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INFLUENCE OF PROBE PRESSURE ON ULTRASOUND-BASED SHEAR WAVE ELASTOGRAPHY OF THE LIVER USING COMB-PUSH 2-D TECHNOLOGY

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Abstract—It has been postulated that in the liver, applying increased probe pressure during ultrasound-based shear wave elastography (SWE) might lead to a false increase in the SWE result. We aimed to determine the influence of increased intercostal probe pressure when performing SWE of the liver. We also investigated the number of measurements required to achieve technically successful and reliable SWE examinations. This prospective, clinical study included 112 patients and 2240 SWE measurements of the liver. We applied probe pressure intercostally, to reduce the skin-to-liver capsule distance (SCD), which could stabilize the SWE signal and thus increase the number of technically successful measurements. We performed 10 measurements with maximum probe pressure and 10 with normal pressure in each patient. Thus, two analysis groups were compared for differences. Compared with normal pressure, maximum probe pressure significantly reduced the SCD (p < 0.001) and significantly increased the number of technically successful measurements from 981 to 1098, respectively (p < 0.001). The SWE results with normal and maximum probe pressure were 5.96 kPa (interquartile range: 2.41) and 5.45 kPa (interquartile range: 1.96), respectively (p < 0.001). In obese patients, a large SCD poses a diagnostic challenge for ultrasound SWE. We found that maximum intercostal probe pressure could reduce the SCD and increase the number of technically successful measurements, without falsely increasing the SWE result. Only three measurements were required to achieve technically successful and reliable SWE examinations. (E-mail: marie.byenfeldt@umu.se) © 2018 The Author(s). Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key Words: Shear wave elastography, Skin-to-liver capsule distance, Probe pressure, Measurements, Obesity, Pre-compressive force, Applied transducer force, Subcutaneous fat, Steatosis.

INTRODUCTION

Shear wave elastography (SWE) of the liver, because of its non-invasive nature, has come to replace liver biopsy for staging patients with liver fibrosis (Barr et al. 2016; Tapper and Loomba 2018). However, several factors are known to have negative effects on SWE measurement reliability (Dietrich et al. 2017), including large patient body mass and long distances between the skin and liver capsule (skin-to-capsule distance [SCD]). Currently, the influence of these factors on SWE measurements remains poorly characterized.

Normal liver tissue is soft and viscoelastic, but during inflammation, liver cells die and are replaced by collagenous fibrils, which increase liver tissue stiffness. Hepatitis and metabolic diseases are associated with liver inflammation, fibrosis, cirrhosis and, at worst, the development of hepatocellular cancer (HCC) (European Association for the Study of the Liver [EASL] 2014, 2015, 2017; Firneisz 2014; Joshi-Barve et al. 2015).

The global prevalence of hepatitis B virus (HBV) and C virus (HCV) was estimated to be 325 million in 2015. Among individuals with HCV, an estimated 21% progress to cirrhosis within 20 years (Freeman et al. 2001). However, >95% of people with HCV can be completely cured within 2–3 months with medication (World Health Organization [WHO] 2017). HCV treatments include several direct-acting antiviral agents, which were approved in 2014. However, treatment regimens are expensive; therefore, it is essential to determine which patients would benefit most from treatment. This can be achieved with diagnostic ultrasound examinations (Lagging et al. 2017).
The worldwide incidence of obesity, defined as a body mass index (BMI) ≥30 kg/m² by the World Health Organization, has nearly tripled since 1975 (WHO 2017). The presence of diabetes, obesity and other comorbidities that make up the metabolic syndrome significantly increase the risk of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). A significant subset of patients will develop progressive fibrosis (Brunt et al. 2015), which may progress to cirrhosis and, at worst, HCC (Augustin et al. 2017). The prevalence of NAFLD is 25.24% in adults worldwide (Younossi et al. 2016). Among patients with NAFLD and NASH, the annual incidence rates of HCC are 0.44 and 5.29 per 1000 person-years, respectively (Younossi et al. 2016). The clinical and economic burdens of patients with liver diseases are high; earlier treatment results in great savings, both by preventing death and by prolonging productive life. The most cost-effective strategy for relieving these burdens is to treat all patients with HCV (Stepanova and Younossi 2017; Tschochatzis et al. 2014). Therefore, it is very important to identify patients with NAFLD that are at high risk of liver fibrosis (Younossi et al. 2018).

These observations have indicated a need for reliable diagnostic methods for determining fibrosis stages and for evaluating treatment regimens. In Europe, the Metavir grading system is commonly used for evaluating fibrosis. That system ranges from F0 to F4, where F0 represents normal liver parenchyma and F4 represents cirrhosis (Goodman 2007). With a grading system, the liver can be monitored and staged (Dietrich et al. 2017; Goodman 2007). Among methods used to detect fibrosis, the current gold standard is liver biopsy. This invasive method is limited by the small tissue sample size, which represents only 1/50,000th of the total liver mass (Lee 1994) and tissue variability (Bedossa et al. 2003). Currently, non-invasive methods are preferred, including serum biomarkers for liver fibrosis, like Fibro Index, Fibro test, Hepascore, the aspartate transaminase-to-platelet ratio index (APRI) and FIB4 (Chou and Wassen 2013; de Luca Schiavon et al. 2014). Currently, SWE, based on transient elastography (TE) or ultrasound technology (Barr 2014), is available for clinical use. SWE is a non-invasive method that can be frequently repeated, and it does not require hospitalization.

Transient elastography can be performed with the FibroScan device. The results correlate well with liver fibrosis (Barr et al. 2016; Carstensen et al. 2008; Kettaneh et al. 2007; Sandrin et al. 2003). Because the scan area is at least 100 times larger than a biopsy sample volume, it is more representative of the liver parenchyma (Cui et al. 2013). TE is also easy to use, reaching 64.7% validity by the 50th FibroScan (Armstrong et al. 2013); however, other authors have claimed that 500 FibroScan examinations are necessary to achieve valid TE results (Dietrich et al. 2017). According to the manufacturer (Echosens, Paris, France), TE validity depends on two parameters: a success rate (SR) of at least 60% and an interquartile range (IQR) ≤30% of the median of 10 successful measurements (Lucidarme et al. 2009). A major limitation with TE is the lack of a conventional ultrasound image in B-mode, which increases the risk of sampling in non-representative areas of the liver. Diagnostic efficacy is limited by the presence of ascites, which precludes measurements; the presence of steatosis, which increases the risk of misclassification (Macaluso et al. 2014); and obesity, because fat can interfere with signal transmission (Castera et al. 2010). The XL-probe was especially designed for obese individuals; compared with the standard M-probe, the XL-probe uses a lower frequency (3.5 MHz), has a deeper focal length (50 mm) and uses a larger vibration amplitude (3 mm), and measurements below the skin surface are acquired a lower depth (35–75 mm). The advent of the XL-probe has facilitated liver stiffness measurements in patients with large SCDs (de Ledinghen et al. 2010). Nevertheless, in some studies, the XL-probe did not provide reliable SWE results (Dietrich et al. 2017). Finally, TE probes must be calibrated every 6–12 month according to the manufacturer.

Ultrasound-based SWE allows imaging in B-mode, which guides the operator to avoid vessels and lesions, also provides the opportunity to choose which liver segment should be measured. This technology uses an acoustic radiation force impulse (ARFI), also called a push pulse, which facilitates measurements, even in the presence of ascites (Dietrich et al. 2017). Moreover, SWE has exhibited high inter-and intra-operator reliability (Hudson et al. 2013); ARFI results were highly correlated with liver biopsy determinations of liver fibrosis (Herrmann et al. 2018; Sporea et al. 2012). SWE operators reached acceptable diagnostic accuracy after 130 examinations (Fraquelli et al. 2016) or after >50 supervised examinations (Dietrich et al. 2017). Ultrasound-based SWE with push-pulse technology can be performed with ultrasound systems that use different push-pulse technologies, such as point SWE, 2-D SWE and comb-push 2-D SWE (Barr et al. 2016; Dietrich et al. 2017; Piscaglia et al. 2016). Current guidelines for performing SWE in the liver recommend at least 10 measurements (Dietrich et al. 2017; Ferraioli et al. 2015). However, it has been suggested that it might be possible to reduce the required number of measurements (Barr et al. 2016). When SWE is performed in the presence of obesity, a large SCD and steatosis contribute to a high risk of misclassifying significant, advanced liver fibrosis (Conti et al. 2017); nevertheless, the reliability of SWE is significantly higher with more experienced operators.
compared with the novice (Gradinaru-Tascau et al. 2013). Factors related to the scanning technique are important, and when there is a risk of insufficient data, a technical scanning assistance system can be applied. For ultrasound-based SWE, the criterion for poor reliability is an IQR/median >30% of 10 measurements (Dietrich et al. 2017). Similar to TE, some SWE studies have had less reliable results in the presence of liver steatosis (Conti et al. 2017), but other studies have had the opposite result (Beland et al. 2014; Perry et al. 2016). Thus, the impact of steatosis on SWE results remains somewhat unclear.

A large SCD was shown to have a negative influence on the reliability of ultrasound-based SWE results (Byenfeldt et al. 2018; Nadebaum et al. 2017). A potential solution to this problem might be to apply maximum intercostal probe pressure when performing SWE. However, among SWE operators, it is commonly believed that increasing the probe pressure might falsely increase the SWE result of the liver (Shiina et al. 2015). It is also difficult to determine the exact amount of pre-compressive force to use in the clinical setting, when measurements are performed on the breast (Barr and Zhang 2012), thyroid (Bhatia et al. 2016) and liver (Barr and Zhang 2012). Furthermore, to date, no study has adequately performed a detailed evaluation of the effect of pre-compressive force on the right liver segments in an intercostal approach (Barr and Zhang 2012). Likewise, studies with increased probe pressure on superficially located organs, such as the breast and thyroid, have reported increased SWE results. Subsequently, discussions have arisen on the difficulties in standardizing how much probe pressure should be applied (Barr and Zhang 2012; Lam et al. 2016). In studies that performed superficial tissue elasticity measurements, where a strain or ARFI approach was used, robot systems were employed to allow control of the pre-compressive force (Bell et al. 2016). An experimental study on patients that received kidney transplants used ARFI and a mechanical device, which allowed control of the applied probe pressure (Syversveen et al. 2012). Nevertheless, no studies have used robotic systems to control probe pressure for SWE measurements in the liver, performed with an intercostal approach. However, increased intercostal probe pressure has been recommended to handle situations with poor acoustic window (Cosgrove et al. 2013).

Our aim with this study was to investigate the influence of increased intercostal probe pressure on liver stiffness assessments with ultrasound-based SWE and comb-push 2-D technology. We applied maximum intercostal probe pressure to decrease the SCD, to improve SWE signal stability and thereby to increase the number of technically successful SWE measurements. Our secondary aim was to determine the number of measurements required to achieve technically successful and reliable SWE examinations.

**METHODS**

This prospective study was approved by the Research Ethics Review Board in Umeå (No. 2017-417-32M). The research was performed in accordance with The World Medical Association Declaration of Helsinki, 2013. Between 1 August and 31 October 2017, this study enrolled 115 consecutive patients who received liver examinations with ultrasound-based SWE at a single radiology department in northern Sweden. Patients included in the study were adults (>17 y) with HBV, HCV, alcoholic steatohepatitis (ASH), NASH, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). All participants provided informed written consent. Three patients were excluded because of age <18 y (n = 2) and inability to communicate (n = 1). Thus, a total of 112 patients were included in the analyses (Fig. 1).

In this clinical study, every patient served as his or her own control in repeated measurements. The first measurement was performed with maximum intercostal pressure, and the next measurement was performed with normal intercostal pressure at the same location in the liver; both measurements were performed during the same SWE exam. This procedure was repeated, and each patient (n = 112) underwent 20 measurements, 10 with normal and 10 with maximum intercostal probe pressure. A total of 2240 measurements were performed in the study (20 measurements * 112 patients) (see Fig. 1).

**2-D SWE liver examination with comb-push technology**

We used the GE Logiq E9 (GE Healthcare, Wauwatosa, WI, USA) with a convex probe (C1-6), for all examinations. The liver volume was explored with the 2-D SWE comb-push method. According to the manufacturer, ARFIs generate shear waves with very small amplitudes that attenuate quickly in the liver, as they propagate away from the excitation source. Thus, multiple push beams can be transmitted to generate shear waves over a large region of tissue. We combined the ARFIs with a time-interleaved tracking scheme to maintain a constant effective temporal sampling rate. To facilitate the calculation of shear wave speed, a directional filter was applied to separate each pulse into a left propagating wave and a right propagating wave; otherwise, the waves can constructively and destructively interfere with neighbouring pushes. A time-of-flight algorithm was used to estimate the shear wave speed at every location in the SWE region of interest (ROI). Comb-push technology uses several simultaneous push-
pulses arranged spatially in the image to compensate for the reduction in amplitude as the waves propagate (GE Healthcare 2018) (Song et al. 2012, 2015). Imaging in B-mode provides several benefits: spatial variations in stiffness can be observed and vessels and lesions can be avoided. Moreover, poor B-mode quality and tissue motion are immediately revealed. As the shear wave propagates through the liver, changes in its speed reflect changes in liver stiffness. Shear waves propagate faster in stiff tissues. Thus, shear wave speed is expressed in meters per second, but in this study, we converted the speed to the Young’s modulus \( E \) expressed in kilopascals (kPa) using \( E = \frac{3 \rho c^2}{\rho} \), where \( c \) is the shear wave speed, and \( \rho \) is tissue density. This equation assumes an elastic, linear, isotropic and homogeneous material that is nearly incompressible (Barr et al. 2016; Dietrich et al. 2017). SWE examinations were performed after patients had fasted 5 h. Because the liver stiffens during physical activity, all patients rested 10 min before the SWE examination (Gersak et al. 2016). Patients were placed in a supine position with the right arm elevated above the head (Barr 2014). To control for the respiratory phase, patients were asked to stop breathing in a relaxed phase during the measurement (Ling et al. 2013). Patients unable to hold their breath were provided a nose clip and instructed to close their mouth to suspend breathing during the SWE measurements. When the patient was in a relaxed breathing phase, the SWE image was placed in B-mode, which presented a colour-coded sample area. The probe was placed in an intercostal position, and the target was liver segment VII/VIII (Dietrich et al. 2017; Ferraioli et al. 2015; Goertz et al. 2010; Liao et al. 2015). In this study, the measurement regions were placed on different shear wave image frames; thus, the non-overlapping measurement regions were never within the same frame. We selected a fixed circular ROI with a diameter of 1.25 cm, and the area \( A = \pi d^2/4 \) was 1.23 cm\(^2\). The selected ROI was placed by moving a trackball over the area, and the measurements were performed within 3–5 cm beneath the liver capsule (Dietrich et al. 2017; Ferraioli et al. 2015; Huang et al. 2014; Wang et al. 2014). Whenever possible, the beam was maintained at a zero angle, and the probe was held perpendicular to the liver (Karlas et al. 2011). The median of 10 measurements was used in the analyses (Dietrich et al. 2017; Ferraioli et al. 2015). Each median value was classified with the Metavir score table (Barr 2014; Goodman 2007).

Directly after the ultrasound-based SWE examination, we investigated the presence of steatosis. TE was performed with a FibroScan program integrated into the GE Logiq S8 (GE Healthcare). The ultrasound-controlled attenuation parameter (CAP) was used to rule out (values <248 dB/m) or confirm (values ≥248 dB/m) the presence of steatosis (Karlas et al. 2017). The manufacturer recommended the M-probe for patients with SCDs ≤2.5 cm and the XL-probe for those with SCDs >2.5 cm, but the FibroScan was not designed to measure patients with SCDs >3.5 cm. Liver tissue was explored...
with the FibroScan settings $d = 1 \text{ cm}$ and length $(l) = 4 \text{ cm}$, which gave a volume of $3.14 \text{ cm}^3 \left( V = \pi r^2 l \right)$, which was 100 times larger than the volume explored with a liver biopsy (Lee 1994).

The presence of ascites in the liver was confirmed or ruled out with a standard B-mode ultrasound examination. According to the manufacturer, the cutoffs were $<5.48 \text{ kPa}$ for Metavir F0, $5.48–8.29 \text{ kPa}$ for Metavir F1, $8.29–9.40 \text{ kPa}$ for Metavir F2, $9.40–11.9 \text{ kPa}$ for Metavir F3, and $>11.9 \text{ kPa}$ for Metavir F4 (GE Healthcare 2018).

**Examination quality**

Patients wore light clothing for all weight and height measurements. The same operator (author M.B.) performed all SWE measurements with the same ultrasound systems, equipped with probes calibrated by the manufacturer. The operator was blinded to the SWE results performed with maximum intercostal probe pressure; those results were calculated after the examinations were completed. Technical failure was defined as a failure to obtain a colour map in at least 50% of the sampling area (GE Healthcare 2018). For technical success, the colour map had to be obtained in 50% or more of the sampling area (GE Healthcare 2018). When this coverage was not achieved, the penetration program was activated by the operator to increase the thermal index (TI), which increased the pulse duration and decreased the frame rate (GE Healthcare 2018). The median SWE measurement (kPa) was saved in a worksheet, printed as an image, in the ultrasound device. All SWE measurements (normal and maximum intercostal probe pressures) were stored in the same worksheet, but only the IQR/median and SWE results for scans performed with normal intercostal pressure were accessible during the SWE examination.

**Serum biomarkers**

Blood samples were drawn within 3 month of the SWE examination to estimate fibrosis markers. The APRI calculation was based on formulas publicly available. APRI scores $\geq 0.7$ had 77% sensitivity and 72% specificity for identifying significant fibrosis ($\geq F2$) (Chou and Wasson 2013; Lin et al. 2011; Sterling et al. 2006).

**Skin-to-liver capsule distance**

For every SWE measurement, the SCD was recorded in the same image (Fig. 2).

**Definition of belly height**

The belly height was measured at the same time as the SWE examination. Belly height was measured as the height from the bed surface to the highest spot in the belly, with the patient lying in a supine position.

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Fig. 2. Ultrasound image with shear wave elastography parameters. Red line: skin-to-liver capsule distance. Circle: region of interest (spherical volume).
Definition of probe pressure
In this study, we defined intercostal probe pressure as follows. Normal intercostal pressure was the pressure required for sufficient contact with the skin. Maximum intercostal pressure was the highest pressure allowed by the patient and/or sufficient pressure to reduce the distance between the probe surface and the outer border of the rib cage to 1 cm, at the most.

Definition of the required number of measurements
According to current guidelines for SWE of the liver, a median of 10 technically successful measurements are required for a reliable SWE examination of the liver (Dietrich et al. 2017; Ferraioli et al. 2015). For technical success, the colour map has to cover 50% or more of the sampling area, according to the manufacturer (GE Healthcare Armonk, NY, USA). When this coverage was not achieved, the penetration program was activated by the operator to increase the TI, which increased the pulse duration and decreased the frame rate (GE Healthcare Armonk, NY, USA; 2018). In the presence of a high SCD, technically successful measurements cannot always be obtained for all 10 measurements; therefore, it would not be considered a reliable exam. However, instead of ruling out exams without the 10 required technically successful measurements, we reasoned that it might be possible to reduce the number of technically successful measurements required for a reliable exam. To explore this possibility, our secondary study aim was to determine the number of technically successful measurements required to achieve a reliable SWE examination. We analysed all images for all measurements in all 112 SWE examinations. We then summarised in a table the number of technically successful measurements performed with normal and maximum intercostal probe pressures. We then evaluated the number of reliable exams that could be obtained, as we stepped down the required number of successful measurements, one-by-one, from the current requirement of 10 successful measurements.

Statistics
All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS), Version 23 (IBM, Armonk, NY, USA).

This study included a total of 2240 measurements, divided equally between the normal and maximum intercostal probe pressure data sets. Liver stiffness measurements (kPa) are expressed as the median (IQR). Continuous variables are expressed as the mean ± standard deviation (minimum—maximum). Categorical variables are expressed as the frequency and percentage. Differences between the two groups were assessed with the Friedman test or a correlation test and Spearman’s ρ. Differences in technical success between the two groups were assessed with the Wilcoxon test. Differences between required amounts of measurements were assessed with the Friedman test. SWE reliability was defined by setting a cutoff with an IQR/median >30% were considered to provide a poor SWE result. To determine the SCD for reliable SWE examinations, we employed a scatterplot analysis. To investigate the influence of probe pressure on abdominal obesity interference, we performed a binary univariate logistic regression analysis on belly height measurements, with an IQR/median >30% as cutoff.

Ninety-five percent confidence intervals (95% CIs) were calculated for statistical tests. A p value <0.05 was considered to indicate statistical significance. All statistical tests were two-sided.

RESULTS
A total of 112 patients were included in this study. Patient characteristics are summarized in Table 1. Ascites was not detected in any patient.

Influence of intercostal probe pressure on SCD
The mean SCDs were 1.98 ± 0.57 cm (range: 1.00—3.87) when measured with normal intercostal probe pressure and 1.74 cm ± 0.45 (range: 0.96—3.18), when measured with maximum intercostal probe pressure. The

| Table 1. Baseline characteristics of patients that underwent shear wave elastography |
|----------------------------------------|------------------|
| Characteristic                        | Measurement*     |
| Number of patients, N                 | 112              |
| Age, y                                | 46.04 ± 16.13    |
| Sex                                   |                  |
| Male                                  | 61 (54.50%)      |
| Female                                | 51 (45.50%)      |
| Body mass index, kg/m²                | 26.84 ± 5.61 (16.32—45.34) |
| Smoking habits                        |                  |
| Non-smoker or former smoker           | 80 (71.40%)      |
| Daily smoker                          | 32 (28.60%)      |
| Diagnosis                             |                  |
| Primary biliary cholangitis           | 1 (0.90%)        |
| Hepatitis C virus                     | 62 (55.40%)      |
| Hepatitis B virus                     | 30 (26.80%)      |
| Alcoholic steatohepatitis             | 4 (3.60%)        |
| Non-alcoholic steatohepatitis         | 1 (0.90%)        |
| Non-alcoholic fatty liver disease     | 8 (7.10%)        |
| Cholestasis                           | 2 (1.80%)        |
| Autoimmune hepatitis                  | 1 (0.90%)        |
| Primary sclerosing cholangitis        | 1 (0.90%)        |
| Methotrexate1                         | 2 (1.80%)        |
| Steatosis                             |                  |
| Absent                                | 57 (50.90%)      |
| Present                               | 55 (49.10%)      |
| Cirrhosis                             |                  |
| Absent                                | 104 (92.90%)     |
| Present                               | 8 (7.10%)        |
| Diabetes                              |                  |
| Absent                                | 104 (92.90%)     |
| Present                               | 8 (7.10%)        |

* Values are expressed as the number, number (%), mean ± standard deviation or mean ± standard deviation (minimum—maximum).
† Including 21 patients treated for hepatitis C virus.
‡ Patients treated with methotrexate.
The difference between means was 0.27 cm (13.79%). The difference between groups was greatest at the high end of the range, where the maximum SCD value decreased from 3.87 cm in the normal pressure group to 3.18 cm in the maximum pressure group; this difference between groups (0.69 cm, 21.70%) was significant ($p < 0.001$). Indeed, the individual with the largest SCD (3.87 cm at normal pressure) had a 78.29% reduction (to 3.03 cm) with maximum intercostal probe pressure.

Our scatterplot analysis revealed that SWE reliability became poor at a SCD of 3.67 cm with maximum intercostal pressure and at a SCD of 2.54 cm, with normal intercostal pressure.

**SWE results at normal and maximum intercostal probe pressures**

Liver stiffness measurements (performed with an intercostal approach, in liver segments VII/VIII, at a depth of 3–5 cm beneath the liver capsule, according to current guidelines) based on the SWE results differed significantly between groups. SWE values were significantly higher in the normal pressure group (mean: 5.96 kPa, IQR: 2.41, median: 5.49 kPa) than in the maximum pressure group (mean: 5.45 kPa, IQR: 1.96, median: 5.02 kPa, $p < 0.001$) (Fig. 3A). SWE examinations were reliable in 93 (83.00%) patients in the normal pressure group and in 101 (90.20%) patients in the maximum pressure group, using IQR/median >30% as cutoff. There was a significant, strong correlation between the median SWE values measured in the normal and maximum pressure groups (Spearman’s $\rho = 0.622$, $p < 0.001$) (Fig. 3B).

**Influence of increased probe pressure on technical success**

The application of maximum intercostal probe pressure significantly ($p < 0.001$) influenced the technical success of the SWE measurement. The normal and maximum intercostal probe pressure groups had 981 (87.59%) and 1098 (98.04%) technically successful SWE measurements, respectively. Thus, technical success increased by 11.93% (117 additional measurements) when maximum intercostal probe pressure was applied.

**Influence of increased probe pressure on detection of significant fibrosis**

With normal intercostal probe pressure, we identified 15 (13.40%) cases of liver fibrosis in stages $\geq$F2.
(cutoff for F2: 8.29—9.40 kPa). With maximum intercostal probe pressure, we identified 12 (10.70%) cases of liver fibrosis in stages ≥F2. The difference between groups was not significant ($p = 0.405$). With evaluations at normal and maximum intercostal probe pressures, we diagnosed similar numbers of cases in the different stages of liver fibrosis ($P = 0.197$) (Table 2).

**Influence of probe pressure on required number of measurements**

For technical success in a measurement, a colour map had to be obtained in at least 50% of the sampling area (GE Healthcare 2018). A reliable SWE examination was defined as a group of technically successful measurements sufficient for a correct diagnosis; according to current guidelines, a reliable SWE examination required 10 technically successful measurements (Dietrich et al. 2017; Forrioli et al. 2015). Depending on how many technically successful measurements were required for a reliable SWE examination, the number of patients with successful, reliable SWE examinations varied. Table 3 lists the numbers of technically successful exams achieved, depending on the number of measurements required for a reliable SWE examination, for examinations with normal and maximum intercostal probe pressures. When 3 technically successful measurements were required, reliable SWE examinations were achieved in all 112 (100%) patients measured with maximum intercostal probe pressure, but in only 107 (95.53%) patients measured with normal intercostal probe pressure. Reliable SWE examination rates ranged from 95.53% to 73.21% with normal intercostal probe pressure and from 100% to 91.07% with maximum intercostal probe pressure. No significant difference ($p = 0.625$) was shown between SWE results from 3 measurements performed with maximum intercostal probe pressure and SWE results from 10 measurements performed with normal intercostal probe pressure.

**Table 2. Number of cases diagnosed with different stages of liver fibrosis, based on the different probe pressures**

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Normal probe pressure</th>
<th>Maximum probe pressure</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0/F1</td>
<td>96 (85.70%)</td>
<td>100 (89.30%)</td>
<td>0.197</td>
</tr>
<tr>
<td>F2</td>
<td>9 (8.00%)</td>
<td>6 (5.40%)</td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td>3 (2.70%)</td>
<td>3 (2.70%)</td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>4 (3.60%)</td>
<td>3 (2.70%)</td>
<td></td>
</tr>
</tbody>
</table>

* Friedman test.
† Number (%).
Table 3. Numbers of patients who had reliable shear wave elastography examinations with normal and maximum intercostal probe pressures

<table>
<thead>
<tr>
<th>Analysis group</th>
<th>No. of technically successful measurements required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal probe pressure</td>
<td>107 (95.53%)* 103 (91.96%) 103 (91.96%) 99 (88.39%) 98 (87.50%) 87 (77.68%) 87 (77.68%) 82 (73.21%)</td>
</tr>
<tr>
<td>Maximum probe pressure</td>
<td>112 (100%) 112 (100%) 112 (100%) 112 (100%) 111 (99.11%) 108 (96.43%) 107 (95.53%) 102 (91.07%)</td>
</tr>
</tbody>
</table>

* Number (%).

**Influence of probe pressure on abdominal obesity interference**

We performed a univariate regression analysis to determine the association between abdominal obesity, measured as belly height in the supine position, and a poor SWE result in men and women. Among the 61 (54.50%) men, this association did not differ between SWEs measured with normal (odds ratio [OR]: 1.25, 95% CI: 1.06–1.47) and maximum (OR: 1.27, 95% CI: 1.04–1.55) intercostal probe pressure; in both cases, a large belly height was similarly associated with poor SWE reliability. However, among the 51 women, the association differed between SWE with normal (OR: 1.00, 95% CI: 0.76–1.32) and maximum (OR: 1.32) intercostal probe pressure; in this case, a large belly height was associated with poor SWE reliability only when normal intercostal probe pressure was applied.

**Validity of the study**

Regardless of probe pressure, the ability of SWE measurements to detect significant liver fibrosis (stages ≥F2) did not significantly differ (p = 0.500) from that of APRI (n = 110).

In this study, of 112 patients, 8 were diagnosed with cirrhosis (Table 1). For these 8 patients, the median SWE of 80 (10 × 8) measurements at normal intercostal probe pressure was 9.77 kPa, and the median SWE of 80 measurements at maximum intercostal probe pressure was 10.21 kPa (Fig. 4A). The cutoff value for cirrhosis (F4) was 11.90 kPa with the GE Logiq E9. Thus, the median SWE measured at maximum intercostal probe pressure was closest to the cutoff value for clinically diagnosed cirrhosis. However, the median SWE measurements did not significantly differ between the probe pressure groups (p = 1.000).

The SWE measurements at both normal and maximum intercostal probe pressures were correlated significantly with results from liver biopsies (n = 9, Spearman’s ρ = 0.563 and ρ = 0.474, p = 0.025, respectively) (Fig. 4B, C).

**Case study**

In Figure 5, the two images for case 109 illustrate the difference between colour maps obtained with normal and maximum intercostal probe pressures. This patient had steatosis and no clinically diagnosed cirrhosis, and the reference APRI method had ruled out significant fibrosis (i.e., no fibrosis ≥F2). When the comb-push 2-D SWE technology and penetration program was performed with normal intercostal probe pressure, it failed to produce a colour map in at least 50% of the sampling area. The SCD was 2.54 cm, and the median SWE result was 10.19 kPa (F3). However, when maximum intercostal probe pressure was applied in the same area, it produced a colour map in more than 50% of the sampling area. The SCD decreased to 2.45 cm, and the median SWE result decreased to 6.32 kPa (F1).

**DISCUSSION**

To our knowledge, no previous studies have investigated the influence of increasing the intercostal probe pressure during ultrasound-based SWE comb-push measurements of the liver, following current guidelines for SWE of the liver (Dietrich et al. 2017; Ferraioli et al. 2015). In the present study, we analysed 2240 measurements and found that the maximum intercostal probe pressure method significantly decreased the SCD (p < 0.001) and significantly increased the technical success rate, compared with the normal pressure method (p < 0.001). Moreover, maximum probe pressure produced a significantly lower median SWE value (p < 0.001), with a narrower IQR, compared with the normal pressure method. Consequently, applying maximum intercostal probe pressure increased the number of reliable SWE examinations, from 93 (83.00%) to 101 (90.20%), using IQR/median >30% as cutoff. Furthermore, with this method, when only 3 technically successful measurements were required to achieve a reliable SWE examination, reliable SWE examinations were achieved in all 112 (100%) cases. Finally, the maximum intercostal probe pressure method could compensate for abdominal obesity in women, but not in men. In men, despite maximum intercostal probe pressure, obesity remained associated with poor SWE results. However, when an SWE IQR/median of ≥30% was considered a reliable SWE result, the upper limit for an amenable SCD increased from 2.54 cm with normal pressure to 3.67 cm with maximum intercostal probe pressure.
Fig. 4. (A). Liver stiffness assessed in patients with clinically diagnosed cirrhosis \((n = 8)\). Box-and-whisker plot of SWE results. The central box represents values from the 25th to 75th quartiles, and the line in the middle is the median. Left: Eighty measurements performed at normal intercostal probe pressure. Right: Eighty measurements performed at maximum intercostal probe pressure. The cut-off for cirrhosis (F4) was 11.90 kPa with the GE LOGIQ E9 \((p = 1.000)\). (B, C). Correlations between SWE and liver biopsy findings of fibrosis stages, classified with Metavir scores. Liver biopsy results \((n = 9)\) were correlated with (B) normal pressure SWE results and (C) maximum probe pressure SWE results. SWE = shear wave elastography.
When studying significant fibrosis (≥F2), both methods provided results that were not significantly different ($p = 0.405$) from those provided by the APRI method. Moreover, results from the two pressure approaches significantly correlated with each other ($p < 0.001$).

In our study, we attempted to determine a standard “maximum intercostal probe pressure.” Our goal was to achieve optimal conditions for imaging and performing SWE measurements, according to the current description of the method for SWE of the liver. We performed a median of 10 measurements with an intercostal approach, in liver segments VII/VIII, at depths of 3–5 cm beneath the liver capsule (Dietrich et al. 2017; Ferraioli et al. 2015). It is known from X-ray examinations that compression reduces attenuation and increases image quality (Olsson et al. 2010; Piippo-Huotari et al. 2018; Rubin et al. 1979). Proximity to the liver capsule is a key factor in securing reliable SWE results, as ultrasound waves in subcutaneous fat attenuate differently (Mast et al. 1999), measurement depth affects SWE result reliability (Zhao et al. 2011), and ARFIs attenuate more rapidly in subcutaneous fat than in other tissues (Barr et al. 2016; Barry et al. 2012). Similar to compression in X-ray imaging, hardly any pressure is required to get close to the liver in thin patients. In heavier patients, it is possible to compress the skin, subcutaneous tissue, and fat to reduce the distance between the probe and the outer border of the rib cage to 1 cm, at most. Further compression is difficult, and it is often uncomfortable for the patient. There are different opinions concerning the usefulness and reliability of increasing the intercostal probe pressure during ultrasound-based SWE measurements. It remains unclear whether excessive intercostal probe pressure is associated with an increase in shear wave speed in the liver, when push pulses are used (Shiina et al. 2015). Nevertheless, previous studies have recommended activating the penetration mode and applying intercostal probe pressure to increase the shear wave signal (Cosgrove et al. 2013). In our study, we assumed that the rib cage effectively prevented significant alterations in conditions within the liver because of the pressure force applied with the transducer, and our results were consistent with that assumption. The maximum intercostal probe pressure significantly lowered the SWE result. Alternatively, when ultrasound is performed on the left lobe (i.e., not intercostally), an increase in probe pressure will most likely affect blood flow in the examined area, among other things (Hudson et al. 2013; Ling et al. 2013).

In our opinion, it is highly relevant to focus on the right lobe for potential liver changes. For unknown reasons, the right lobe is typically affected earliest and most extensively in patients with alcohol-induced liver disease (Ham 1990). Moreover, in patients treated with chemotherapy, early, and sometimes dramatic, changes are detected with CT selectively in the right, but not the left lobe (Ham 1990). In a compensated liver, it is

Fig. 4. Continued.
Fig. 5. Examples of the different SWE colour maps obtained in the same sampling area, when normal or maximum intercostal probe pressure was applied. (A) Measurement obtained with normal intercostal probe pressure. (B) Measurement obtained with maximum intercostal probe pressure.
important to diagnose cirrhosis early, and at early times (Berzigotti 2017), ARFI diagnostic accuracy was significantly higher in the right liver lobe than in the left liver lobe (Pfeifer et al. 2014). However, the difference in ARFI accuracy between the liver lobes seemed to disappear with increasing fibrosis (Karlas et al. 2011), and another study revealed higher ARFI accuracy in the right lobe (Toshima et al. 2011). Discrepancies between studies might be due to differences in disease aetiology; some diseases might exhibit heterogeneity in liver fibrosis (Goldstein et al. 2005). In one study, morphometric changes caused by cirrhosis associated with all aetiologies commonly exhibited atrophy of the medial and anterior segments and right lobe and hypertrophy of the lateral segment and caudate lobe (Ozaki et al. 2016).

Finally, the standardization of maximum intercostal probe pressure with a robot force-controlled method (Bell et al. 2016) would not improve reliability because the SCD differs in every patient, and different conditions of subcutaneous fat cause the ultrasound waves to attenuate differently (Mast et al. 1999). Therefore, the SWE examination performed with an intercostal approach is highly dependent on a B-mode image of high quality (Dietrich et al. 2017), which is very difficult to achieve with a robot. Thus, in our opinion, a robot force-controlled method would not be applicable to the SWE liver method (Dietrich et al. 2017), which requires an intercostal approach to achieve good-quality ultrasound images of the right liver lobe, preferably in liver segments VII and VIII.

In our study, the SCD was reduced significantly with maximum applied intercostal probe pressure. This SCD reduction significantly increased the technical success rate and also reduced the IQR, which, in turn, increased SWE reliability from 83.00% to 90.20%. Technically, subcutaneous fat can increase the absorption and reflection of the push pulse, which affects the displacement contrast (Bamber et al. 2013) and boundary conditions (Dahl and Sheth 2014). These effects could explain the differences observed in our case reports; when SWE was performed with maximum intercostal probe pressure, a lower SWE result and a more accurate diagnosis were obtained, compared with the reference APRI method. Additionally, in a study with 429 patients, high BMIs were associated with high SWE results, consistent with our results for normally applied probe pressure (Roulot et al. 2008). Another explanation for high SWE results might be the role of the input boundary conditions in SWE propagation (Guo et al. 2013). This effect was observed in our study, where SWE results increased in technically failed measurements because of increases in the signal-to-noise ratio and shear wave speed. We found that squeezing down the subcutaneous fat with probe pressure decreased SWE results, which provided more diagnostic accuracy. In addition, shear wave attenuation was reported to increase with increasing fat concentrations (Barry et al. 2012). The greatest challenges in obtaining reliable SWE examinations are obesity, increased waist circumference and limited operator experience. These limiting factors were identified in a prospective study of 13,369 examinations (Castera et al. 2010). Moreover, in an earlier study that included 188 individuals, increased subcutaneous fat was significantly associated with poor SWE reliability, with an OR as high as 3.08 (Byenfeldt et al. 2018). The ARFI pulse has a “sweet spot” at a depth of 3–5 cm, where the pulse is focused. It is assumed that SWE results will vary less when the ROI is placed at this depth (Barr et al. 2016). Therefore, it is important to squeeze down the subcutaneous fat to achieve these conditions.

Other potential ways to increase the power needed for the push pulse might be to increase the mechanical index (MI) or the thermal index (TI). For patients with high SCDs and failed SWEs, successful exams could be accomplished with higher push-pulse energy (Deng et al. 2015). However, these approaches can increase the risk of bio-effects by inducing acoustic cavitation (MI) and tissue heating (TI) (Shiina et al. 2015). In a previous study, measurements with 2-D SWE and comb-push technology failed to produce a colour map in at least 50% of the sampling area in a patient with a SCD of 3.40 cm, despite a normal BMI (Lee et al. 2017). This result emphasized the need to consider the SCD when performing ultrasound-based SWE in the liver, even in patients with normal BMIs. The notion that the SCD must be considered was supported in another study, which suggested that the SCD could be used prospectively to identify cases that might require elevated push-pulse energy (Deng et al. 2015). This notion was also supported in a previous study that included 188 individuals (Byenfeldt et al. 2018). The ability to manage this factor (SCD) in ultrasound-based SWE represents a significant advantage over Fibro-Scan, which does not allow pressure. Additionally, the penetration mode for ultrasound-based SWE can be used whenever needed, to output more acoustic energy to produce stronger shear waves (Song et al. 2016). Moreover, the M-probe is limited to an SCD of 2.5 cm, and even the XL-probe is limited to an SDC of 3.5 cm. Also, a previous study reported that the XL-probe was less reliable (Dietrich et al. 2017). In comparison, our scatterplot analysis indicated that with an SWE result with an IQR/median of ≤30% as the definition of a reliable SWE exam, the detection limit increased from a 2.54-cm SCD with normal pressure to a 3.67-cm SCD with maximum pressure. This finding suggested that by squeezing down the subcutaneous fat, maximum
intercostal pressure allowed the push pulses to traverse a larger SCD. Additionally, a previous meta-analysis revealed that ultrasound-based SWE and magnetic resonance elastography (MRE) might provide the highest diagnostic accuracy in patients with obesity (Xiao et al. 2017).

Both children and adults would benefit from shorter SWE exam times. The current definition that 10 measurements are required for a reliable SWE examination (Dietrich et al. 2017; Ferraioli et al. 2015) was originally based on measurements performed with TE (Lucidarme et al. 2009). Over time, the technology has developed; for instance, the force used to create shear waves was improved from mechanical force, in TE, to ARFI (also known as push pulses); then, different solutions were invented, such as point SWE, 2-D SWE and comb-push 2-D SWE, to mention a few (Piscaglia et al. 2016). It is reasonable to suppose that there might be differences between these technologies, and therefore, it might be possible to reduce the required number of measurements for a reliable SWE exam, compared with TE. A previous study investigated differences among technologies, where factors, including age, probe type and gender, were studied to determine their benefit to 2-D SWE results (Dietrich et al. 2018). With TE, shear waves are made only with axial displacements; in contrast, shear waves from ARFI are made with both axial and lateral displacements; this combination solves problems in situations where the axial displacements are lower than the lateral displacements (Tanter et al. 2002). Our results indicated that maximum intercostal probe pressure significantly reduced the SCD (p ≤ 0.001). In our study, the largest SCD was reduced from 3.87 to 3.03 cm (78.29%) with maximum intercostal pressure. As a result, in this case, instead of achieving only 3 of 10 technically successful measurements (i.e., with normal intercostal probe pressure), all 10 measurements were technically successful (with maximum intercostal probe pressure). Another clinical advantage of using maximum intercostal probe pressure is that it shortens the time required to evaluate a patient; we discovered that only 3 measurements were required to achieve technically successful and reliable measurements in all 112 (100%) patients. This result was supported by results from a previous study with 449 patients, in which no significant difference in liver stiffness assessments was found with 3 or 5 SWE measurements (Sporea et al. 2013). Another study with 232 patients found that the required number of measurements could be reduced to 6 (Fang et al. 2018) for a reliable SWE examination. Our results are consistent with a previous study that found that for children >6 y old who held their breath during SWE, only 3 measurements were sufficient for reliability (Shin et al. 2016). Moreover, another study compared 5 and 10 measurements, and found that 5 measurements were sufficient for reliability, except when steatosis was present and SWE values were >10 kPa (Choi et al. 2016). A potential explanation for the smaller number of measurements required for reliability in our study could be that the comb-push technology effectively enhanced multiple shear waves simultaneously in the sample region; this possibility was supported by the finding that every image pixel was close to a shear wave (Song et al. 2012, 2013, 2015). To avoid a poor-quality signal, one must consider temporal, spatial and noise information. Reducing the scan time is important for children and convenient for adults, as found in a study that required only 2 measurements for reliability (Hong et al. 2018).

Our study had several limitations. First, we lacked an accepted standard reference for validating the SWE result obtained with maximum intercostal probe pressure, apart from the liver biopsy. Moreover, we could acquire liver biopsies from only 9 patients, and only 8 patients had clinically diagnosed cirrhosis. In addition, 4 patients with cirrhosis had been successfully treated for HCV; according to a recent study, the fibrosis stage decreases when HCV treatment eliminates HCV in the patient (Korda et al. 2018). Thus, the fibrosis stages of those 4 patients were somewhat unclear. Nevertheless, no significant differences (p = 0.500) in SWE results were detected between our two intercostal probe pressure methods, with the APRI (n = 110) as reference. When comparing how many patients had liver fibrosis stages ≥F2, the normal intercostal probe pressure method identified 15 patients (13.40%) and the maximum intercostal probe pressure method identified 12 patients (10.70%). This result indicates that the maximum intercostal pressure method had better specificity than the normal intercostal probe pressure method. A previous study found that according to a receiver operating characteristic analysis, liver stiffness values at 2-D SWE with comb-push technology for fibrosis stages ≥F2 were 0.87 (95% CI: 0.79–0.93) and 0.90 (95% CI: 0.83–0.95) for ≥F3. This indicated that 2-D SWE comb-push technology was a reliable, non-invasive method for assessing liver fibrosis, when using normally applied intercostal probe pressure (Lee et al. 2017). Another study that compared MRE and ultrasound-based SWE reported significant, moderate-to-strong correlations between those methods for assessing fibrosis stages F0/F1 and F2/F3 (r = 0.68 in normal livers, r = 0.75 in livers with fibrosis stage F0 or F1 and r = 0.90 in livers with fibrosis stage F2 or F3; p < 0.001). However, they found no significant correlation between those methods for fibrosis stage F4 (r = 0.30, p = 0.31) (Yoon et al. 2014). In our study, we found a significant, strong correlation between SWE results obtained with maximum intercostal probe pressure and SWE results obtained
with normal intercostal probe pressure. Therefore, applying maximum intercostal probe pressure during the SWE measurement can be considered a valid method; it significantly reduced the SCD and increased the shear wave signal, which significantly increased the technical success of the measurements.

Another study limitation was the small number of patients in stages >F1. However, we found that the stage was not a concern because the issue we addressed was whether increased intercostal probe pressure could increase SWE results, and this issue could be addressed in patients staged as F0/F1. Instead, we found that the greater limitation was the number of patients with a SCD >2.54 cm (i.e., above the SCD range for normal intercostal probe pressures); our study included 15 of these patients. Another study that included 13 patients with SCDs >3.50 cm found that increased acoustic power was necessary to obtain successful measurements (Deng et al. 2015).

Several factors affect the SWE result, including body position (Goertz et al. 2012, Iwao et al. 1999), type of transducer (Goertz et al. 2012), food intake (Goertz et al. 2012), blood flow variations in the liver (depending on body position) (Grgurevic et al. 2011; Iwao et al. 1999), transjugular intrahepatic portosystemic shunt (TIPS) implantation (Piecha et al. 2018), respiratory phase (Goertz et al. 2012; Ling et al. 2013), physical effort (Gersak et al. 2016) and gender (Bota et al. 2013, 2014; Castera et al. 2010; Corpechot et al. 2006; Ling et al. 2013).

In this study, we found that abdominal obesity had different effects in men and women. Our binary logistic regression analysis revealed that in 61 (54.46%) men, a large belly height was associated with poor SWE reliability, regardless of whether SWE was measured with normal or maximum intercostal probe pressure. In contrast, in women, a large belly height was associated with poor SWE reliability only when SWE was measured with normal pressure. Our result suggested that abdominal obesity was more likely to lead to a false SWE result in men than in women. Our finding of a difference between men and women is interesting because several other studies have reported increased SWE results in men (Bende et al. 2018; Bota et al. 2013, 2014; Castera et al. 2010; Colombo et al. 2011; Corpechot et al. 2006; Ling et al. 2013; Roulot et al. 2008; Sirli et al. 2013). Thus, our finding might explain the difference between men and women in SWE results: it could be due to differences in abdominal fat.

CONCLUSIONS

In patients with obesity, the increased SCD poses a diagnostic challenge for ultrasound SWE measurements. Hitherto, clinicians were not well informed of the advantages of using increased intercostal probe pressure when performing ultrasound-based SWE to assess liver stiffness. We found that applying maximum intercostal probe pressure significantly decreased the SCD and significantly increased the technical success rate without compromising the SWE results. In fact, only three measurements were necessary to achieve a reliable, technically successful SWE examination.

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