Does standoff material affect acoustic radiation force impulse elastography? A preclinical study of a modified elastography phantom

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Purpose: This study was conducted to determine the influence of standoff material on acoustic radiation force impulse (ARFI) measurements in an elasticity phantom by using two different probes.

Methods: Using ARFI elastography, 10 observers measured the shear wave velocity (SWV, m/sec) in different lesions of an elasticity phantom with a convex 4C1 probe and a linear 9L4 probe. The experimental setup was expanded by the use of an interposed piece of porcine muscle as standoff material. The probe pressure on the phantom was registered.

Results: Faulty ARFI measurements occurred more often when quantifying the hardest lesion (74.0 kPa ≙ 4.97 m/sec) by the 9L4 probe with the porcine muscle as a standoff material interposed between the probe and the phantom. The success rate for ARFI measurements in these series was 52.4%, compared with 99.5% in the other series. The SWV values measured with the 9L4 probe were significantly higher (3.33±1.39 m/sec vs. 2.60±0.74 m/sec, P<0.001 in the group without muscle) and were closer to the reference value than those measured with the 4C1 probe (0.25±0.23 m/sec vs. 0.85±1.21 m/sec, P<0.001 in the same group). The SWV values measured when using the muscle as a standoff material were lower than those without the muscle (significant for 9L4, P=0.040). The deviation from the reference value and the variance increased significantly with the 9L4 probe if the muscle was in situ (B=0.27, P=0.004 and B=0.32, P<0.001). In our study, the pressure exerted by the operator had no effect on the SWV values.

Conclusion: The presence of porcine muscle acting as a standoff material influenced the occurrence of failed measurements as well as the variance and the accuracy of the measured values. The linear high-frequency probe was particularly affected.

Keywords: Elasticity imaging techniques; Ultrasonography; Standoff material; Muscles; Transducers

Introduction

Ultrasound-based shear wave elastography is a novel method to quantify tissue stiffness. There are multiple possibilities for its utilization, and many organs have been examined using this new method, with examples such as the abdominal organs [1–3] including transplanted organs [4,5], prostate [6], testis [7] cervix [8], muscles [9], vessels [10], thyroid [11], and salivary glands [12]. It has mostly been used to differentiate between benign and malignant focal lesions [2,6,11,13] or to evaluate fibrotic changes [4,14]. This method is now gradually becoming routine in clinical practice, particularly for the liver. However, as it is still quite a novel method, many possible confounding factors have not been investigated yet. One possible confounding factor is the influence of standoff material, which is defined as the material between the transducer and the region of interest. For example, when measuring the shear wave velocity (SWV) in an abdominal organ, the standoff distance contains the muscle and fat of the abdominal wall. Moreover, edema, lymphatic fluid, or heterogeneous scar tissue might be present. To date, it is not known how to proceed if such structures are present. In the current guidelines, there is only a recommendation for endoscopic ultrasound elastography that simply notes that one should avoid the interposition of large vessels, cystic lesions, or dilated ducts between the probe and the target during endoscopic measurements of the liver, as this might impair the measurements [15].

We chose to conduct a phantom study, as this enabled us to perform measurements under standardized conditions. The aim of this study was to evaluate how the SWV was influenced by the interposition of a standoff material (by placing a piece of porcine muscle between the probe and the phantom), and also whether there were significant differences in these values depending on the probe used. By conducting this study, we endeavored to obtain useful information on how to choose the best probe and measurement site and how to evaluate the SWV individually, depending on the patient´s constitution.

Materials and Methods

Technical Principles

For this study, we used Virtual Touch tissue quantification (VTTQ; product version VB21, Siemens Acuson S2000, Siemens, Erlangen, Germany) which applies acoustic radiation force impulse (ARFI) technology. This technology was described by Nightingale et al. [16] and Lazebnik [17]. In short, the investigator positions the region of interest (ROI; a fixed size of 6×10 mm for the convex 4C1 probe and 6×5 mm for the linear 9L4 probe) using B-mode

ultrasound for guidance. By the touch of a button, an acoustic push pulse is applied, and as a result the adjacent tissue experiences a small displacing mechanical force that leads to the transversal propagation of shear waves traveling perpendicular to the direction of the push pulse. The SWV is detected by tracking beams (Fig. 1) [18] and is displayed on the ultrasound monitor next to the measurement depth in meters per second (m/sec).

The SWV value characterizes the elasticity of the measured material: the higher the SWV measurement, the stiffer the target material.

When the symbol "XXXX" is shown, no valid measurement has been acquired, meaning that the confidence level determined by the SWV estimation algorithm was below 0.8 on a 0–1 scale. This can occur because the individual velocity estimates between the tracking beams differed too much to provide a reliable value. This feature helps to ensure measurement quality and to prevent the misinterpretation of invalid measurements [19].

Phantom

We performed measurements using the 049 Elasticity QA Phantom (Computerized Imaging Reference Systems, Norfolk, VA, USA) with
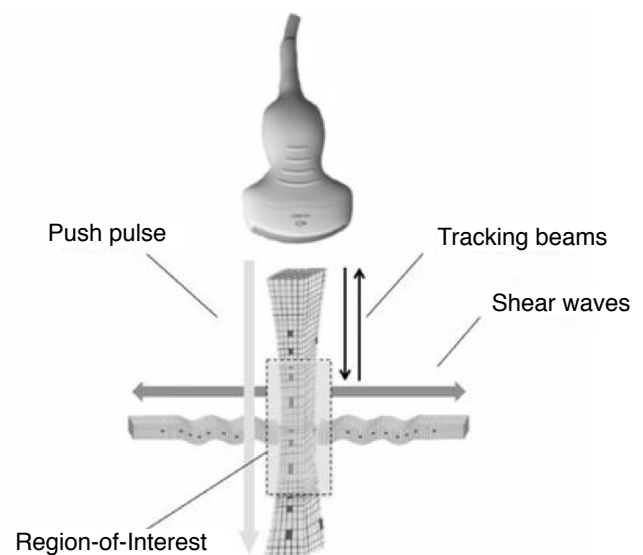
Fig. 1. Principles of acoustic radiation force impulse quantification. Acoustic push pulse (longitudinal wave) generates minimal deformation of the tissue, inducing shear waves in a user-defined region of interest, which propagate in a perpendicular direction (transverse waves). By applying tracking beams in multiple locations and revealing arrival time, the shear wave propagation speed can be quantified. It correlates closely with the tissue stiffness. Reprinted from Hollerieth et al. Ultrasonography 2016;35:345-352 [18], according to the Creative Commons licence Korean Society of Ultrasound in Medicine.

the linear 9L4 probe (7 MHz) and the convex 4C1 probe (4 MHz). This phantom contains four spherical lesions, with a diameter of 20 mm at a 35-mm depth, of different, defined stiffness (denoted by the Young's modulus E [kPa], with values of 12.0, 18.0, 47.0, and 74.0) embedded in a homogenous mass of Zerdine (E=26.0 kPa).

Conversion of the Elasticity Properties from the Young's Modulus to SWV

The Young's modulus can be related to the SWV as shown in Palmeri and Nightingale [20]:

$$SWV = \sqrt{(E/(2\times(1+\nu)\times\rho)},$$

where E indicates Young's modulus, ν, Poisson's ratio; and ρ, density.

According to the manufacturer of the phantom, Poisson's ratio can be approximately estimated to be 0.5 and the density to be 1.0 g/cm³ [21]. By simplifying the above equation, the following is obtained:

$$SWV = \sqrt{(E/3)}.$$

By means of the latter equation, the Young's modulus of the manufacturer's data (denoted in kPa) can be–at least approximately–converted into SWV (denoted in m/sec). Therefore, the SWV measured by VTTQ can be directly compared with the "true" stiffness values given by the manufacturer.

Experimental Set-up

The phantom was positioned on a digital weighing scale (Soehnle Page Profi Küchenwaage, Leifheit AG, Nassau an der Lahn, Germany) placed on a wooden board (as a stable base). The instant pressure coming from the transducer weight and the forced pressure from the investigator were monitored using the scale. As the pressure from the investigator was naturally not constant, the range of the various pressures was registered by a second investigator (K.H.) and the mean was calculated. This mean (range, 300 to 4,800 g) was used for further analysis.

To construct an experimental set-up as close as possible to the everyday clinical examination setup (when examining patients), an underlying structure was used as an arm rest. Generally, in a clinical environment, the investigator supports his or her arm on the patient; in this set-up, a sturdy object positioned in front of the phantom was used (Fig. 2A).

Ten investigators with experience in ultrasonography performed measurements on the phantom. Each of them made 10 single measurements with both probes in each of the four spherical lesions using three different methods. In the first test series, they exerted subjectively little pressure, then in the second test series, they exerted subjectively great pressure, and in the third test series, porcine muscle (close to room temperature, coated with ultrasound gel on both sides) was positioned on the surface of the phantom to provide a standoff material between the probe face and the phantom (Fig. 2B). Overall, each investigator made 2 (probes)×4 (spherical lesions)×3 (different methods)×10 (number of repetitions

A   B

Fig. 2. Experimental setup.
A. The phantom contained four spherical lesions (diameter, 20 mm; depth, 35 mm) of different, defined stiffness values (12.0, 18.0, 47.0, and 74.0 kPa), and was positioned on a weighing scale. The scale gave an indicator of the pressure exerted by the operator. The operator used an underlying object as an arm rest. B. The measurement setup when using porcine muscle as a standoff medium interposed between the probe and phantom is shown.

per measurement site)=240 single measurements. In the following analysis, the results of the first two methods were combined into a single group, corresponding to measurements made without porcine muscle. This decision was made because our phantom studies showed that the possible confounding factor of pressure did not affect the SWV measurements of the phantom and thus would not have any impact on the analysis of the data obtained from set-ups without porcine muscle. If a measurement was not valid, "XXXX" was shown on the screen. This was noted and the measurement was repeated until a valid value was obtained.

Statistical Analysis

For statistical analysis, SPSS ver. 20 and 22 for Windows (IBM Corp., Armonk, NY, USA) were used. As is generally recommended for the ARFI method, we used the average of several single measurements for our analysis, corresponding to the mean of 10 values per measurement site. Hence, the resultant sample size (as displayed in the tables) represents one-tenth of all individual measurements performed.

The mean of all SWV values, the standard deviation (SD), and the divergence from the reference value are denoted as mean±SD for each probe and for each group both with and without porcine muscle as a standoff material. To quantify the pressure exerted on the phantom by the 10 observers, the mean, SD, minimum, and maximum values were calculated.

The divergence of the SWV from the reference value was defined as the absolute value of the difference between the reference value and the average SWV of 10 measurements.

The success rate was calculated as the number of valid measurements divided by the total number of measurements performed.

Linear regression analysis was employed to evaluate the relationship between the possible influencing factors (independent variables: pressure exerted by the probe and the presence of porcine muscle as a standoff) and the standard deviation of the measured SWV (dependent variable), as well as to evaluate the relationship between the possible influencing factors (pressure exerted by the probe and the presence of porcine muscle as a standoff) and the divergence of the measured SWV from the reference value. The regression coefficient (B), the 95% confidence interval (CI), and the two-sided P-value were calculated.

The t test for two independent samples was used to compare the means of two groups, such as with or without porcine muscle or measurements made with a linear probe or a convex probe.

Two-sided P-values <0.05 were considered to indicate statistical significance.

Results

When the observers subjectively exerted more pressure, the mean and the maximum values of pressure were higher than when the observers subjectively exerted less pressure (mean±SD; higher pressure, 2,180±945 g; lower pressure, 944±480 g). However, there was a marked overlap, as the same amount of pressure that was regarded as low by some observers was regarded as high by the others (more pressure: minimum, 600 g; maximum, 4,800 g; less pressure: minimum, 300 g; maximum, 2,400 g). The regression coefficient, showing the possible association between the pressures exerted and the SD or the deviation of the measured value from the reference value, was almost zero, indicating that there was no association between pressure and the dependent variable in our study.

With the 9L4 probe, there were many more invalid measurements of lesion IV (74.0 kPa ≙ 4.97 m/sec) with the porcine muscle standoff in place; with seven investigators, between four and 40 invalid single measurements were performed before the series of 10 valid repetitions could be completed. This corresponds to a success rate of 52.4% (number of measurement attempts, 191) for those measurement series. In comparison to this, the number of invalid measurements for the other methods and/or lesions was a maximum of 2 (occurring twice); the success rate of the other measurements in these studies was 99.5% (number of measurement attempts, 2,311). The agreement between different investigators was high: the intraclass correlation coefficient was 0.981 (95% CI, 0.968 to 0.991; P<0.001).

The results of all measurements, both with and without using porcine muscle as a standoff medium, for each probe and the total difference between the probes are summarized in Table 1.

The SWV measurements obtained with the 9L4 probe were significantly higher than those measured with the 4C1 probe (P<0.001 in measurements without muscle standoff, P=0.014 in measurements with muscle standoff). Moreover, the SWV measurements made with 9L4 were significantly closer to the reference value (P<0.001 for measurements without muscle standoff, P=0.049 for measurements with muscle standoff). In the measurement series using the muscle standoff, the variation in SWV obtained with the 9L4 probe was not significantly greater than the variation in SWV measured using the 4C1 probe (P=0.063). In the series without muscle between the probe and phantom, no difference was detected between the SDs of the measurements obtained by the two different probes.

The means of the measurements with muscle as a standoff material were smaller than those without muscle (Table 1, Figs. 3, 4). This was significant for the 9L4 probe (mean difference, 0.47±0.23

Table 1. Results of the ARFI measurements with and without porcine muscle interposed as a standoff between each probe and the phantom

Parameter	Mean±SD		Average difference (4C1−9L4)	95% CI of the average difference	P-value
	4C1	9L4			
Without a muscle standoff					
Mean	2.60±0.74	3.33±1.39	−0.73	−1.08 to −0.38	<0.001[a]
SD	0.16±0.27	0.12±0.22	0.04	−0.03 to 0.12	0.273
Abs_D	0.85±1.21	0.25±0.23	0.60	0.33 to 0.87	<0.001[a]
With a muscle standoff					
Mean	2.36±0.72	2.86±1.04	−0.51	−0.90 to −0.11	0.014[a]
SD	0.22±0.35	0.44±0.65	−0.22	−0.45 to 0.01	0.063
Abs_D	1.02±1.42	0.51±0.76	0.51	0.00 to 1.02	0.049[a]

Results of the descriptive analysis and t tests; the average difference was defined as the difference of the means of both probes with a 95% CI; P-values show whether the difference between the probes was significant. The sample size (n) was 80 for each probe in measurements without the use of muscle as a standoff and 40 for each probe in measurements with the muscle standoff.

ARFI, acoustic radiation force impulse; CI, confidence interval; SD, standard deviation; Abs_D, divergence of the measured value from the reference value.

[a]A significant result.

m/sec; P=0.040), but just above the threshold of significance for the 4C1 probe (0.24±0.14 m/sec; P=0.090).

The correlation between the presence of a muscle standoff and the divergence of the measured values from the reference value was significant for the 9L4 probe. When the muscle standoff was positioned between the probe and phantom, the measured values deviated more from the reference value (regression coefficient B=0.27; 95% CI, 0.09 to 0.45; P=0.004); furthermore, the standard deviation of the SWV was significantly higher (B=0.32; 95% CI, 0.16 to 0.48; P<0.001). For the 4C1 probe, there was no significant correlation between the presence of muscle standoff and the standard deviation (B=0.06; 95% CI, −0.06 to 0.17; P=0.343) or the divergence of the measured value from the reference value (B=0.18; 95% CI, −0.31 to 0.67; P=0.474). Figs. 3 and 4 show the scatter plots of the measured SWV values versus the reference values with and without porcine muscle interposed between the probe and the phantom. A reference line was drawn: by trend, one can see that the scatter points in Fig. 4 (with muscle standoff) are lower than in Fig. 3 (without interposed muscle), while the scatter points in Fig. 4 seem to disperse little more than in Fig. 3. In both scatter plots, considerable dispersion of the measurement values of lesion IV for both probes can be observed.

Discussion

In the present study of the influence of a muscle standoff on ultrasound-based shear wave elastography, we performed measurements on a phantom with and without porcine muscle interposed between the probe and the phantom.
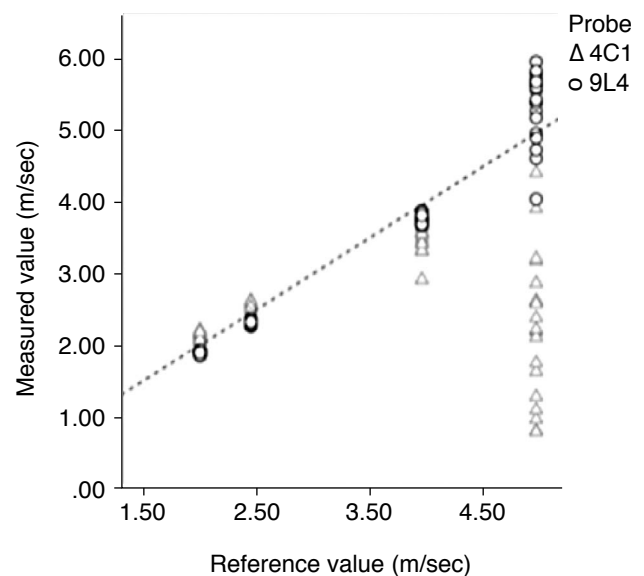

Fig. 3. Reference values versus measured shear wave velocity (SWV) values when no porcine muscle was interposed between the probe and the phantom. The scatter points in lesion I–III lie close to the reference line (dotted line), suggesting a high correlation between the measured SWV values and the reference SWV values. In lesion IV, acoustic radiation force impulse measurements did not seem to be feasible given its considerable stiffness. Especially when measuring the lesion using the convex 4C1 probe, the scatter points disperse considerably, lying below the reference line.

The association of invalid measurements ("XXXX") in measurement series performed with the 9L4 probe in lesion IV (74.0 kPa ≙ 4.97 m/sec) with the presence of the muscle standoff was noticeable, and on occasion up to 50 repetitions were necessary
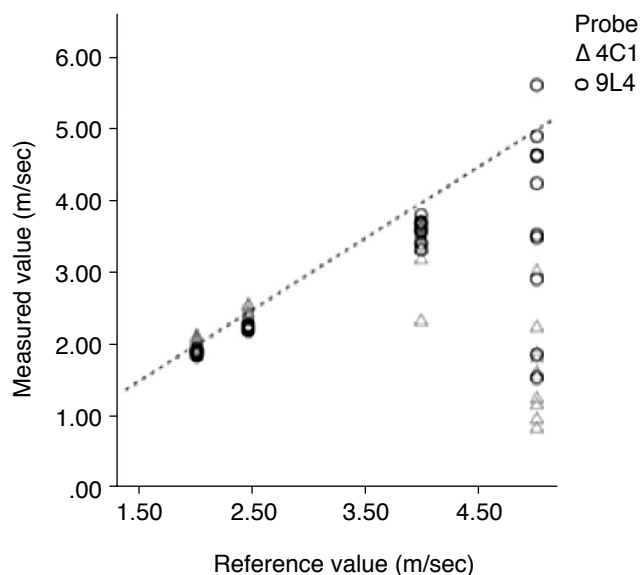
Fig. 4. Reference values versus measured shear wave velocity (SWV) values when porcine muscle was interposed between the probe and the phantom as standoff material. The scatter points tend to lie below the reference line (dotted line), suggesting an underestimation of the reference values. Espacially in lesion III and IV, the SWV values seem to disperse more than in the scatter plot without interposed porcine muscle (Fig. 3).

to obtain 10 valid measurements. The success rate of those series was 52.4%, which is dramatically lower than that of the other measurements (99.5%) or the phantom study by Yamanaka et al. (100%) [21]. It took considerably more time to perform those measurements. In studies of ARFI measurements of transplanted kidneys, success rates of 95% [22], 90% [23], and 55% [4] were reported.

"XXXX" is shown when the individual velocity estimates between the tracking beams differ too much to provide a reliable value. This helps to ensure measurement quality.

Conditions in which these high deviations occur are mentioned by the manufacturer in the user manual of the Virtual Touch tissue quantification software [24], and others have been added on the basis of the results of some research groups: strong movement of the measured object (e.g., pulsation of the heart), distinct attenuation of the signal (e.g., in obese patients) and measurements in very hard (or very soft) lesions beyond a range of SWV from 0.5 to 4.4 m/sec (in this range, SWV measurements are supposed to be valid, according to the manufacturer) [19], measurements in fluids [25], in heterogeneous structures [13], or between impediments (e.g., between the ribs) [26].

Two of these conditions apply to the measurement series discussed above. First, the porcine muscle causes attenuation of the signal, so the energy of the push pulse might not be sufficient to

generate shear waves, or the progression of the SWV peak cannot be detected or followed adequately by the system. Second, the lesion in question, with a known stiffness of 74.0 kPa (△4.97 m/sec), was outside the measurable range of stiffness described above. Moreover, waves scatter and reflect at boundaries of structures of different stiffness (muscle-phantom, background–spherical lesion) which might have contributed to the attenuation of the signal and to the increased variability of the estimated values [27]. The 9L4 probe was affected more than the 4C1 probe, which might be explained by the frequency-dependent absorption and divergence of the sound field.

In both scatter plots (Figs. 3, 4), a large dispersion of the measurement values for lesion IV (for both probes) is shown. Most likely, this lesion, with a known stiffness of 74.0 kPa (△4.97 m/sec), was too stiff for a feasible measurement (4.97 m/sec lies outside the measurable range of stiffness presented above).

Conceivably, attenuation of the signal could be the reason for the significant decrease of the mean SWV values obtained by the linear 9L4 probe with the muscle standoff in situ, compared to measurements without muscle interposed between probe and phantom.

When measuring the SWV of the lesions with 9L4 through the muscle, the values also varied, and differed more from the reference value. This agrees with the results of another phantom study, in which Hollerieth et al. [28] performed measurements with and without porcine muscle as a standoff material, with measurements made independently of any examiner by using a supporting arm to hold the probe in position.

A possible explanation for these observations may again be found in the phenomena of attenuation, scattering, and reflecting. Muscle is anisotropic tissue composed of many single fibers [9]. It can be expected that the fibers in the piece of meat that was used were not always oriented in the same direction (longitudinal fibers or cross-section), so were partly met vertically, partly in parallel, and partly obliquely by the push pulse and the tracking beams.

Despite the stronger influence of the standoff on the SWV measured by the 9L4 probe, this probe was closer to the reference value than 4C1 in both subgroups of our measurements (with and without porcine muscle). As the 9L4 probe seems to be more susceptible, it remains disputable whether it still measures more accurately than the 4C1 probe when there are more interfering factors under real examination conditions.

Disparities in measurements made using the 4C1 and 9L4 probes have also been reported in other studies on phantoms and on the liver [21,29,30]. Potential reasons for the divergence between the probes and the different reactions to standoff distance are the diverse parameters of elevation and the supporting surface due to

the geometric variation (convex vs. linear), the frequency of the push pulse used to generate the shear waves (2.67 MHz vs. 4.00 MHz), and the frequency of the tracking beams (4 MHz vs. 7 MHz).

With regard to the clinical use of VTTQ on patients, it is not inconceivable to compare the porcine muscle standoff with the skin and muscle layers of the human abdominal wall. Although this is limited by the fact that porcine muscle is dead animal tissue without perfusion and innervation, similarities exist in terms of structure, appearance in the B-mode image, and thickness. The thickness of the pieces of porcine muscle used in this study varied between 0.3 and 1.1 cm, with an average of 0.6 cm. Measurements of the stored images of 12 patients (chosen at random) showed a thickness of the muscle in the region of the lateral lower abdomen of around 0.6 cm (range, 0.1 to 1.2 cm) and 0.8 cm (range, 0.1 to 1.7 cm) when including the skin and the subcutaneous fatty tissue. Using B-mode ultrasound, the thickness of the abdominal wall also varies considerably when the muscle contracts.

The abdominal wall was considered to be an important interfering factor in other studies of shear wave elastography. In measurements of the liver, Ingiliz et al. [31] found that the thoracic skin fold thickness−an anthropometric parameter used to estimate body fat−was significantly associated with discordance of SWV values measured in different positions of the liver.

Horster et al. [32] detected a significant association of skin-liver-distance and ARFI measurements in their study comparing measurements made using Virtual Touch tissue quantification (using ARFI technology) versus FibroScan (transient elastography) on the liver of healthy subjects.

The body mass index, which is often related to an increase of the thickness of the abdominal wall, was also investigated in several studies as a factor potentially interfering with ARFI elastography. In some studies, a decrease of the SWV was observed [32], or an increase in invalid measurements and increased variability of the measured values [33,34]; however, other studies did not confirm these associations [33,35,36].

The current study is the first to show that the presence of muscle standoff between the probe and the area of interest could itself influence the SWV. Further studies are needed to evaluate the impact of other potential standoff contributors, such as edema or scar tissue.

Another possible influencing factor that was evaluated in the current study was the pressure exerted by the probe. Ten observers made measurements by subjectively exerting greater or lesser pressure on the phantom with the probe. In theory, when exerting greater pressure on an object, the material is compressed, which leads to a higher density and hardening, assuming that the object measured is compressible by the amount of pressure used and that

the volume of the object stays constant (i.e., that it is not able to be displaced laterally). Thus, SWV values and dispersion should change when the amount of pressure exerted varies. Interestingly, no significant effect was obtained in our study, although a marked compression of the spherical lesions in B-mode imaging was observed when pressing firmly. Furthermore, the phantom was surrounded by a stable box, so displacement of the material seemed to be unlikely, but could not be excluded. Some studies have reported an association between the pressure exerted and the SWV values. Tozaki et al. [13] reported that the SWV values of breast tissue were significantly higher when compressing the tissue than SWV values made without compression (subcutaneous fat, 3.33 m/sec vs. 2.66 m/sec; mammary gland parenchyma, 3.84 m/sec vs. 3.03 m/sec). Syversveen et al. [37] observed an association between the pressure exerted by the probe and the SWV values when measuring transplanted kidneys by a supporting arm which could be loaded with different amounts of weight (22 to 2,990 g); the main effect was noted for increasing pressure up to 500 g. Other studies showed that SWV values increased with increases in the internal pressure. For example, this may occur when measuring the liver if there is a biliary obstruction [14], increased central venous pressure [38], or portal hypertension [39]. Similarly, in experimental studies of the kidney, an increase of the SWV values was observed when there was an occlusion of the renal vein or hydronephrosis [40]. It is possible that the amount of pressure exerted on the phantom in our study was not high enough to compress the material to an extent that its stiffness changed. To systematically investigate the influence of pressure on shear wave elastography, another phantom and/or special equipment enabling use of a higher pressure would be necessary.

We showed that the estimation of the amount of pressure was highly dependent on investigators, as some observers felt 2,400 g to be low, whereas others regarded 600 g to be high. Statements that "less pressure was used" may correspond to a wide range of actual values.

There are some limitations of this study. First, it is unknown to what extent the results obtained from the phantom data could be applied in clinical settings. The advantage of using a phantom was the possibility to compare the measured values with a reference standard and to make measurements in a more standardized setting. Second, we could not always measure at the same depth. As the lesions had a fixed position, the measurements with muscle as a standoff material were on average 0.6 cm deeper than the measurements made without muscle. Some studies have shown that depth can influence SWV; with increasing acquisition depth, the SWV decreased [26,30]. Thus, part of the effect we saw using the muscle standoff may have been due to the deeper placement of the

ROI, even if the thickness of the muscle was only 0.6 cm on average. These limits should be kept in mind when interpreting our results and should be considered in further scientific investigations.

In conclusion, the use of porcine muscle as a standoff between the probe and the phantom influenced the occurrence of failed measurements as well as the variance and the accuracy of the measured values. The linear high-frequency probe was particularly affected. For the first time, this was shown under standardized conditions using a phantom.

Thus, considering previous studies and our results, the probe should, if possible, be positioned in a way that the distance to the target is short and does not contain any heterogeneous structures. However, it is appreciated that the practicality of these recommendations might be limited in clinical settings, and that further studies are necessary to estimate the actual influence of this factor on measurements in patients.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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