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The measurements of ultrasound parameters on calcaneus by two-sided interrogation techniques

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Abstract
Recently, ultrasound techniques have become an important alternative in the assessment of osteoporosis. The speed of sound (SOS) and broadband ultrasound attenuation (BUA) on calcaneus are commonly used in ultrasound densitometer for osteoporosis evaluation. However, the quantitative ultrasound (QUS) parameters provided by densitometer using most commercial ultrasound instruments are based on the assumption of a fixed bone thickness. Information on bone thickness is a critical factor for accurate estimation of SOS through conventional approaches; yet, the thickness of bone tissue is not available through *in vivo* measurements and it is almost impossible to obtain the thickness of bone tissue via conventional approaches. Therefore, the SOS measurements will be incorrect. The purpose of this work is to develop a two-sided interrogation technique for the SOS measurements that is less susceptible to bone thickness. The results show that this proposed technique can obtain a better SOS estimation on bone tissue. Using bone phantoms that mimic actual tissue, the validity of the approach is confirmed with measurement showing high accuracy (>99%) and low standard deviation (<0.5%). Finally, the measurements of 14 healthy subjects are also reported. The results show that this technique can provide the bone thickness information to reduce the SOS estimation errors compared with the fixed bone thickness assumption.

Keywords: quantitative ultrasound (QUS), calcaneus, two-sided interrogation techniques, osteoporosis, ultrasound densitometer

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue. Osteoporosis will lead to increased fragility of the bone and increased risk of bone fractures either spontaneous or under relatively mild trauma. Numerous studies have indicated that the interaction of ultrasound with biological tissue may result in a variation of quantitative ultrasound (QUS) parameters, such as the speed of sound (SOS), broadband ultrasound attenuation (BUA) and acoustic impedance [1]. QUS measurements can reflect the bone structure and elasticity [2–4] and predict the risk of future osteoporosis fracture [5]. Therefore, QUS has become an alternative way to evaluate the osteoporosis in clinic that eliminates x-ray exposure is highly portable and offers low cost. There are different measurement sites, including calcaneus, phalanges, patella and tibia that are used in commercial densitometers [6]. Many studies have shown that there is a strong association between QUS at the heel and fracture risk, and that the calcaneus QUS is able to predict osteoporotic fractures [6–11] including hip fractures [12, 13] and vertebral fractures [14, 15]. The calcaneus offers the most popular measurement sites since it contains high percentages of cancellous bone with high surface-to-volume ratio, and it has approximately eight times the metabolic turnover rate of cortical bone [16]. Moreover, the media-lateral surface of calcaneus is fairly flat and parallel and it is easily accessible [17, 18].

In recent years, the quantitative ultrasound (QUS) parameters obtained from the calcaneus by most commercial densitometry assumed a preset bone thickness. The preset value used for bone thickness is a critical factor for accurate estimation of SOS in conventional approaches. Unfortunately, the thickness of bone tissue cannot be determined by *in vivo* measurements. Some contact-type ultrasound densitometers use the separation distance between the transmitter and receiver as the calcaneus thickness, but this includes both the thickness of soft tissue and bone tissue. Accuracy of SOS estimation can be affected by actual bone thickness. Häusler [19] calculated the bone velocity under different calcaneus widths and compared the results with the SOS obtained from a constant preset heel width. He found that the heel width was not strongly correlated with bone thickness. Moreover, normalizing BUA measurements for bone width show no significant improvement in fracture discrimination *in vivo*. However, he found that the dry system, such as CUBA system, presses transducers against the skin to obtain the calcaneus width and the mean speed of sound (SOS) measured by contact type (soft tissue intact) is lower, 89 m s^{-1}, than the mean bone SOS (no soft tissue) *in vitro* measurements [19]. Brandenburger also indicated that uncorrected velocity differences due to bone and soft tissue thickness could be comparable to the differences between normal and fragile bone [20]. Chappard reported that the measurement errors caused by soft tissue are 3–20 times higher than the SOS short-term precision [21]. These results indicate that the inaccuracies in SOS measurements caused by the soft tissue cannot be neglected.

It is worth noting that in one important prospective study of 5662 elderly women, the baseline sound speed measurements were 1479.9 ± 23.8 m s^{-1} for subjects who experienced a hip fracture over a subsequent 2-year period as compared to 1493.4 ± 24.2 m s^{-1} for subjects who had no hip fracture [22]. The average difference is only 13.5 m s^{-1}. Another recent ultrasound study reported on calcaneus QUS measurements of postmenopausal women with and without various nontraumatic fractures. The results also indicated that women (n = 1129) with fractures (n = 656) had the lower QUS values (1481.4 ± 20.2 m s^{-1}, 98.7 ± 9.4 dB MHz^{-1}) than the women without fractures (n = 474; 1508.2 ± 26.5 m s^{-1}, 107.7 ± 9.9 dB MHz^{-1}) [11]. The differences

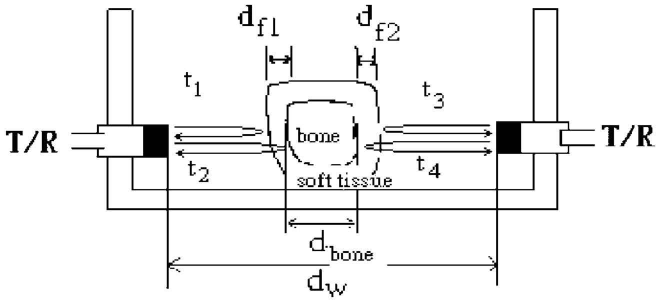

Figure 1. Ultrasound system using two-sided interrogation.

are only 26.8 m s^{-1} for SOS and 9.8 dB MHz^{-1} for BUA. Both studies used the Lunar Achilles system which employed the preset values for calcaneus width (40 mm). The SOS estimation errors were the result of the difference between the true bone thickness and the preset bone thickness. In the two-sided interrogation techniques presented in this study, bone thickness information is used to provide more accurate SOS estimation.

2. Material and methods

2.1. Theoretical development

In general, most commercial ultrasound densitometers measure the SOS by utilizing the substitution method based on the following equation [23, 24]:

$$V = \frac{V_w d_{\text{bone}}}{d + V_w\,\Delta\tau} \tag{1}$$

where the V_w is the SOS in water and is a constant value at a fixed water temperature. The time of flight (TOF) difference, $\Delta\tau$ is the travel time difference of the pulses through water or through bone tissue. The SOS in bone can be determined from the bone thickness, the TOF difference and sound speed on water. Unfortunately, the thickness of bone tissue, d_{bone}, is not commonly available in *in vivo* measurements. Therefore, most commercial ultrasound densitometers, such as Lunar Achilles and UBIS 5000 system, assume a preset value for bone thickness. Actually, the thickness of calcaneus and the thickness of soft tissue are subject to inter-subject variation. The SOS estimation errors that occur between the measurements based on true bone thickness versus those based on present values can be represented by

$$\frac{V - V_p}{V} = \frac{1 - \frac{d_p}{d_{\text{bone}}}}{1 + \frac{d_p}{V_w\,\Delta\tau}} \tag{2}$$

where V and V_p represent the SOS derived from equation (1) using true bone thickness (d_{bone}) or preset value (d_p), respectively. Again, equation (2) shows that the SOS estimation errors are highly dependent on the variation of the true bone thickness with respect to the preset value.

To eliminate the bone thickness effect on calcaneus QUS measurements, a two-sided interrogation technique is proposed in this study as shown in figure 1. The two transducers placed on both sides of the test object act as transmitter or receiver as in the traditional substitution approach. Those transducers can also switch to reflection mode on both sides. In this configuration, the following

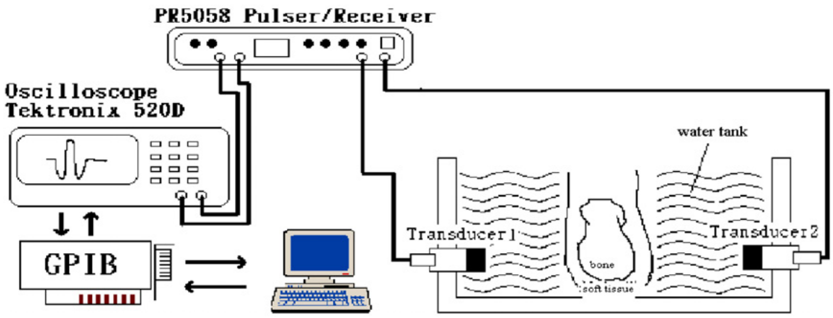

Figure 2. The experimental set-up of the two-sided interrogation system.

equations can be directly derived:

$$\frac{d_{f1}}{V_f} = \frac{t_2 - t_1}{2} \tag{3}$$

$$\frac{d_{f2}}{V_f} = \frac{t_4 - t_3}{2} \tag{4}$$

$$d_{\text{bone}} = d_w - V_w\left(\frac{t_1}{2} + \frac{t_3}{2}\right) - V_f\left(\frac{t_2 - t_1}{2} + \frac{t_4 - t_3}{2}\right) \tag{5}$$

$$t_d = \frac{d_{f1} + d_{f2}}{V_f} + \frac{d_{\text{bone}}}{V_b} + \frac{d_w - d_{\text{bone}} - (d_{f1} + d_{f2})}{V_w} \tag{6}$$

$$V_{\text{bone}} = \frac{V_w d_{\text{bone}}}{d_{\text{bone}} + \frac{V_f}{2}(t_2 - t_1 + t_4 - t_3) + V_m\left(t_d - t_w - \frac{t_2 - t_1 + t_4 - t_3}{2}\right)} \tag{7}$$

where t_1 and t_2 are the TOFs from the front and the rear boundaries of the soft tissue layer as received in reflection mode for the left side transducer. The t_3 and t_4 are the TOFs from the front and the rear boundaries for the soft tissue layer as received in the reflection mode for right side transducer. The t_d and t_w are the TOF with and without the test object also from transmission mode. The TOF can be determined using different criteria to define the transit time of the pulse: first arrival, 10% threshold, first zero crossing or the envelope maximum. The first arrival means the time marker was placed at the point of first apparent deviation from the time axis of the
Q1 pulse. The 10% threshold means the time marker positioned at a point on the rising edge of the signal corresponding to 10% of that amplitude and the first zero crossing is the time marker was placed at the point where received waveform first crossing the time axis [25]. The envelope maximum is the time marker placed at the envelope peak (local maximum) position where the received or echo signal [26]. The d_{f1} and d_{f2} represent the thickness of the soft tissue on both sides of the calcaneus. If the separation distance between the transducers (d_w) and the SOS in soft tissue (V_f) and water (V_w) are known, then the thickness of bone tissue (d_{bone}) can be obtained from equation (5). Finally, the true bone velocity (V_{bone}) can be calculated from equation (7).

Similarly, the attenuation coefficient can also be obtained from the amplitude spectrum difference as shown in the following equation [23]:

$$\alpha = \frac{1}{d_{\text{bone}}} \ln\left(\frac{A_w(f)}{A_d(f)}\right) \tag{8}$$

where A_w is the amplitude of the signal in water and A_d represents the amplitude in calcaneus. The BUA is obtained by calculating the slope between 200 kHz and 600 kHz using equation (8).

2.2. System description

The experimental set-up of the proposed system is shown in figure 2. Two identical broadband 500 kHz focused transducers (Panametrics V391, 28.6 mm aperture, 38.1 mm focal distance) were mounted aligned and submersed in water tank. The separation distance of two transducers is 130 mm long. Both transducers were connected to a commercial ultrasound pulser/receiver (Panametrics 5058PR) that can operate in either transmission mode or pulse echo mode. Signals were acquired by a digital oscilloscope (Tek.520D, Beaverton, OR, USA, 100 MHz sampling rate) and were transferred via a GPIB interface to a personal computer for further processing. The interface was designed using LabVIEW and the stored signals were analysed off line to automatically obtain the t_1, t_2, t_3 and t_4 based on the envelope maximum criterion developed on the software package MATLAB® (Math Works, Natick, MA, USA). To reduce the temperature effects on acoustic velocity, an electrical thermal-controlled system was also immersed in the water tank to keep the water temperature at 21.0 ± 0.2 °C.

2.3. Test materials

Two commercial bone phantom mimics were used to represent normal bone tissue and osteroporotic bone tissue. Both phantoms were manufactured by CIRS Inc. (Norfolk, VA, USA). One was designed to mimic normal bone tissue (73.0 mm × 59.0 mm (L × W), thickness = 36.3 mm, BUA = 69 dB MHz^{-1}, SOS = 1576 m s^{-1}) while the other was designed to mimic osteoporotic bone tissue (73.0 mm × 59.0 mm (L × W), thickness = 36.4 mm, BUA = 48 dB MHz^{-1}, SOS = 1501 m s^{-1}). The BUA values specified by the manufacturer were evaluated over the frequency range from 250 kHz to 550 kHz. Porcine skin tissues of different thicknesses were attached to simulate bone tissue with different amount of soft tissue. Finally, 14 healthy volunteers, including 6 males and 8 females, with an averaged age of 25 ± 3 years (ranging from 21 to 48 years) were recruited for this test. Informed consent was obtained from all volunteers.

3. Results and discussion

3.1. Simulation

To investigate the SOS estimation errors that occur when preset values of calcaneus thickness are used versus true calcaneus

Table 1. The QUS evaluation of bone phantoms with attached porcine tissue.

	QUS					
Phantom	d_{bone} (mm)	d_{soft} (mm)	V_{heel} (m s^{-1})	V_{bone} (m s^{-1})	V_{bare} (m s^{-1})	BUA (dB MHz^{-1})
Normal bone phantom	34.3 ± 1.6	8.0 ± 0.4	1586.4 ± 4.0	1567.0 ± 5.6	1567.4 ± 5.4	76.4 ± 2.2
Osteoporotic phantom	35.0 ± 1.1	8.2 ± 0.8	1537.4 ± 4.4	1498.4 ± 6.4	1495.0 ± 1.1	62.4 ± 2.5

Porcine tissue thickness = 7.3 mm; normal bone phantom thickness = 36.3 mm; osteoporotic phantom thickness = 36.4 mm; d_{bone}: the bone thickness measured by the two-sided interrogation techniques; d_{soft}: the porcine tissue thickness measured by the two-sided interrogation techniques; V_{bare}: the SOS (bare phantom without soft tissue attached) measured by the substitution method; V_{heel}: the accumulated SOS estimated by the substitution method but assuming constant thickness (includes bone phantom and porcine tissue); V_{bone}: the calcaneus SOS estimated by two-sided interrogation technique.

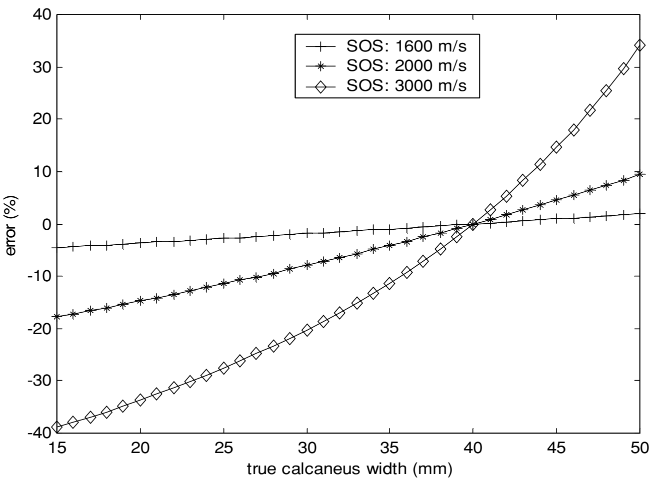

Figure 3. The SOS estimation errors versus true bone tissue thickness for different bone velocities assuming a preset bone thickness of 40 mm. ((+) 1600 m s^{-1}, ($*$) 2000 m s^{-1} and ($\Diamond$) 3000 m s^{-1}) in equation (1).

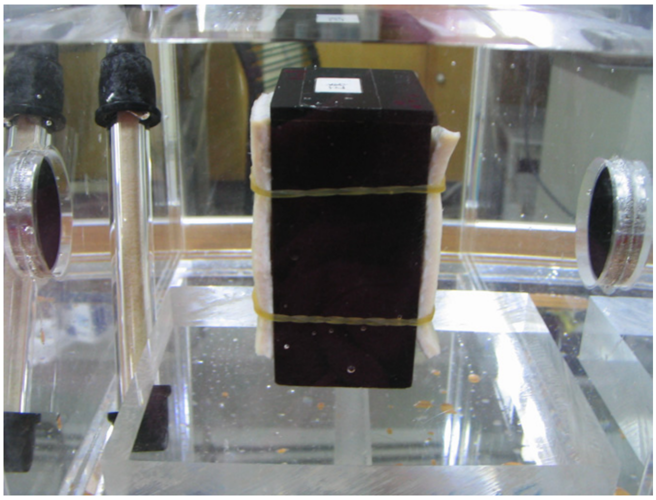

Figure 4. A picture of *in vitro* measurements using a bone phantom with porcine tissue attached to both the sides. The two-sided transducers are visible.

thickness, we used the Lunar Archilles system as an example clinical instrument. The preset bone thickness is 40 mm on the Lunar Achilles system for SOS calculation. If the true bone thickness ranged between 15 mm and 50 mm and the calcaneus SOS values ranged between 1600 m s^{-1} and 3000 m s^{-1}, then the SOS estimation errors are as shown in figure 3. As expected, these results show that the larger the difference between true bone thickness and preset bone thickness, the larger the errors of the SOS measurements. Similarly, if the SOS of bone tissue increases, then the SOS estimation errors also increase.

3.2. Bone mimic phantom tests

To validate the system performance with the two-sided interrogation techniques both sides of bone phantoms were padded with porcine tissue to simulate soft tissue. A porcine tissue with 7.3 mm thickness was attached on the phantoms as shown in figure 4. The SOS of porcine tissue obtained from the substitution method is 1660.0 ± 5.3 m s^{-1}. V_{bone} represents the modified SOS after eliminating soft tissue influences using the two-sided interrogation technique and V_{heel} represents the accumulated SOS estimated by the substitution method but using constant thickness assumptions of 43.6 mm for normal bone phantom and 43.7 mm for osteoporosis phantom, respectively. Utilizing the two-sided interrogation techniques, the results shown in table 1 indicate that the porcine tissue leads to an increase in the bone SOS value while the influence of the soft tissue is neglected. The porcine tissue increases the SOS estimation by 2.65 m s^{-1} per mm porcine skin thickness for a normal bone phantom and by 5.34 m s^{-1} per mm porcine tissue thickness for osteoporotic phantom. However, the BUA decreases less than 1.12 dB MHz^{-1} per mm porcine tissue attaching the normal and osteoporostic phantoms. These results imply that the porcine tissue increases the SOS evaluation, but decreases only slightly the BUA measurements in both bone phantoms. Although the accuracy of predicting the thickness of bone and soft tissue using the two-sided interrogation system was only 88%, however, comparing the modified SOS (V_{bone}) and the real SOS (V_{bare}) in table 1 indicates that the accuracy could be as high as 99% for SOS measurements *in vitro* based on 5 measurements for each phantom.

3.3. In vivo measurement

Fourteen healthy volunteers were also tested using the two-sided interrogation measurement system. Five measurements were made on each subject as shown in figure 5. The V_f is assumed as 1540.0 m s^{-1} in equation (7). The results are shown in table 2 which shows that the calcaneus widths of males are generally greater than the widths of females. The widths of calcaneus (averaged 40.18 mm, ranged from 32.0 mm to 47.5 mm) as evaluated by the two-sided interrogation

Table 2. The results of SOS and nBUA measurements on 14 subjects.

No	Sex (F, M)	$V_{27\text{ mm}}$ (m s^{-1})	V_{bone} (m s^{-1})	V_{UBIS} (m s^{-1})	d_{bone} (mm)	nBUA$_{\text{m}}$ (dB (MHz cm)$^{-1}$)
1	M	1595.3 ± 19.6	1537.8 ± 9.6	1579.5 ± 5.1	46.5 ± 3.5	20.7 ± 2.6
2	M	1502.2 ± 1.8	1487.9 ± 3.6	1483.2 ± 4.5	42.8 ± 0.7	20.6 ± 1.4
3	M	1517.1 ± 9.9	1496.1 ± 7.1	1517.0 ± 3.6	41.2 ± 1.7	20.4 ± 0.8
4	M	1545.3 ± 5.6	1512.0 ± 2.7	1522.6 ± 2.4	47.5 ± 0.6	18.1 ± 1.2
5	M	1565.9 ± 9.7	1529.7 ± 3.4	1548.1 ± 5.7	42.5 ± 1.1	23.4 ± 1.7
6	M	1563.7 ± 7.9	1499.6 ± 4.5	1533.4 ± 6.5	38.7 ± 3.4	24.0 ± 2.1
7	F	1559.8 ± 1.6	1525.1 ± 2.1	1553.0 ± 6.0	42.4 ± 2.1	22.0 ± 1.8
8	F	1563.7 ± 7.9	1520.6 ± 4.5	1542.2 ± 4.4	39.6 ± 1.6	21.6 ± 3.3
9	F	1522.5 ± 1.8	1501.6 ± 1.8	1528.4 ± 5.3	40.0 ± 1.5	21.5 ± 1.0
10	F	1533.4 ± 7.7	1511.2 ± 4.9	1532.6 ± 7.4	33.3 ± 1.9	29.1 ± 2.2
11	F	1544.9 ± 9.3	1521.0 ± 9.4	1555.2 ± 6.8	39.3 ± 1.4	21.6 ± 1.9
12	F	1492.3 ± 11.0	1473.7 ± 11	1500.0 ± 5.2	41.8 ± 5.6	18.1 ± 2.8
13	F	1556.3 ± 7.7	1517.2 ± 7.3	1563.2 ± 3.2	32.0 ± 1.4	26.2 ± 3.1
14	F	1542.1 ± 11.5	1518.5 ± 7.7	1551.6 ± 7.5	35.0 ± 0.8	25.4 ± 2.3
Average		1539.64 ± 30.27	1510.86 ± 17.36	1536.43 ± 25.44	40.18 ± 4.46	22.34 ± 3.05

$V_{27\text{ mm}}$: the calcaneus SOS obtained from the substitution method assuming a constant bone width (27 mm); V_{bone} : the calcaneus SOS estimated by two-sided interrogation technique; V_{UBIS} : the calcaneus SOS measured using UBIS 5000 system; d_{bone} : the calcaneus width estimated by two-sided interrogation technique; nBUA : normalized BUA.

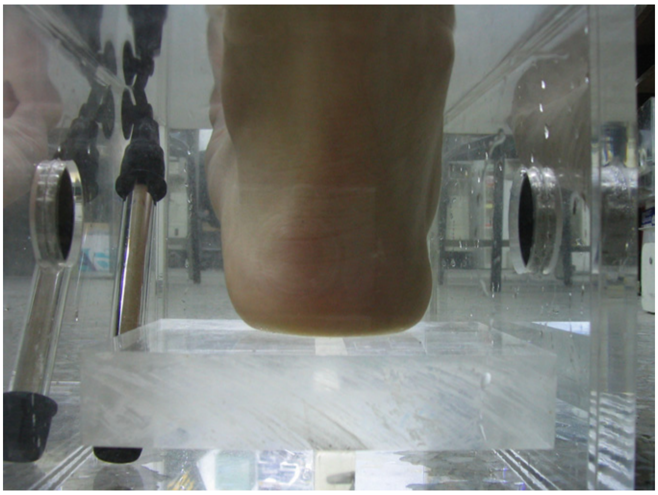

Figure 5. A picture of the two-sided interrogation technique for calcaneus measurements applied to a human subject.

techniques are greater than those that have been measured post-mortem using caliper (25.0–26.7 mm) [23]. This may be because the measuring site in our system was not in the same location as the caliper measurements. Nevertheless, the calcaneus SOS measurements ranged from 1489.7 m s^{-1} to 1545.1 m s^{-1} (averaged 1510.86 ± 17.36 m s^{-1}) are close with the results based on *in vitro* and *in vivo* measurements [11, 24, 27]. Besides, the mean normalized BUA (nBUA) value (22.34 ± 3.05 dB (MHz cm)$^{-1}$) found in this study was higher than the value measured by Wear [24] (9.88 ± 5.67 dB (MHz cm)$^{-1}$), but still in the range reported by Nicholoson [23] (24.8 ± 7.3 dB (MHz cm)$^{-1}$). The calcaneus SOS and BUA found using the two-sided interrogation techniques were also compared with the accumulated SOS (V_{UBIS}) and BUA from commercial ultrasound densitometry system, UBIS 5000. The results shown in table 2 reveal that the SOS values evaluated with the two-sided system are smaller than the values evaluated with V_{UBIS}. We suspected that this is because the UBIS 5000 system assumes constant value for calcaneus width and neglects the soft tissue effect when performing the calcaneus QUS measurements.

4. Conclusions

Acoustic speed is a fundamental property that has been measured in many soft tissues and conveys important information regarding tissue composition [1]. In addition to its importance to soft tissues, sound speed has been revealed to be highly correlated with calcaneal mass density [28]. The calcaneus is a major site that is used by most commercial densitometry systems. However, the true thickness of calcaneus is not commonly available in *in vivo* measurements, although some approaches have proposed ways to eliminate the need for thickness measurements in SOS evaluation *in vitro* measurement [29–32]. X-ray images can also be used to obtain the bone thickness, but carry added cost, inconvenience and radiation exposure. To overcome these disadvantages, we present a two-sided interrogation technique to estimate the SOS and BUA on calcaneus. The technique presented and experimentally validated is aimed at eliminating soft tissue effects from *in vivo* measurements of calcaneus QUS.

The main advantage of the proposed two-sided interrogation techniques is to obtain measurements of QUS without the preliminary measurement of bone and soft tissue thicknesses. The idea is very straightforward and easy to implement. Using transducers placed on both sides of the test site in both reflection and transmission modes, measurements of the SOS are made without the need for information on bone thickness. *In vitro* studies for phantom measurements support the idea. The standard deviation of SOS measured by the two-sided interrogation system with commercial bone phantoms is smaller than 0.5% and the accuracy is as high as 99%. Finally, *in vivo* measurements were performed on 14 healthy volunteers. Preliminary results as shown in table 2 indicate that the calcaneus widths varied from 32.0 mm to 47.5 mm. This demonstrates a potential source of error in single-site measurements of SOS using commercial ultrasound densitometries since the width of calcaneus is set as a constant in these system. Although the measurements of SOS using the two-sided interrogation technique are smaller than those measured using a commercial system (UBIS 5000) that used a fixed calcaneus width (27 mm), we believed that our results represent the SOS more accurately and better reflect the bone properties of calcaneus. The ultimate goal is to use the two-sided interrogation technique to detect subtle changes in bone caused by osteoporosis or in response to treatment. More *in viv*o measurements are currently ongoing to demonstrate the validity of our technique to clinical assessment of osteoporosis.

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Queries

(1) Author: Meaning of the sentence 'The 10% threshold means . . . received or echo signal [26]' is unclear. Please check.

(2) Author: Please be aware that the colour figures in this article will only appear in colour in the Web version. If you require colour in the printed journal and have not previously arranged it, please contact the Production Editor now.