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The Effect of Phase Cancellation on Estimates of Calcaneal Broadband Ultrasound Attenuation in Adult Women

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Abstract

Broadband Ultrasonic Attenuation (BUA) is a clinically-accepted measurement for diagnosis of osteoporosis. Typical clinical BUA measurements are performed with phase sensitive receivers and therefore can be affected by phase cancellation. In order to separate the effects of conventional attenuation (absorption plus scattering) from phase cancellation, BUA was measured on phantoms with acrylic wedge phase aberrators and on 73 women using both phase sensitive (PS) and phase insensitive (PI) reception. A clinical bone sonometer (GE Lunar Achilles Insight ®) with a two dimensional receiver array was used. PI BUA measurements on phantoms with acrylic wedge phase aberrators were found to be far more resistant to phase cancellation than PS BUA measurements. In data from 73 women, means and standard deviations for BUA measurements were 81.4 ± 21.4 dB/MHz (PS) and 67.2 ± 9.7 dB/MHz (PI). The magnitude of the discrepancy between PS BUA and PI BUA tended to increase with bone mineral density (BMD).

Keywords

trabecular bone; cancellous bone; frequency dependent attenuation

Introduction

Quantitative Ultrasound (QUS) is now a well-established modality for osteoporotic fracture risk assessment [1, 2]. Broadband ultrasonic attenuation (BUA) and speed of sound (SOS) reflect bone mineral density (BMD) [3–15] and mechanical properties [8, 9, 12, 16], both of which are related to fracture risk. Calcaneal BUA (sometimes combined with SOS) has been demonstrated to be predictive of osteoporotic fractures in women in prospective [17–24] and retrospective [25–32] studies. Anisotropy studies suggest that BUA, unlike BMD, is sensitive not only to the quantity of bone intercepting the ultrasound beam but also the physical arrangement (i.e. micro-architecture) of the bone [33–35]. QUS is less expensive, faster, simpler, and more portable than its x-ray counterparts: dual-energy x-ray absorptiometry (DEXA) and quantitative computed tomography (QCT). Unlike x-ray methods, QUS produces no ionizing radiation. A recently-developed handheld, through-transmission, calcaneal ultrasound system appears to represent a significant advance in portability compared with current commercial ultrasound devices [36]. Despite recent

progress in QUS, improvements are needed in order to foster greater clinical acceptance [37].

BUA is usually measured using two broadband transducers in a through-transmission geometry around the calcaneus. Most studies listed above report that attenuation exhibits an approximately linear dependence on frequency in the diagnostic frequency range (about 300 – 700 kHz). Two studies have confirmed quasi-linearity up to about 2 MHz [38, 39].

Ultrasonic attenuation measurements can be affected by phase cancellation [40–45]. Phase cancellation reduces the amplitude of the attenuated signal and therefore tends to lead to overestimation of conventional attenuation (absorption plus scattering). Phase cancellation usually increases with frequency and therefore also tends to lead to increased attenuation slope. Phase cancellation can be suppressed using so-called phase-insensitive (PI) processing [40–43]. PI processing is impossible with single element phase-sensitive (PS) receivers but possible with arrays (see Methods section).

Petley *et al.* were the first to systematically investigate the effect of phase cancellation on BUA estimates in human calcaneus [44]. They compared PS and PI estimates of BUA on 10 normal volunteers. They transmitted with a single cycle of 400 kHz ultrasound and received with a small aperture (5 mm diameter) 5 MHz resonant ceramic transducer that was scanned in order to sweep out an area equal to that of the transmitter (25 mm diameter circle). They found that PS measurements of BUA were, on the average, higher than PI measurements by 31.2 dB/MHz. Strelitzki *et al.* [45], however, compared PS and PI measurements of BUA on 10 calcanea *in vitro* (with soft tissue removed) using a 3×3 receiver array and found a much smaller difference, with PS BUA only about 4.3 dB/MHz greater than PI BUA.

Langton *et al.* investigated the role of phase cancellation due to uneven propagation paths through cortical plates on BUA. They measured BUA in calcaneus samples *in vitro* with and without cortical plates present and found an average increase of about 7 dB/MHz due to cortical plates [8, 46]. They pointed out that this difference could not be explained by absorption alone since “a cortex of 1 mm thickness would only provide a BUA of approximately 0.1 dB/MHz.” They then showed, using computer simulation and experimental measurements on Perspex plates, that the 7 dB/MHz difference could be explained by phase cancellation artifacts produced by curved interfaces. Xia *et al.* developed a theoretical model and performed experiments on 18 cadaver calcanea, to show that cortical plates have a significant effect on BUA [47]. Eddin *et al.* reported a phase aberration correction that they implemented in a bone sonometer that used two dimensional arrays (24×24) for both transmission and reception of ultrasound through the calcaneus [48].

In this paper, a clinical study to further probe the effect of phase cancellation on BUA measurements is presented. The present study has advantages over previous ones. Compared with the 5 mm receiving transducers used by Petley *et al.* and Strelitzki *et al.*, the approximately 2 mm array elements used in the present study provided better spatial resolution for measurement of the attenuated ultrasound field. Unlike the *in vitro* study by Strelitzki *et al.*, the present study was conducted *in vivo*. Compared with the 9 element array used by Strelitzki *et al.*, the 52 element receiver array used in the present study provided

finer sampling in order to more closely approximate a typical single element phase sensitive receiver. Unlike the study by Langton and Subhan, the present study was conducted on human calcaneus instead of Perspex. While the previous investigations used non-imaging data acquisition systems, the present study was aided by real-time attenuation imaging, which facilitated accurate and reproducible positioning of the calcaneus. The present study was based on a larger number of measurements in bone (73 vs. 10 by Petley *et al.* and Strelitzki *et al.*), resulting in lower standard errors of estimates of mean values. The present study is the first to investigate the dependence of phase cancellation artifact on BMD. Finally, the present study is the first to measure phase cancellation artifact with a commercial clinical bone sonometer.

Methods

Ultrasonic Data Acquisition and Analysis

A GE Lunar Achilles Insight ® clinical bone sonometer was used. This system uses a circular (25.4 mm diameter) broadband piston transducer (center frequency = 500 kHz) for transmission of ultrasound into the heel. Radiofrequency (RF) data were acquired using 52 central elements of the Insight's 590 element 2D receiver array. The central 52 elements were roughly bounded by a circle that was co-axial with the transmitter. The element spacing was 3.175 mm. The element size was about 2 mm. The beam propagation distance was 10 cm. Data were digitized at 10 MHz. The Achilles Insight displays a real-time attenuation image in order to permit accurate positioning of the foot prior to data acquisition.

PS power spectra were obtained by 1) summing time domain RF signals from the central 52 elements of the 2D receiver array, and 2) taking the squared modulus of the Fast Fourier Transform (FFT). PI power spectra were obtained by 1) computing the magnitude of the FFT for each of the 52 time domain RF signals, 2) summing the 52 FFT magnitudes, and 3) squaring.

A calibration spectrum was obtained by performing a measurement with only a water path between the transmitting and receiving transducers. BUA was computed from the slope of a least-squares regression to the log spectral difference between calibration and data spectra. The analysis bandwidth was from 240 kHz to 600 kHz. Often in biomedical ultrasound, this slope is normalized to the thickness of the sample to yield "attenuation slope" or nBUA (normalized BUA). This is usually not done in clinical bone sonometry, however, since the bone thickness is usually unknown. (However, a recent system that performs two-sided pulse-echo interrogation has been reported to accurately measure calcaneal thickness *in vivo* [49]). Thicker bones tend to have less fracture risk so it can be useful for a diagnostic measurement to convey bone thickness information in addition to bone material properties. (Similarly, BMD is an areal rather than a volumetric measurement, measured in g/cm^2 rather than g/cm^3 .) Therefore, BUA is generally reported in units of dB/MHz rather than dB/cmMHz.

Phantom Measurements

Figure 1 shows the experimental setup for phantom measurements. An ultrasound bone phantom (General Electric, Madison, WI), with values of BUA and SOS mimicking human calcaneus, was placed in a miniature water tank between the transmitter and receiver of the Achilles Insight. In order to produce phase cancellation, an acrylic wedge was also placed in the acoustic path. Since the speed of sound in acrylic (2727 m/s) is much faster than that in water (1480 m/s), acoustic energy passing through thicker portions of the wedge arrived at the receiver sooner than acoustic energy passing through thinner portions. Five different wedges, with deflection angles of 0° , 1.5° , 3° , 4.5° , and 6° , were used (see Figure 2). The wedge thickness at the beam midpoint was the same for all five wedges. Therefore, the bulk amount of acrylic intercepted by the propagating ultrasound beam (and the total amount of attenuation) was the same for all five wedges. Seven independent transmission measurements (with repositioning) were performed for each wedge.

Excess attenuation was characterized by $n\text{BUA} = \text{nBUA} - \text{nBUA}_{\text{PI},0}$ where $\text{nBUA}_{\text{PI},0}$ was the value measured using PI processing on the data acquired from the $\theta = 0^\circ$ wedge.

In a second set of phantom experiments, water in the tank was replaced with isopropyl alcohol. The speed of sound in isopropyl alcohol (1170 m/s) created a bigger sound speed mismatch with acrylic than water, exacerbating phase cancellation artifacts. Again, seven independent transmission measurements (with repositioning) were performed for each wedge.

Simulation

Wedge experiments were simulated using MATLAB. The effect of a wedge was modeled by introducing a linear phase shift across the lateral dimension of the receiver array. The phase shift was $\Delta\phi(x) = (k_2 - k_1)x \tan\theta$ where $k = 2\pi/\lambda$, λ is the ultrasonic wavelength, x is lateral position across the array, θ is the deflection angle of the wedge, and subscripts 1 and 2 indicate properties for the fluid (water or alcohol) and the wedge (acrylic) respectively. The phase shift was applied to digitized measurements of signals measured experimentally with only the phantom and the fluid present. The wedge angle could be continuously adjusted, which allowed interpolation between, and extrapolation beyond, experimental measurements at $\theta = 0^\circ$, 1.5° , 3° , 4.5° , and 6° .

Clinical Protocol

The GE Lunar Achilles Insight® was used to measure BUA in the non-dominant feet of 73 ambulatory, non-pregnant women who were free of conditions that may be associated with altered bone metabolism including chronic renal disease, chronic liver disease, hyperparathyroidism, active hyperthyroidism, hypothyroidism, diabetes (type I or type II), cancer, Paget's disease, anorexia, bulimia, lactose intolerance, milk allergy, malabsorption syndrome, osteomalacia (Rickets), Vitamin D deficiency, or rheumatoid arthritis. Each subject removed shoes, socks, and/or stockings. A mist of isopropyl alcohol was sprayed on the foot in order to enhance coupling between the ultrasound beam and the foot. Table I gives demographic information. The set of volunteers included 5 African American women, 9 Asian American women, and 59 Caucasian women. A GE Lunar PIXI DEXA calcaneal

bone densitometer was used to measure areal BMD, which was reported in absolute units (g/cm^2) and also as a T-score (the number of standard deviations above or below the mean value for the normal reference population). The World Health Organization stratifies subjects as follows: $T > -1$ (normal), $-2.5 < T < -1$ (osteopenia or low bone density), and $T < -2.5$ (osteoporosis) (see <http://www.nof.org/osteoporosis/bmdtest.htm>). Some experts have expressed concern regarding application of these thresholds, originally derived from axial skeletal data, to peripheral sites such as calcaneus [50–52]. However, in the absence of a widely-accepted alternative, they remain the clinical standard for calcaneal measurements and at least serve as a useful approximate method to stratify subjects.

Results

Figures 3 and 4 show PS and PI spectra with and without a bone-mimicking phantom and an acrylic wedge in the water path. In the absence of an aberrating medium, the two spectra were nearly identical (Figure 3). In the presence of an aberrating medium (wedge), the PS spectrum was substantially lower than the PI spectrum (Figure 4).

Figure 5 shows PS and PI estimates of excess nBUA as functions of wedge deflection angle (θ) for acrylic wedges immersed in water. The PI measurements showed far less variation with θ and therefore were a much more reliable indicator of the bulk quantity of acrylic intercepting the ultrasound beam (which was constant for all wedges). The simulation accurately predicted the dependences of excess nBUA on θ for both PS and PI cases.

Figure 6 shows PS and PI estimates of excess nBUA as functions of wedge deflection angle (θ) for acrylic wedges immersed in alcohol. The same trends that were observed for water occurred with alcohol. The values of excess nBUA were greater, however, because the mismatch in sound speed between the fluid and the acrylic were greater than in the previous case.

Figure 7 shows the two-dimensional array of pulses transmitted through the calcaneus of a volunteer. The heterogeneity of the calcaneus is apparent.

Figure 8 shows PS and PI spectra of pulses transmitted through the calcaneus of a volunteer. As was seen with the acrylic wedges, the PS spectrum is markedly lower than the PI spectrum, particularly at high frequencies.

Figure 9 shows average attenuation versus frequency for the 73 women. The means and standard deviations for BUA measurements were 81.4 ± 21.4 dB/MHz (PS) and 67.2 ± 9.7 dB/MHz (PI). Therefore, conventional PS processing overestimated true BUA by about 14.2 dB/MHz.

Figure 10 shows PS BUA and PI BUA versus BMD and linear least-squares regression fits for the 73 women. Figure 11 shows the difference between PS BUA and PI BUA for the 73 women. It can be seen that the range of the discrepancy between the two tended to increase with BMD. The level of scatter in Figures 10 and 11 may be due, in part, to imperfect co-registration of ultrasonic and x-ray regions of interest.

Figure 12 shows a scatter plot of PS BUA and PI BUA measurements on the 73 women. The correlation coefficient between the two measurements was $r = 0.71$ (95% CI: $0.57 - 0.81$). Figure 13 shows a scatter plot of data in the format used in Bland Altman analysis [53]: BUA differential (PS BUA – PI BUA) vs. mean BUA $((\text{PS BUA} + \text{PI BUA})/2)$.

Discussion

This paper describes the first comparison of PS BUA and PI BUA measured with clinical bone sonometer hardware. It also describes the first investigation into the effect of BMD on the discrepancy between the two. The superior resistance to phase cancellation of PI BUA was confirmed using acrylic wedge phase aberrators. The number of subjects measured in this study exceeded numbers from previous studies by a factor of seven. In data from 73 women, means and standard deviations for BUA measurements were 81.4 ± 21.4 dB/MHz (PS) and 67.2 ± 9.7 dB/MHz (PI). The range of discrepancies between PS BUA and PI BUA tended to increase dramatically with BMD (see Figure 11).

PS BUA is the standard upon which current clinical QUS fracture-risk data is based. Therefore, it is not inappropriate that commercial bone sonometers measure PS BUA rather than PI BUA. The point of this investigation was to analyze the relative contribution of conventional attenuation (i.e. absorption plus scattering) as opposed to phase cancellation in determining PS BUA. A greater understanding of these physical processes that underlie the clinical BUA measurements may lead to improvements in future bone sonometry technology.

The discrepancy between PS BUA and PI BUA in the present study, 14.2 dB/MHz, is less than that reported in the seminal paper by Petley *et al.* [44], 31.2 dB/MHz. Petley *et al.* may have observed greater phase cancellation artifacts on average if their subjects tended to have bigger calcanea and therefore perhaps more potential for phase cancellation. As shown in Figure 11, the magnitude of the discrepancy between PS BUA and PI BUA in the present study tended to increase with BMD. While the present study investigated normal, osteopenic and osteoporotic women, the study of Petley *et al.* investigated 5 normal men and 5 normal women. Another source of disparity between the two studies is the receiver element size (2 mm in the present study versus 5 mm in the study of Petley *et al.*). A smaller element size would be expected to result in more accurate sampling of the local ultrasonic field. Finally, the present study had the benefit of real-time attenuation imaging, which may have enabled more accurate positioning of feet prior to data acquisition. Unfortunately, real-time calcaneal attenuation imaging systems were not available at the time of Petley *et al.*'s study.

The discrepancy between PS BUA and PI BUA in the present study, 14.2 dB/MHz, is more than that reported by Strelitzki *et al.* [45], 4.3 dB/MHz. Strelitzki *et al.* performed measurements on calcanea from human cadavers. While Strelitzki *et al.* did not report demographic statistics, it is possible that the bones were taken from relatively old subjects with low BMD, which might lead to a comparatively small discrepancy between PS BUA and PI BUA (again, see Figure 11). In addition, Strelitzki *et al.* removed all soft tissues from their specimens, which would also likely tend to reduce phase cancellation artifacts.

The tendency for phase-sensitive receivers to produce overestimates of attenuation has ramifications with respect to investigations of backscatter from calcaneus. Previous studies have reported backscatter coefficients from human calcaneus *in vitro* between 0.01 to 0.1 cm⁻¹Sr⁻¹ for frequencies between 300 kHz and 1 MHz [54, 55]. These studies found that average calcaneal backscatter coefficient was approximately proportional to frequency to the nth power with values for n in the range of 3 to 3.5. In order to estimate backscatter coefficient, it is necessary to compensate measurements of frequency-dependent backscatter with assumed frequency-dependent attenuation coefficients, which in these studies was measured with phase-sensitive transducers. Overestimation of magnitude and frequency dependence of attenuation coefficient would result in overestimation of magnitude and frequency dependence (e.g. power law exponent) of backscatter coefficient. These studies investigated purely trabecular bone samples in water and therefore were exempt from the aberrating effects of skin, muscle, fat, marrow, and lateral cortical plates that contributed in the present clinical study. Therefore, the magnitude of the overestimation of backscatter coefficient and power-law exponent in *in vitro* studies remains unclear. This issue warrants further investigation.

In summary, it has been shown here that phase cancellation effects 1) are significant in conventional (phase-sensitive) BUA, and 2) can be mitigated by using phase insensitive detection. Whether phase-insensitive detection can outperform phase-sensitive detection for fracture-risk prediction (the principal clinical task), however, remains to be seen.

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Biography

Keith A. Wear graduated from the University of California at San Diego with a B.A. in Applied Physics in 1980. He received his M.S. and Ph.D. in Applied Physics with a Ph.D. minor in Electrical Engineering from Stanford University in 1982 and 1987.

He was a post-doctoral research fellow with the Physics department at Washington University, St. Louis from 1987–1989. He has been a research physicist at the FDA Center for Devices and Radiological Health since 1989. He has performed research in biomedical applications of ultrasound and magnetic resonance spectroscopy for 15 years. His research has included measurements of ultrasonic scattering properties from tissues, high-resolution spectral estimation, magnetic resonance spectroscopic image reconstruction methods, and analysis of statistical properties of ultrasonic echoes from tissues.

He is an adjunct professor of Radiology at Georgetown University. He is a Fellow of the American Institute for Medical and Biological Engineering and the American Institute of Ultrasound in Medicine (AIUM). He is a senior member of IEEE. He is a member of the Acoustical Society of America, IEEE Ultrasonics Society, the National Osteoporosis

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Figure 1.
Experimental Setup.

Figure 2.
Five acrylic wedges investigated.

Figure 3.

Spectra of calibration pulses transmitted through water only (no wedge, no bone-mimicking phantom), processed phase sensitively (PS, dashed line) and insensitively (PI, dotted line).

Figure 4.

Spectra of pulses transmitted through a bone-mimicking phantom and an acrylic wedge ($\theta = 6^\circ$) immersed in water, processed phase sensitively (PS, dashed line) and insensitively (PI, dotted line).

Figure 5. Phase sensitive (PS) and phase insensitive (PI) estimates of excess (relative to value at $\theta = 0$) $nBUA$ as functions of wedge deflection angle (θ). Error bars denote standard deviations.

Figure 6.

Same as Figure 5 except with wedges immersed in alcohol instead of water.

Figure 7.
Array of 52 pulses transmitted through the calcaneus of a volunteer.

Figure 8.

Spectra of pulses transmitted through the calcaneus of a volunteer processed phased sensitively (PS, dashed line) and insensitively (PI, dotted line).

Figure 9.

Average attenuation vs. frequency for 73 women. Error bars represent standard deviations.

Figure 10.

PS BUA and PI BUA for 73 women. The vertical dashed lines show the osteopenic (low bone density) range. BMD values above that range are considered normal. BMD values below that range are considered osteoporotic. See Clinical Protocol section for stratification thresholds for normal, osteopenic, and osteoporotic.

Figure 11.

The difference between PS BUA and PI BUA for 73 women. The vertical dashed lines show the osteopenic (low bone density) range. BMD values above that range are considered normal. BMD values below that range are considered osteoporotic. See Clinical Protocol section for stratification thresholds for normal, osteopenic, and osteoporotic.

Figure 12.
Phase insensitive BUA vs. phase sensitive BUA.

Figure 13.
BUA differential vs. mean BUA.

Table I.

Demographic information for clinical study

	Mean	Standard Deviation	Range
Age (years)	47	13	(21, 78)
Height (inches)	64	2	(59, 68)
Weight (lb.s)	136	26	(95, 220)
BMD (gm/cm ²)	0.467	0.092	(0.241, 0.700)
DEXA T-score	-0.4	1.1	(-3.2, 2.5)

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