Acoustic radiation force impulse quantification: repeatability of measurements in selected liver segments and influence of age, body mass index and liver capsule-to-box distance

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Objective: To assess the inter- and intra-observer variability of acoustic radiation force impulse (ARFI) quantification in liver segments with influence of age, body mass index (BMI) and liver capsule-to-box (CB) distance.
Methods: 10 healthy volunteers were examined twice, by three experienced operators, separated by a 1-week interval. 10 readings were obtained, from segments 3, 5/6 and 7/8. Age, BMI and the CB distance were noted. The Cronbach α statistic for analysis of reliability was performed for the inter- and intra-observer studies. Multivariate linear regression models determined significance of the other parameters.
Results: 1800 velocity measurements were recorded. Mean values $\pm$ standard deviation: segment 3, 1.31 ± 0.19 m s^{-1}; segment 5/6, 1.12 ± 0.22 m s^{-1}; segment 7/8, 1.12 ± 0.17 m s^{-1}. For both the inter- and intra-observer study, the Cronbach α statistic was $\geq$0.7 (reliable) when taken from segments 5/6 and 7/8 but $<$0.7 (unreliable) for segment 3. BMI and age showed significant ($p<0.0001$) but contrasting correlation (segment 5/6: BMI $r=0.02$, age $r=-0.02$; segment 7/8: BMI $r=-0.01$, age $r=0.01$) with ARFI velocities when analysed for the segments deemed reliable. A weak negative correlation between ARFI velocities and liver CB distance was demonstrated for both assessed segments (segment 5/6, $r=-0.08$; segment 7/8, $r=-0.06$; $p<0.001$).
Conclusion: With trained operators, ARFI is a reliable and reproducible method of liver stiffness quantification in segments 5/6 and 7/8 but acquisition of measurements from segment 3 should be avoided. Values obtained deeper to the liver capsule allow more reliable liver stiffness quantification.

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In patients with chronic liver disease, precise staging of fibrosis not only is necessary for the estimation of prognosis but also is an important parameter when determining appropriate treatment decisions [1]. Liver biopsy to obtain histology is the currently accepted method of choice for the majority of aetiologies in evaluating the degree of liver fibrosis. A liver biopsy, however, is an invasive procedure and is associated with recognised risks, limitations and monetary costs, both direct and indirect. Potential adverse effects range from patient discomfort to more serious complications such as haemoperitoneum, biliary peritonitis and death [2, 3]. In addition, sampling errors and observer variation can affect histological grading and staging [4, 5]. Recognition of these constraints has led to a search for a safe, inexpensive and reliable non-invasive method to evaluate patients with chronic liver disease. The ideal surrogate to the biopsy should not only allow an accurate initial quantitative assessment of the stage of fibrosis but also have a role in disease monitoring and determine the efficacy of any prescribed treatment regimes.

Acoustic radiation force impulse (ARFI; Virtual Touch™ tissue quantification; Siemens, Mountain View, CA) is a sonographic technique that determines the local mechanical properties of tissue. During a standard B-mode sonographic examination of the liver, a standardised region of interest (ROI) box is positioned in a predetermined anatomical site within the liver parenchyma for evaluation. Short-duration acoustic pulses are subsequently generated in the vicinity of the designated ROI, with each pulse lasting less than 1 ms. The corresponding localised mechanical excitation of tissue results in tissue displacement and the formation of a shear wave away from the site of excitation. The velocity of the wave propagation, expressed in metres per second, is calculated and allows assessment of the viscoelastic properties of the tissue. The more elastic the tissue, the greater degree of displacement it undergoes [6]. In a practical sense, this allows a quantitative assessment in patients with chronic liver disease, as the shear wave propagation velocity is proportional to the square root of tissue elasticity; therefore, the stiffer the liver, the higher the recorded shear wave velocity [7]. A single transducer is used to generate

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the radiation force and track the subsequent displacement. The equipment will then calculate and display the shear wave velocity and the depth (from the skin surface) at which the reading was attained (Figure 1).

The potential applications of ARFI technology have been explored in many areas, including the liver, pancreas, kidney, heart, vascular structures and the nervous system [8–13]. Several studies have published promising preliminary results on the accuracy of the technique when assessing liver fibrosis [14–16]. The aim of our study was to ascertain the reproducibility of the technique in assessing liver stiffness in normal volunteers. In addition, we ascertained the influence that age, body mass index (BMI) and capsule-to-box (CB) distance have on measurements. To our knowledge, the merit of using specific liver segments has not been studied, nor has intra-observer and interobserver agreement been assessed within a three-operator format.

Methods and materials

The study was approved by the local ethics committee, with individual subjects giving informed consent for participation.

Study observers and subjects

10 healthy volunteers were recruited (mean age 31 years, range 27–40; 5 males, 5 females). All the participants had responded to a study recruitment notice posted within our institution, signed a written informed consent and completed a health questionnaire prior to the commencement of the prospective study. The subjects confirmed that they had no concomitant medical conditions (liver, heart, pulmonary); had not undergone any previous investigation for liver disease; and had not been subject to an abnormal biochemical liver function test result within the preceding 5 years. None of the subjects was on regular medication, nor had they taken any illicit drug or alcohol within 24 h prior to imaging. All the female patients confirmed that they were not pregnant at the time of scanning. All subjects were examined in the morning following an overnight fast. An initial conventional B-mode sonographic examination of all the subjects was performed, confirming no general or focal liver abnormalities, allowing participation in the study.

All subjects were examined independently by three trained radiologists familiar with the ultrasound equipment used in the study and competent in the ARFI imaging technique.

The subjects were randomly divided into two groups of five and each group was examined twice, on separate occasions; the second time each group was examined was 1 week after the first session. The division into two groups was undertaken so that the observers were not examining more than five subjects at each session, reducing observer fatigue and potential error. Each subject was assessed by the three operators consecutively but independently, with the observers blinded to the results obtained by the other observers performing the study. The results displayed on the ultrasound monitor were blinded to the observers, with an independent person confirming that each reading taken was a ''valid'' measurement. When the subjects were re-examined after a 1-week interval, the observers were prohibited from attaining the prior readings. Only when all the measurements had been taken were the data collected from the stored hard copy and analysed. Data were initially recorded on the hard drive of the ultrasound machine and then transferred to a picture archiving and communication system (GE Healthcare, Barrington, IL) for subsequent review.

Sonographic imaging

B-mode standard ultrasonography and quantitative ARFI measurements were carried out using an Acuson^{TM} S2000 (Siemens, Mountain View, CA), equipped with a 4C1 transducer. Tissue stiffness analysis was performed using the Virtual Touch quantitative imaging application. This calculates a numerical measurement (shear wave velocity), in metres per second for the selected ROI tissue, using a standardised ROI box (fixed dimensions of 1×0.6 cm). All subjects were examined in the conventional supine position, with oblique views obtained as needed, and breath-hold (immediate suspension of respiration followed by quick acquisition) when required.

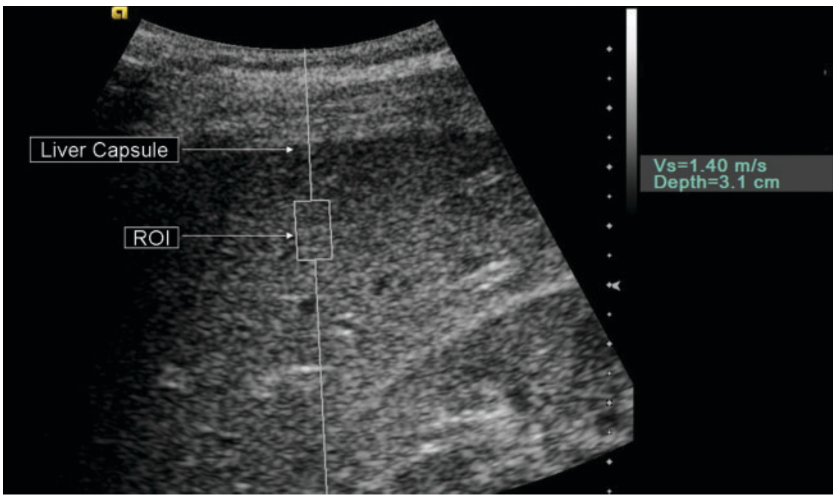

Figure 1. The position of the sampling box [region of interest (ROI)] is placed distant to the liver capsule within the liver parenchyma, and the shear wave velocity is measured and displayed on the image.

Each subject was scanned by all three operators in three specific liver anatomical sites, namely segments 3, 5/6 and 7/8, according to the standard accepted Couinaud classification of segmental liver anatomy. A total of 10 consecutive readings were obtained from each region (as per the manufacturer's recommendations); none of the measurements was taken within the vicinity of any visible vascular or biliary structures, targeting solely the liver parenchyma. When no valid measurement could be acquired, the software would return ''XX.XX'' on the screen. The independent observer would inform the operator and the measurement was repeated until the designated 10 readings acquired were all numerically quantifiable.

When in the Virtual Touch tissue quantification mode, the subjects were required to momentarily suspend respiration, at which point the ''update'' key was activated and a tissue quantification measurement acquired. All operators were required to be vigilant and not to apply any external transducer skin pressure while scanning. The operators were free to determine the precise location of assessment within each segment and the depth at which the readings were performed (up to the maximum evaluable depth from the skin surface of 8 cm). Segment 3 measurements were performed in the subcostal plane, whereas segments 5/6 and 7/8 measurements were taken from an intercostal position. In total, all three operators acquired 30 measurements per subject in each sitting. All measurements taken by each operator were recorded and the median shear wave velocity derived from the 10 readings for each analysed segment was determined.

Physical examination

Body weight (kg) and height (m) were obtained for all subjects in order to establish the BMI: weight divided by the square of the height (kg m^{-2}). A note of each subject's age was made.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences® for Windows v. 18.0.0 (IBM, Armonk, NY). For the ARFI imaging measurements of the individual segments attained by all operators, the differences in the median values were analysed. As the ARFI imaging values were not normally distributed, the Cronbach α statistic for analysis of reliability was performed for both the inter- and intra-observer studies. Segments 3, 5/6 and 7/8 were assessed independently for the inter- and intra-observer study. For the purposes of the study, values $\geq$0.7 were taken to confer internal consistency and hence reliability. Multivariate linear regression was used to determine the association between the shear wave velocities and the parameters of BMI, age and CB distance for each designated region.

Results

A total of 1800 measurements were obtained. The overall median, minimum and maximum values and range of shear wave velocity measurements for each designated segment are summarised in Table 1. The results are given for each individual operator and are divided into the two-session format used for the study. Table 2 details the mean depth and CB distances.

The results of the Cronbach α statistic to measure reliability are documented in Table 3. When assessing the interobserver agreement, the Cronbach α statistic was $\geq$0.7 when taken from segments 5/6 and 7/8 but <0.7 for segment 3. This was found to be the case for both sessions. On assessment of the intra-observer reliability, all operators again show similar results, with measurements taken from segments 5/6 and 7/8 found to be >0.7, but not for segment 3.

The mean age of the subjects was 31$\pm$3.9 years, with a mean BMI of 23.6$\pm$4.0. 5 (50%) of the subjects had BMI readings >25, whereas 2 (20%) had a reading <20. The mean CB distance was 2.0 cm (range 0.6–4.2 cm). Table 4 shows the correlation between the shear wave velocity evaluated by ARFI elastography and the parameters of BMI, age and CB distance. The results are presented individually for segments 5/6 and 7/8. Segment 3 has been excluded from the analysis because of the preceding Cronbach α statistic demonstrating unreliability. The findings show a significant but weak negative correlation between shear wave velocities and CB distance for both segments 5/6 ($r=-0.084$; $p\leq0.0001$) and 7/8 ($r=-0.056$; $p\leq0.0001$). The analysis of age and BMI shows significant but inconsistent correlation with shear wave velocities between the two regions.

Discussion

Quantification of liver fibrosis in patients with abnormal liver biochemistry and chronic liver disease has become an integral part of both the initial and follow-up assessments. Moreover, other non-invasive imaging techniques such as Fibroscan™ (Echosens, Paris, France) or transient elastography (TE) have been validated in patients with chronic hepatitis C virus infection and are widely used to triage patients into appropriate treatment paradigms [17]. Similarly, serological and biochemical markers have been amalgamated into scoring systems in order to minimise the need for a liver biopsy in certain patient groups [18]. The merits of a non-invasive, practical, inexpensive and reproducible method for analysing the degree of liver fibrosis are well recognised and have been the subject of recent widespread interest.

This interest has led to the introduction of various imaging modalities for the assessment of tissue stiffness. As discussed above, TE is a more established ultrasound-based method with recent meta-analyses concluding it to be reliable in the diagnosis of advanced fibrosis and cirrhosis [19]. The main drawback of the TE system is that, unlike ARFI imaging, the apparatus is not integrated into a conventional ultrasound system and only produces an M-mode image for localisation. This not only prohibits simultaneous B-mode imaging, which is now a conventional assessment in patients with chronic liver disease, it also precludes the operator from determining the presence of any adjacent biliary or vascular structures that may interfere with the accuracy of measurement. Real-time elastography is a more novel

Table 1. Individual median velocities acquired per operator, per session, with inclusion of the maximum and minimum values obtained

Session/region	Median SWV (m s^{-1})	Minimum SWV (m s^{-1})	Maximum SWV (m s^{-1})	Range
Session 1				
Segment 3				
Operator 1	1.31	0.95	1.49	0.54
Operator 2	1.34	1.08	1.84	0.76
Operator 3	1.26	0.99	1.45	0.46
Segment 5				
Operator 1	1.17	0.69	1.35	0.66
Operator 2	1.08	0.83	1.46	0.63
Operator 3	1.04	0.88	1.47	0.59
Segment 6				
Operator 1	1.15	0.78	1.53	0.75
Operator 2	1.10	0.91	1.38	0.47
Operator 3	1.15	0.92	1.47	0.55
Session 2				
Segment 3				
Operator 1	1.17	0.98	1.66	0.68
Operator 2	1.26	1.04	1.66	0.62
Operator 3	1.28	1.03	1.54	0.51
Segment 7				
Operator 1	1.07	0.85	1.20	0.35
Operator 2	1.03	0.83	1.85	1.02
Operator 3	1.16	0.74	1.53	0.79
Segment 8				
Operator 1	1.08	0.87	1.31	0.44
Operator 2	1.06	0.86	1.20	0.34
Operator 3	1.10	0.76	1.41	0.65

SWV, shear wave velocity.

non-invasive method for the assessment of tissue elasticity; the modality uses conventional ultrasound probes and is integrated into a sonographic machine (EUB-8500™ and EUB-900™; Hitachi, Tokyo, Japan). Echo signals before and under slight compression are compared and analysed; this allows the underlying physical property of imaged tissue to be determined [20]. Although the technique has demonstrated promising preliminary results, further studies are required to truly determine the efficacy of the method [21]. In MR elastography, the whole three-dimensional displacement vector is assessed with analysis performed using several liver sections, as opposed to the defined ROI box used for ultrasound scanning. The assumption, therefore, is that the known heterogeneity of advanced fibrosis can be addressed and the sampling variability reduced. Although recent studies have shown that MR elastography is superior to TE for staging of liver fibrosis, the known disadvantages of the modality remain, with the procedure proving to be more costly and requiring a longer examination time than sonography [22].

ARFI imaging technology, through tissue displacement, allows the possibility to derive a quantifiable measurement of tissue stiffness (shear wave velocity), allowing for simple comparison over time [7]. ARFI technology also has the distinct advantage of being integrated into a conventional ultrasound machine. This enables the operator to perform a routine B-mode examination of the liver as part of the diagnostic workup and ARFI imaging quantification of the degree of liver abnormality within the same sitting.

Table 2. Mean depth and capsule-to-box (CB) distances given for each segment

	Session 1		Session 2	
Region	Mean depth (cm)	Mean CB distance (cm)	Mean depth (cm)	Mean CB distance (cm)
Segment 3				
Operator 1	4.15	1.50	3.81	1.35
Operator 2	4.5	1.85	4.86	2.18
Operator 3	3.87	1.31	3.71	1.26
Segment 5/6				
Operator 1	3.74	1.96	3.60	1.90
Operator 2	4.46	2.68	4.55	2.75
Operator 3	3.97	2.2	3.46	1.68
Segment 7/8				
Operator 1	3.42	1.85	3.57	1.99
Operator 2	4.37	2.78	4.16	2.57
Operator 3	3.93	2.46	3.35	1.83

Table 3. Cronbach α statistic for both inter- and intra-observer reliability

	Segment 3	Segment 5/6	Segment 7/8
Interobserver reliability (Cronbach α)			
1st session	0.202	0.688	0.913
2nd session	0.545	0.813	0.861
Intra-observer reliability (Cronbach α)			
Operator 1	−0.13	0.774	0.739
Operator 2	0.146	0.937	0.919
Operator 3	−0.043	0.789	0.701

Interoperator evaluation shows that the most reliable and consistent shear wave velocities are derived from segments 5/6 and 7/8; this is shown in both the preliminary assessment and the subsequent recordings taken after a 1-week interval. Segment 3 results for both sittings were found to be unreliable. The negative Cronbach α statistic in the intra-observer study reflects the heterogeneity of the sample and confirms the high variance between the obtained readings. These findings can be explained by factors known to cause measurement inaccuracies either individually or in combination. The effect of excessive tissue motion, such as that secondary to cardiac pulsation, can disrupt shear wave velocity readings; this is most acutely demonstrated on the left lobe of the liver, because of both its close vicinity to the heart and its reduced thickness compared with the right lobe. The lower CB distance for segment 3 readings makes the superficially located readings more prone to the effects of cardiac motion. The readings are also more likely to be taken from the tissue immediately deep to the capsule; this region is known to be more fibrous than the deeper parenchyma. The discrepancy, therefore, between the shear wave velocity readings taken from the immediate subcapsular liver and that of the deeper parenchyma will result in a greater dispersion of results and hence less reliability. Interestingly, it is also well known that liver biopsies obtained from subcapsular regions in any part of the liver fail to accurately estimate the degree of fibrosis [23]. The intra-observer findings for all three operators concur with the results of the interobserver study, with measurements taken from segments 5/6 and 7/8 found to be the most reliable. When analysing the stated parameters, the findings of segment 3 were excluded because of the proven unreliability of measurements. A significant negative correlation was attained for the CB distance for both of the designated regions, confirming that deeper measurements are more desirable. Although the findings for BMI were significant for both regions, they differed in the direction of correlation. This may be accounted for by the opposing negating factors of a lower CB distance for a fixed depth in more obese participants, compared with a greater likelihood of compression of liver parenchyma in thinner subjects. Similar to BMI, the findings for age were significant for both regions but differed in the direction of correlation. This finding may be a consequence of the narrow range of ages evaluated.

Table 4. Regression analyses of patient parameters and acoustic radiation force impulse readings

Parameter	Multivariate analysis[a]	*p*-value
Age		
Segment 5/6	−0.017 (−0.026–0.009)	<0.0001
Segment 7/8	0.008 (0.003–0.014)	<0.0001
Body mass index		
Segment 5/6	0.018 (0.010–0.026)	<0.0001
Segment 7/8	−0.014 (−0.020–0.008)	<0.0001
Capsule box		
Segment 5/6	−0.084 (−0.12–0.047)	<0.0001
Segment 7/8	−0.056 (−0.082–0.029)	<0.0001

[a]Values are expressed as unstandardised B coefficients (95% confidence intervals).

One limitation of the study is the small number of subjects, with the number of participants, as well as operators, defined by practical considerations. A larger study population is perhaps warranted to increase the power of the study. Also, the study design has been applied in healthy volunteers; therefore, further studies need to be conducted in patients with known chronic liver disease to evaluate whether similar findings are evident within this clinical population. The limitations of the technique of ARFI imaging are the fixed maximum depth allowable for quantification (~8 cm); the negative influence of motion (both cardiac and respiration); and the detrimental effect of compression.

In conclusion, we have demonstrated that ARFI imaging is a reliable and reproducible method for quantifying liver stiffness when measurements are derived from segments 5/6 and 7/8. Segment 3 ARFI imaging appears unreliable, and its use in analysis should be avoided. In addition, measurements taken at the maximal allowable CB distance are more accurate. Further studies in a larger number of healthy volunteers and in patients with chronic liver disease are required to further evaluate the described intersegmental variations in ARFI measurements and association with CB distance.

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