The effect of applied transducer force on acoustic radiation force impulse quantification within the left lobe of the liver

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Abstract

Introduction: Acoustic Radiation Force Impulse (ARFI) Quantification measures shear wave velocities (SWVs) within the liver. It is a reliable method for predicting the severity of liver fibrosis and has the potential to assess fibrosis in any part of the liver, but previous research has found ARFI quantification in the right lobe more accurate than in the left lobe. A lack of standardised applied transducer force when performing ARFI quantification in the left lobe of the liver may account for some of this inaccuracy. The research hypothesis of this present study predicted that an increase in applied transducer force would result in an increase in SWVs measured.

Methods: ARFI quantification within the left lobe of the liver was performed within a group of healthy volunteers (n = 28). During each examination, each participant was subjected to ARFI quantification at six different levels of transducer force applied to the epigastric abdominal wall.

Results: A repeated measures ANOVA test showed that ARFI quantification was significantly affected by applied transducer force (p = 0.002). Significant pairwise comparisons using Bonferroni correction for multiple comparisons showed that with an increase in applied transducer force, there was a decrease in SWVs.

Conclusion: Applied transducer force has a significant effect on SWVs within the left lobe of the liver and it may explain some of the less accurate and less reliable results in previous studies where transducer force was not taken into consideration. Future studies in the left lobe of the liver should take this into account and control for applied transducer force.

Keywords: ARFI, applied transducer force, left lobe, liver.

Introduction

Liver fibrosis with its endpoint, cirrhosis, is the main complication of chronic liver disease (CLD) and staging of the disease helps determine a patient's prognosis and course of treatment. While liver biopsy remains the 'gold standard' for staging liver fibrosis, there are a number of drawbacks to this technique. Liver biopsy obtains a specimen representing a very limited amount of the total liver volume and given liver fibrosis is unevenly distributed, sampling error can occur.[1] Additionally, it is uncomfortable for the patient and exposes the patient to rare but potentially serious complications.[2] As a result there has been increasing interest in non-invasive means for staging liver fibrosis including elastography methods which can measure the resultant increase in parenchymal stiffness associated with the disease.[3]

Acoustic Radiation Force Impulse (ARFI) quantification is a promising ultrasound based elastography technique which quantifies fibrosis of the liver by measuring shear wave velocities (SWVs).[4] ARFI quantification is non-invasive, inexpensive and has been integrated into a conventional ultrasound machine so can be performed in conjunction with a routine liver ultrasound scan. Multiple studies have shown ARFI quantification as a reliable method for predicting the severity of liver fibrosis with the potential to reduce the number of patients requiring liver biopsy.[5–8] As a promising technique for quantifying liver fibrosis, it has good reproducibility but does demonstrate significant heterogeneity when comparing between individual studies for all fibrosis stages.[9]

The vast majority of clinical research involving ARFI quantification has focussed on measurements in the right lobe of the liver using an inter-costal approach.[5,7,10] An advantage of ARFI is the potential to assess fibrosis in any part of the liver, which could lead to a better overall estimation of liver fibrosis distribution.[4] A small number of studies investigating the left lobe of

Figure 1: a) A mechanical device used to regulate applied transducer force. b) Spirit level used to ensure cross-bar was horizontal.

the liver via an epigastric approach have been reported albeit with low sample sizes. Authors have found both less accurate results in the left lobe and a significant increase in SWVs in the left lobe using an epigastric approach compared to the right lobe inter-costal approach.[11–13] Two authors have noted the difference in SWVs between the right and left lobes only in non-cirrhotic livers,[13,14] with one study reporting ARFI within the left lobe as feasible and that comparison of SWVs between the right and left liver lobe could potentially improve accuracy of fibrosis staging.[14]

To improve accuracy of the technique and reduce heterogeneity of results between studies, a thorough understanding of the factors influencing ARFI measurements is required. One of these factors which could influence strain and therefore SWVs in the liver is applied transducer force. Variations in external compression applied by the ultrasound transducer changes the inherent stiffness of tissue[15] and studies within both the breast[16] and transplant kidney[17] have shown that an increase in external compression or applied transducer force significantly increases measured SWVs. To date, research that quantifies the influence of applied transducer force within the liver has not been undertaken.

The amount of force applied by the transducer during an ultrasound examination varies and has been linked to variables such as operator experience level and patient size.[18] This force also varies depending on the location or type of ultrasound examination being performed. In one study simulating the push force used to conduct an ultrasound examination, a push/pull strain gauge showed an average push force of 36.5N ± 11.9 (8.7–52.4) and 32.9N ± 12.8 (13.1–65.5) within the left and right abdominal region respectively.[19] Given a lack of standardised applied transducer force in studies involving the left lobe of the liver, some of the differences in findings may be explained by variations in applied transducer force.

The aim of the present study was to assess the significance of applied transducer force on SWVs within the left lobe of the healthy liver when using ARFI quantification. The influence of the applied transducer force may have the greatest impact within the left lobe of the liver given the relative compliance of the epigastric abdominal wall and susceptibility to external compressive forces. An understanding of its significance will assist future research within the left lobe of the liver as standardised applied transducer force may produce more accurate and reliable results. The research hypothesis of this present study is based on previous studies involving external compression in other regions of the body and predicts an increase in applied transducer force would result in an increase in SWVs measured.

Methods

Ethics approval was sought and granted by the Human Research Ethics Committee of Charles Sturt University prior to the commencement of the study.

A sample of convenience was recruited between June 2014 and September 2014. The volunteers were recruited from two sources: employees of a private radiology clinic (n = 22) and patients of the same clinic who had undergone a comprehensive liver ultrasound on the same day which had shown no demonstrable signs of fibrosis/cirrhosis (n = 6). Signs on ultrasound which were suggestive of fibrosis/cirrhosis and led to exclusion of the participant from the study were heterogeneity of the liver parenchyma, liver surface nodularity and/or irregular

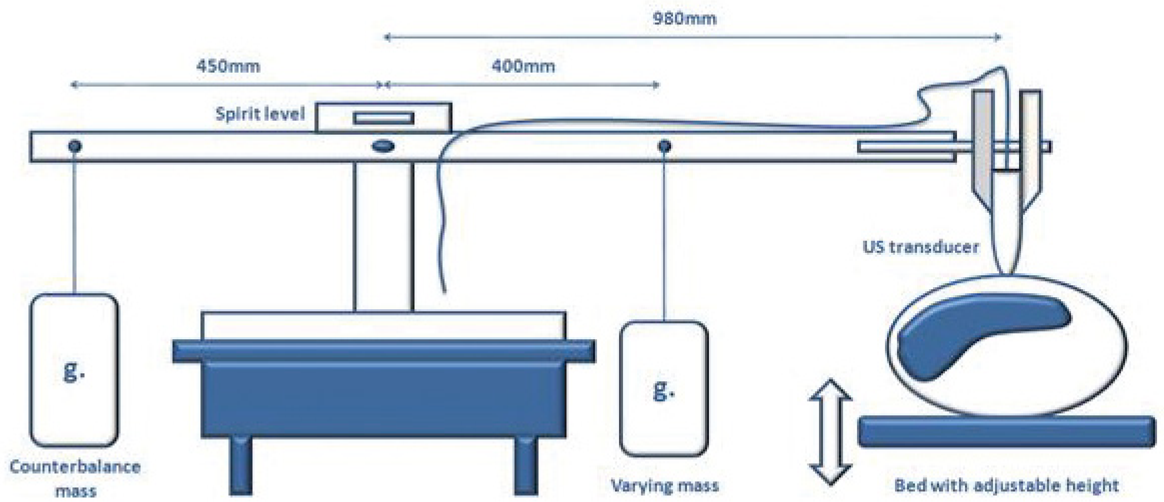

Figure 2: Schematic of mechanical device. The amount of applied transducer force applied to the abdomen increased when the mass at the 400 mm point from fulcrum was increased. Standardised levels of mass at 400 mm from fulcrum allowed the regulation of applied transducer force to the abdomen.

right hepatic vein wall morphology. Participants with signs of portal hypertension such as a dilated portal vein (> 13 mm), recanalised peri-umbilical vein and/or ascites were also excluded from the study. No participant had a history of liver disease and all had fasted at least 6 hours prior to the experiment. Patient demographics recorded included age, sex, height and weight. Written consent was obtained from each participant prior to commencement.

ARFI measurements were performed using a Siemens Acuson S2000 ultrasound system (Siemens Acuson, Mountain View, CA) equipped with ARFI quantification capabilities (Virtual Touch^{TM}, Tissue Quantification package) and using a 6-MHz curved linear array transducer (Acuson Sequoia -6C1).

All measurements were performed by a single qualified operator (principal investigator) who had previous experience using ARFI quantification. The device used to apply transducer force was based on a design by Syversveen, *et al.* (2012) who experimented with varying levels of applied transducer force on transplant kidneys. The device used to regulate the applied transducer force was a crossbar freely movable around a fulcrum with the US transducer fixed at one end, 980 mm from the fulcrum with its long axis perpendicular to the crossbar (Figure 1.). The aluminium crossbar had a total length of 1530 mm and had a fixed mass attached to the end opposite the transducer, 450 mm from the fulcrum to act as a counterbalance. To regulate the amount of force applied to the abdominal wall by the transducer, varying levels of mass were hung at the point 400 mm from the fulcrum on the same side as the US transducer. An increase in mass hung 400 mm from the fulcrum, would increase the applied transducer force to the abdominal wall. As long as the crossbar was horizontal, the applied transducer force to the abdominal wall could be calculated. Given the applied transducer force was proportional to applied weight the force was expressed in units of weight (g) (Figure 2.).

For each level of mass hung at point 400 mm from the fulcrum, the corresponding force applied by the transducer to the abdominal wall was established before the beginning of the study using electronic weight scales. Applied transducer forces (mean of five calibrations) applied to the abdominal wall of each participant were: 5g ± 2.6 (1-8), 249 g ± 4.8 (244–254), 495 g ± 4.1 (489–519), 1000g ± 2.2 (997–1003), 2015g ± 26.0 (1990–2046) and 2972 g ± 24.2 (2945–3000). Calibration of the device was repeated after every 10 patients and following completion of the study.

Each participant was examined in a supine position with the transducer applied to the epigastric region. The ultrasound field of view (FOV) was assessed under varying levels of participant inspiration and a level of inspiration was established by the researcher that ensured adequate visualisation of the left lobe of the liver. The participant was asked to repeat this level of inspiration with each subsequent applied transducer force. The crossbar could move freely in a vertical direction and with application of each level of applied transducer force, the height of the bed was adjusted to ensure the crossbar was kept horizontal as established by the spirit level at the fulcrum (Figure 1). Measurements were performed one after another but the order of applied transducer force was randomised using a random numbers table (established using Microsoft Excel) to reduce the influence of potential carryover effects between forces. At an applied transducer force of 5 g, the abdominal wall thickness was measured using the distance from transducer-skin interface to anterior liver edge. Participant comfort levels were monitored and if a participant became uncomfortable because of the applied transducer force then there was cessation at that level of force and higher levels were not attempted.

During ARFI quantification, a targeted region of interest (ROI) (5 mm axial by 4 mm width) was selected on the conventional B-mode image and acoustic push pulses were generated alongside. These push pulses were of short-duration (262µsec) with a fixed transmit frequency of 2.67 MHz and mechanically excited the tissue to generate localised tissue displacement. The displacements resulted in the propagation of shear-waves away from the region of excitation in a plane perpendicular to the acoustic push pulse. Shear waves were subsequently tracked within the ROI using US correlation-based methods.[20,21] The shear wave propagation velocity is

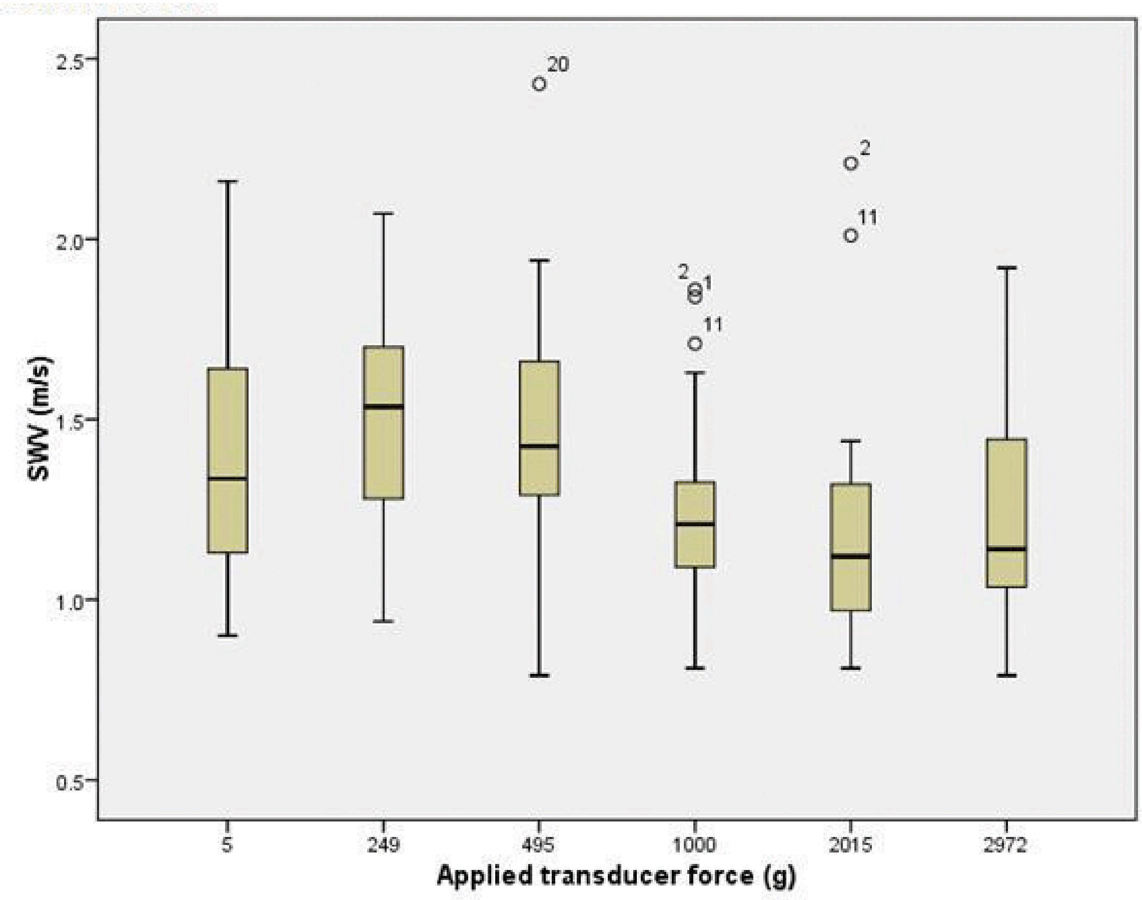

Figure 3: A box-whisker diagram plotting SWV at different levels of applied transducer force. At the centre of each plot is the median, the top and bottom of the box indicate the middle 50% (IQR). The ends of the whiskers represent the top and bottom 25% and circles indicate ouliers.

Table 1: Participant demographics.

Male / Female	3 / 25
Age of participant (years)	39 ± 14.1 (18–70)
BMI (kg/m^2)	25.6 ± 4.0 (19–35)
Thickness of abdominal wall (mm)	32.8 ± 13.1 (14–76)

Mean, SD and range for each demographic

Table 2: Measurement success rate for each applied transducer force.

Force (g)	Participants	SWV measurements Total	Valid	Invalid	Success rate (SR)
5	28	143	140	3	0.98 (0.71–1.00)
249	28	145	140	5	0.97 (0.71–1.00)
495	28	144	140	4	0.98 (0.71–1.00)
1000	28	140	140	0	1.00 (1.00–1.00)
2015	26	140	130	0	1.00 (1.00–1.00)
2972	24	140	120	0	1.00 (1.00–1.00)

Mean and range for success rate at each applied transducer force.

proportional to the square root of tissue elasticity.[22] Therefore, by measurement of shear wave velocity the stiffness of tissues could consequently be evaluated; the stiffer a tissue was, the greater the shear wave velocity (m/s).[11]

The ROI was placed in a region of the left lobe, absent of visible blood vessels, 1–4 cm from the liver capsule and as close as possible to the centre of the FOV. ARFI measurements at each applied transducer force were obtained within the same region of the left lobe and depth of the ROI from the transducer was recorded. At each level of transducer force, ARFI measurements were repeated until five valid SWV measurements had been obtained, with the number of invalid SWV measurements (designated by the system as X.XX m/s) also recorded. These invalid measurements resulted if the shear wave propagation was not accurately detected by the system.[6]

Statistical analysis

Microsoft Office Excel 2007 (Microsoft, Redmond, WA, USA) was used to collect data. For statistical data analysis, SPSS software (SPSS Statistics 22 for Windows; SPSS Inc., Chicago, IL, USA) was used. For each participant, at each level of applied transducer force, the median of five valid measurements was used as a representative SWV. The mean SWV for each applied transducer force was then compared using repeated measures ANOVA, followed by pairwise comparisons for each exerted force using Bonferroni correction for multiple comparisons. All tests were two sided and statistical significance was assumed when $p < 0.05$.

For each participant, the interquartile range (IQR, the difference between the 75th percentile and the 25th percentile) and success rate (SR, number of valid measurements divided by total number of measurements) for each level of applied transducer force was recorded. The mean IQR and SR were then calculated across all participants for each magnitude of applied transducer force. Where means were presented, the standard deviation and overall range of the data were included.

Table 3: Results.

Force (g)	SWV (m/s)	Depth (cm)	Interquartile range (IQR)
5	1.37 ± 0.29 (0.90–2.16)	4.5 ± 1.2 (2.7–8.0)	0.39 ± 0.18 (0.14–0.92)
249	1.51 ± 0.31 (0.94–2.07)	3.9 ± 1.2 (2.0–8.0)	0.38 ± 0.17 (0.11–0.75)
495	1.45 ± 0.33 (0.79–2.43)	3.8 ± 1.1 (2.0–7.3)	0.34 ± 0.16 (0.10–0.63)
1000	1.24 ± 0.27(0.81–1.86)	3.7 ± 1.0 (1.9–6.9)	0.26 ± 0.17 (0.04–0.76)
2015	1.19 ± 0.32 (0.81–2.21)	3.5 ± 0.9 (2.1–6.2)	0.29 ± 0.16 (0.06–0.66)
2972	1.25 ± 0.31 (0.79–1.92)	3.5 ± 0.9(1.8–6.1)	0.27 ± 0.12 (0.06–0.52)

Mean, SD and range for SWV, depth of ROI from skin, and IQR at each applied transducer force.

Results

A total of 31 participants agreed to take part in the present study. From this group, three participants were found inappropriate for the study because the epigastric approach did not allow a sufficient FOV. Therefore only results from 28 participants were recorded and analysed. Table 1 summarises participant demographic characteristics including Body Mass Index (BMI) and abdominal wall thickness.

A total of 822 measurements of SWV were made within the left lobe of the liver. Of these, 810 were valid measurements (signified by a numerical value for SWV) and were consequently analysed using repeated measures ANOVA. There were 12 invalid measurements (represented by X.XX m/s), each of which were repeated and in all cases a subsequent valid measurement was obtained.

Measurements were completed with an applied transducer force of 5 g–2972 g (n = 24), 5 g–2015 g (n = 2) and 5 g–1000 g (n = 2). Table 2 summarises the measurement success rate for each applied transducer force. The range of applied force was limited in four participants because of either participant discomfort (n = 2), or a failure to sufficiently visualise an appropriate FOV within the left lobe of the liver (n = 2).

When calculating repeated measures ANOVA for the significance of applied transducer force, Maulchy's test indicated that the assumption of sphericity had been violated, x2(14) = 46.806, p = 0.000, therefore Greenhouse-Geisser corrected tests were reported ($\varepsilon = 0.582$).

Table 3 summarises the results for each applied trasducer force. The repeated measures ANOVA test showed that SWVs in the left lobe of the liver were significantly affected by applied transducer force, F = (2.91, 66.95) = 5.77, p = 0.002, 1 - β = 0.934. Pairwise comparisons using Bonferroni correction for multiple comparisons showed that there was a significant difference between 249 g vs 1000 g (p = 0.009, mean difference = 0.26 m/s), 249g vs 2015g (p = 0.028, mean difference 0.31 m/s), 495 g vs 1000g (p = 0.031, mean difference = 0.23 m/s), 495 g vs 2015 g (p = 0.045, mean difference = 0.28 m/s). All other comparisons had no significant difference (p > 0.05).

Discussion

This experimental study found that variations in applied transducer force had a statistically significant effect on SWVs within the left lobe of the liver in healthy patients (p = 0.002). While the significance of this effect was expected, the direction of the relationship between force and SWVs within the liver was unexpected. All significant pairwise comparisons (249 g vs 1000 g, 249 g vs 2015 g, 495g vs 1000 g, 495 vs 2015 g) found that an increase in applied transducer force resulted in a decrease in SWVs. This contradicted the research hypothesis which dictated that an increase in applied transducer force would result in an increase in SWVs measured within the left lobe based on the underlying theoretical perspective that an increase in external compression applied by the ultrasound transducer would increase the inherent stiffness of a soft tissue being investigated. Changes in tissue stiffness with external compression is a theory underpinning early ultrasound based elastography methods such as strain imaging which uses an external force to deform tissue.[15] ARFI quantification does not use external force, instead relying on an acoustic push pulse to cause deformation, but it is not unreasonable to expect external compression to influence SWVs measured using ARFI. This theory was tested and verified in previous research assessing the influence of applied transducer force on SWVs in the transplant kidney[17] and the influence of external compression on SWVs in breast tissue.[16] This theory has also been proposed as an explanation for the higher SWVs found in the left lobe of the healthy liver, when compared to SWVs within the right lobe.[11–14]

Our findings did not support the research hypothesis which raises the probability that external influences caused the significant reduction in SWVs within the left lobe of the liver. A compressor of limited size such as an ultrasound transducer tends to generate stress and strain with limited penetration and poor homogeneity[23] and anatomical variables may have inadvertently affected the transmission of applied transducer force to the liver parenchyma. There were variations in abdominal wall thickness between participants (Table 1) and previous studies correlating applied transducer force and SWVs have been conducted in structures more superficial than the left lobe of the liver. There was the potential that participants with an increased abdominal wall thickness may have absorbed a greater level of applied transducer force therefore limiting its effects on the liver parenchyma. The small study sample size did not allow sufficient statistical power to investigate the influence of this variable, but in any case the absorption of force related to the abdominal wall thickness does not help explain the observed relationship of decreasing SWVs with increasing applied transducer force. A more probable explanation was that reactive abdominal muscle contraction in response to increasing applied transducer force may have influenced the transmission of force. It is theoretically possible that an increase in force applied to the abdominal wall resulted in the participant contracting their abdominal wall muscles, effectively 'guarding' their liver from the external force and therefore reducing its effect on the liver parenchyma. However, subjective observation of the B-mode images by the principle investigator during the study was not consistent with this theory. Even if participants were contracting their abdominal muscles, when compared to lower levels of applied transducer force, a greater level of visible deformation of the liver was observed in participants under moderate to high levels of applied transducer force.

An important consideration regarding our study was the limited range of transducer force applied to the abdominal wall during the experiment. The highest applied transducer force was 2972 g and force greater than this may have led to an increase in SWVs within the liver more consistent with the research hypothesis. However, given some participants (n = 2) were unable to tolerate 2972 g due to discomfort, it was deemed unethical by the researcher to apply greater force and potentially expose an increased number of participants to discomfort. The range of applied transducer force was designed to mimic that experienced during a normal ultrasound scan and followed the forces used to assess the effect of applied transducer force in the transplant kidney.[17]

While the underlying explanation for the direction of change with applied transducer force is difficult to elucidate, the finding that there was a significant effect on SWVs regardless of direction has an important implication. Previous research measuring SWVs within the left lobe of the liver has not taken into account applied transducer force and assuming there was no standardisation of this confounding variable during their research, our findings could help explain the less accurate and less reliable results within the left lobe when compared to those within the right lobe of the liver using an intercostal approach. We therefore recommend that future research in the left lobe of the liver controls for applied transducer force.

Previous research within the healthy liver has shown more variable SWVs within the left lobe of the liver when compared to the right lobe.[12] Though not statistically significant, a potentially important observation from our study was that with increasing applied transducer force there was a reduction in mean IQR and therefore a decrease in the variability of the data. This seems to indicate that more reliable results could be obtained in the left lobe of the liver if moderate to high applied transducer force (1000–2972 g) was used. Furthermore, previous research has shown that when comparing between lobes of the healthy liver, there have been significantly higher SWVs in the left lobe when compared to the right lobe.[11–14] Interestingly, our study found the lowest SWVs were seen when moderate to high applied transducer force (1000–2972 g) was used and while not part of our study, we hypothesise that this level of force may give SWVs that correlate more closely with SWVs found in right lobe of the liver. Acknowledging these two observations and given that 1000g gave a sufficient FOV and was tolerated by all participants, future research in the left lobe of the liver should use an applied transducer force of 1000g however further research is required to validate such a recommendation.

While the method used in this study to standardise the applied transducer force may not have been conducive to daily practice, given the size and weight of the apparatus and the set up time required prior to performing each examination (10 mins), this method has highlighted the importance of applied transducer force in a clinical setting. Further research in this field would benefit from modification of this method and a more efficient and portable means of monitoring the applied transducer force, such as a hand-held force gauge attached to the ultrasound transducer, would make standardisation of force by the operator easier if used in daily practice.

Limitations of our study included the limited range of transducer forces applied to the abdominal wall and the method of participant recruitment. This purposive cohort of healthy volunteers sourced from patients and employees of a private radiology clinic was chosen to control for the potential influence on SWVs of variations in both the underlying aetiology and progression of CLD but means it cannot be generalised to groups outside a healthy population. Additionally, an unforeseen result of this voluntary sampling was a cohort dominated by female participants (89%) and this may be a limiting factor for our study however its potential effect on the result is not known. Future studies with a more even mix of male and female participants and a mix of both healthy participants and those with CLD is required to evaluate the relationship between applied transducer force and liver SWVs within the broader population.

Conclusion

While the findings of this study contradicted the research hypothesis, the study found that applied transducer force had a significant effect on SWVs within the left lobe of the liver. This effect may not have related to a change in inherent stiffness associated with applied transducer force, but variations in applied transducer force in previous studies may help explain some of the less accurate and less reliable results involving the left lobe. The findings of this study suggest future studies using ARFI quantification in the left lobe of the liver should control for applied transducer force.

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