248.
19. Sporea I, Șirli R, Popescu A, et al. Is it better to use two elastographic methods for liver fibrosis assessment? World J Gastroenterol 2011; 17: 3824-3829.
20. Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. World J Gastroenterol 2009; 15: 5525-5532.
21. Rizzo L, Calvaruso V, Cacopardo B, et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol 2011; 106: 2112-2120.
22. Boursier J, Zarski JP, de Ledinghen V, et al; Multicentric Group from ANRS/HC/EP23 FIBROSTAR Studies. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013; 57: 1182-1191.
23. Bota S, Sporea I, Sirli R, Popescu A, Dănilă M, Sendroiu M. Factors that influence the correlation of acoustic radiation force impulse (ARFI), elastography with liver fibrosis. Med Ultrason 2011; 13: 135-140.
24. Bota S, Sporea I, Sirli R, Popescu A, Jurchis A. Factors which influence the accuracy of acoustic radiation force impulse (ARFI) elastography for the diagnosis of liver fibrosis in patients with chronic hepatitis C. Ultrasound Med Biol 2013; 39: 407-412.