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The Dependence of Ultrasonic Backscatter on Trabecular Thickness in Human Calcaneus: Theoretical and Experimental Results

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Abstract

Trabecular thickness within cancellous bone is an important determinant of osteoporotic fracture risk. Noninvasive assessment of trabecular thickness could potentially yield useful diagnostic information. Faran's theory of elastic scattering from a cylindrical object immersed in a fluid has been employed to predict the dependence of ultrasonic backscatter on trabecular thickness. The theory predicts that, in the range of morphological and material properties expected for trabecular bone, the backscatter coefficient at 500 kHz should be approximately proportional to trabecular thickness to the power of 2.9. Experimental measurements of backscatter coefficient were performed on 43 human calcaneus samples *in vitro*. Mean trabecular thicknesses on the 43 samples were assessed using micro computed tomography. A power law fit to the data showed that the backscatter coefficient empirically varied as trabecular thickness to the 2.8 power. The 95% confidence interval for this exponent was 1.7 to 3.9. The square of the correlation coefficient for the linear regression to the log transformed data was 0.40. This suggests that 40% of variations in backscatter may be attributed to variations in trabecular thickness. These results (1) reinforce previous studies that offered validation for the Faran cylinder model for prediction of scattering properties of cancellous bone, and (2) provide added evidence for the potential diagnostic utility of the backscatter measurement.

Introduction

Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength is determined by bone density and bone quality. Bone quality refers to architecture, turnover, damage accumulation (e.g. microfractures) and mineralization. In the United States, 10 million individuals have osteoporosis and an additional 18 million have low bone mass, placing them at increased risk for osteoporosis. The probability for a 50-year old female to have a hip fracture during her lifetime is 6% for African-Americans and 14% for non-Hispanic Whites. Almost one

third of patients with hip fractures are placed in assisted living situations within a year following a fracture. One in five patients dies within one year following an osteoporotic hip fracture [1].

Bone Sonometry

Ultrasound techniques are recognized for effectiveness in osteoporosis detection [2,3]. Calcaneal broadband ultrasonic attenuation (BUA) and speed of sound (SOS) are highly correlated with calcaneal bone mineral density (BMD) [2–17] which is in turn an useful indicator of osteoporotic fracture risk in the hip [18]. In a major prospective study involving over 5000 women, BUA in combination with SOS has been demonstrated to be as predictive of fractures of the hip (the most debilitating site for osteoporotic fractures) as dual-energy x-ray absorptiometry (DEXA) (the current gold standard) [19]. In a subsequent prospective study involving over 6000 women, BUA was found to be almost as predictive of hip fractures as DEXA [20]. Similar findings have been reported from retrospective studies [21–24]. Bone sonometry is less expensive, faster, and more portable than its x-ray counterparts: DEXA and quantitative computed tomography (QCT). In addition, ultrasound produces no ionizing radiation. For these reasons quantitative ultrasound has an important niche as a screening modality and in the management of osteoporosis.

Determinants of Fracture Risk

Measures of bone density account for up to 75% of bone strength [3, 25]. The remaining 25% or more of bone strength is attributable to bone microarchitecture and material properties. The extent to which new features, such as backscatter are able to supply complementary diagnostic information to that provided by BMD will depend in part on their sensitivity to microarchitecture and material properties of bone.

Ultrasonic Scattering from Trabecular Bone: Theoretical Models and Empirical Results

Ultrasonic scattering from bone has received less attention than attenuation and propagation speed. However the study of scattering is important for two reasons. First, it can elucidate mechanisms responsible for attenuation (the combined result of absorption and scattering). In addition, scattering measurements have shown diagnostic promise in their own right in studies *in vitro* [26–29] and *in vivo* [30–35]. Since measurement of backscatter may be performed with a single transducer in pulse-echo mode, it has the potential to be measured at sites with more diagnostic importance than the calcaneus, such as the hip and spine. Backscatter is known to provide information regarding size, shape, number density, and elastic properties of scatterers [36–37]. Cancellous bone contains many approximately cylindrically-shaped scatterers (trabeculae) arrayed in a mesh. See Figure 1. The spaces between the trabeculae are filled with marrow (for the *in vivo* case) or water (for *in vitro* experiments). Trabeculae are likely candidates for scattering sites due to the substantial disparity in acoustic properties between mineralized trabeculae and marrow [38, 39]. A reduction in trabecular thickness would be expected to be associated with increased fracture risk and reduced backscatter coefficient.

In a previous investigation, measurements of average frequency-dependent backscatter coefficient, $\eta(f)$, from human calcaneal trabecular samples closely obeyed a power law

dependence on frequency, $\eta(f) = Af^n$ throughout the typical diagnostic range (300 – 700 kHz) with exponent n having a value slightly greater than 3, close to the cubic dependence expected from cylindrically shaped scatterers (e.g. trabeculae) [38]. A subsequent study reported similar results [40]. This result has implications with regard to the relative roles of scattering and absorption in determining attenuation in trabecular bone. Attenuation in the diagnostic range has been found in numerous studies to be approximately proportional to frequency to the first power. These two different co-existing frequency dependences could be consistent only if absorption is a larger component of attenuation than scattering [38]. This result has been reinforced by studies of the anisotropy of backscatter and attenuation in trabecular bone [41].

Empirical estimates of the exponent (n) of the frequency dependence of backscatter coefficient have been demonstrated to be consistent with a model in which trabeculae correspond to cylinders that are long (longer than the beam width) and thin (relative to the ultrasonic wavelength) [38]. Measurements have also exhibited compatibility with an autocorrelation model [40]. Another model in which scattering is assumed to be proportional to the mean fluctuation in sound speed in a random continuum has been proposed [42]. The random continuum model predicts variations in measured acoustic parameters with porosity and scatterer size that are consistent with observations, including the reported nonlinear dependence of attenuation on porosity [43]. This approach is based on the models of Sehgal and Greenleaf [44] and Sehgal [45].

A further test of the cylinder model is to investigate the dependence of backscatter on mean trabecular thickness. In this paper, experimental measurements of the relationship between mean trabecular thickness and backscatter in human bone samples are compared with predictions based on the cylinder model.

THEORY

Previously, a model based on elastic scattering from a cylinder [36] was adapted to bone. By assuming published *average* values for material and morphometric properties of bone, this model was shown to successfully predict the frequency dependence of backscatter coefficient from human calcaneus *in vitro* [38]. The model predicts backscatter from a single cylindrical scatterer immersed in a fluid as a function of diameter (d), density (ρ), longitudinal velocity (c_l), Poisson's ratio (ν), and frequency, f . (Shear velocity, c_s , may be computed from c_l and Poisson's ratio, ν [36]).

Reported measurements for ranges of morphometric parameters for human calcaneus are given in the Table 1. Mean values for material properties (ρ , c_l , and ν) for bone and bone-like materials may also be found in the literature. See Table 2. It is important to recognize that the relevant properties here are the *material* properties of the individual trabeculae as opposed to the *structural* properties, which correspond to the macroscopic cancellous bone medium (the composite of the trabecular network and the marrow). It is technically difficult to measure material properties on specimens as small as individual trabeculae. Therefore, many of the values in Table 2 are derived from macroscopic measurements of cortical bone and other bone-like substances.

The dependence of backscattered intensity on trabecular thickness from an individual scatterer, according to Faran's theory at 500 kHz over the entire expected range of trabecular thicknesses, material densities, and material longitudinal sound speeds is shown in Figure 2. (In Figure 2, Poisson's ratio has been assumed to be 0.30. As shown in Table 2, this value is appropriate for a wide variety of bones and bone-like substances). It can be seen that the functional dependence of backscatter on trabecular thickness (denoted here by $d = Tb.Th$, according to the standardized notation for bone histomorphometry [48]) is similar regardless of the values of ρ and c_l assumed. It can also be seen that backscatter can vary by about one order of magnitude over the range of expected values of trabecular thicknesses, from 93 microns (two standard deviations below Ulrich's mean [47]) to 228 microns (Trebecz and Natali's maximum [16]) suggesting that expected variations in $Tb.Th$ result in relatively large variations in backscatter while conceivable variations in ρ and c_l have considerably smaller impact.

These observations suggest the potential utility of a simple multiple regression model for the logarithm of backscattered intensity at 500 kHz, $I_{500\text{ kHz}}(Tb.Th, \rho, c_l)$. Applying a multiple regression to log-transformed data set from Figure 2 yields

$$\log I_{500\text{ kHz}}(Tb.Th, \rho, c_l) = B + 2.90\log(Tb.Th) + 1.54\log(\rho) + 0.31\log(c_l) \quad (1)$$

where $Tb.Th$, ρ , and c_l are measured in microns, mm, g/cc, and m/s respectively. As seen in Figure 2, the regression model fits the data quite well. The regression model elucidates the relative roles of the various determinants of backscatter. In particular, Equation 1 predicts that backscattered intensity at 500 kHz from a single cylindrical scatterer, with properties in the expected range for bone, is proportional to $Tb.Th$ to a power of 2.9.

Equation 1 may be extended to describe the *expected value* for intensity from a collection of identical scatterers provided that (1) all scatterers are oriented approximately perpendicular to the ultrasound propagation direction (as is the case under mediolateral insonification), (2) the effects of multiple scattering are small, and (3) coherent scattering may be neglected relative to incoherent scattering. The third assumption applies for sufficiently long gate durations, sufficiently randomly positioned scatterers [57], and sufficient spatial averaging of measurements. This assumption is commonly made in the study of scattering from tissues [57] and is also supported somewhat by previous measurements of frequency-dependent scattering in trabecular bone [38]. In this case, K would be related to the effective number of scatterers per resolution cell but the coefficients (2.90, 1.54, and 0.31) would remain the same as for the single scatterer case.

METHODS

Calcaneus Samples

The methods for obtaining, preparing, and interrogating calcaneus samples were the same as previously reported [41]. 43 human (genders and ages unknown) calcaneus specimens were defatted using a trichloro-ethylene solution. Many studies suggest that defatting does not significantly affect measurements since attenuation [10, 58] and speed of sound [58, 59] of defatted trabecular bone have been measured to be only slightly different from their

counterparts with marrow left intact. However one recent investigation suggests that these differences may be somewhat greater than previously believed [60]. At any rate, for the present purpose of investigating the dependence of backscatter on trabecular thickness, it is presumed here that experiments with defatted calcaneus samples provide useful insight into the *in vivo* (non-defatted) case. The dimensions of the samples were approximately 15 mm (mediolateral) $\times$ 15 mm (anteroposterior) $\times$ 35 mm (craniocaudal).

The cortical lateral sides were sliced off leaving two parallel surfaces with direct access to trabecular bone. In order to remove air bubbles, the samples were vacuum degassed using vacuum pump underwater. After vacuum, samples were allowed to thermally equilibrate to room temperature prior to ultrasonic interrogation. Ultrasonic measurements were performed in degassed distilled water at room temperature. The water temperature was measured for each experiment using a digital thermometer. The relative orientation between the ultrasound beam and the calcanea were same as with *in vivo* measurements performed with commercial bone sonometers, in which sound propagates in the mediolateral direction.

Ultrasonic Methods

Samples were interrogated in a water tank using a Panametrics (Waltham, MA) 5800 pulser/receiver and Panametrics 1" diameter, focussed (focal length = 1.5"), broadband transducers with center frequencies of 500 kHz. Bone samples were placed in the focal plane. Received signals were digitized (8 bit, 10 MHz) using a LeCroy (Chestnut Ridge, NY) 9310C Dual 400 MHz oscilloscope and stored on computer (via GPIB) for off-line analysis.

Backscatter coefficients were measured using a reference phantom method [61] as described previously [38]. Good agreement between experimental measurements using this method and theoretical predictions based on Faran's theory of scattering (Faran 1951) for ultrasonic backscatter coefficients from phantoms consisting of glass spheres embedded in gelatin has previously been reported by this laboratory [62].

Faran's model predicts the intensity of backscatter from a cylindrical scatterer exposed to an incident plane wave. Experimental measurements of scattering from a wire target suggest that Faran's expression is approximately proportional to the measured differential scattering cross section (from which the backscatter coefficient is derived) [38]. The dependences of Faran's expression and the backscatter coefficient on trabecular thickness would be expected to be the same.

A through-transmission method was used to measure attenuation coefficient, which was required in order to compensate backscatter measurements. Using two opposing coaxially-aligned transducers (one transmitter and one receiver), transmitted signals were recorded both with and without the bone sample in the acoustic path. The bone samples were larger in cross-sectional area than the receiving transducer aperture. Attenuation coefficient was estimated using a log spectral difference technique [63]). Attenuation was characterized by a least-squares linear fit of attenuation coefficient (dB/cm) vs. frequency. Since the SOS in calcaneus, approximately 1475–1650 m/s [64] is comparable to that in distilled water at room temperature, 1487 m/s [65], potential diffraction-related errors [66] in this substitution technique may be ignored [64].

Micro Computed Tomography

3D reconstructions of the trabecular bone samples were generated using micro computed tomography [67]. A Scanco μ CT 40 micro CT system situated at Scanco Medical AG in Bassersdorf, Switzerland was used. This is a desktop fan-beam microCT scanner. It utilizes a microfocus X-ray source with 7 μ m spot size, 70 kVp, 8 W (160 μ A). The detector is a CCD array containing 2048×64 elements with 24 μ m pitch. The resolution is 8 μ m (10% MTF). Quantitative microstructural properties were extracted from the 3D data sets using methods of Hildebrand and co-workers [68, 69]. Individual measurements of mean trabecular thickness (Tb.Th) were performed on each calcaneal specimen. The voxel size (nominal resolution) was 5 microns. 300 transverse slices (9 mm) were acquired from each specimen. From these 300 slices, a complete (square) cross region was taken, resulting in a volume of interest of about $12 \times 12 \times 9$ mm for each bone sample.

Mean trabecular thickness was measured using a “Distance Transformation” method as follows. For every bone voxel in the 3D reconstruction, the three dimensional distance to the nearest bone surface was determined. Then the 3D bone region was filled with spheres with positions and diameters chosen to best fit the trabecular surface. The local trabecular thickness was taken to be equal to the diameter of the local sphere. The mean trabecular thickness was computed from the average diameter of all the spheres occupying the bone region.

Results

A micro computed tomography reconstruction of a volume of interest from a bone sample is shown in Figure 1. The mean and standard deviation for trabecular thickness measured on the 43 samples was 163 ± 38 microns. The apparent densities of the 43 specimens ranged from 0.16 – 0.43 g/cc. These values were obtained by dividing the mass of each dry specimen by the volume it occupied. (These *structural* densities are lower than the *material* densities listed in Table 2 since the volume contained a considerable amount of air between the trabeculae). The mean and standard deviation for density was 0.27 ± 0.07 g/cc. The mean and standard deviation (standard error) for attenuation slope was 10.01 ± 5.56 (0.85) $\text{dBcm}^{-1}\text{MHz}^{-1}$.

The measurements of Tb.Th from human calcaneus reported here (163 ± 38 microns) tended to be somewhat higher on average than other published values (see Table 1) including Dr. Laib’s previous work [12]. These differences may be attributable in part to differences in regions of interest for the different studies and the considerable heterogeneity of the calcaneus. In addition, differences among donor populations may have also introduced a degree of disparity.

A scatter plot of measurements of trabecular thickness versus backscatter coefficient is shown in Figure 3. Also shown is a power law fit to the data. The empirical exponent (2.8) is very close to the theoretically expected value of 2.9. The 95% confidence interval for the empirical exponent was 1.7 to 3.9. The square of the correlation coefficient for the linear regression to the log transformed data was 0.40. This suggests that 40% of variations in backscatter may be attributed to variations in trabecular thickness. The scatter in the data

may be due in part to biological variation and in part to random interference effects related to coherent addition of echoes from different trabeculae [70].

Discussion

It has previously been shown that ultrasonic backscatter from cancellous bone exhibits a moderate correlation with BMD, a known predictor of osteoporotic fracture risk. The results presented here suggest that backscatter measurements also provide important information regarding trabecular microarchitecture, another independent predictor (besides BMD) of osteoporotic fracture risk. This gives further illustration of the potential clinical promise for this diagnostic measurement. In addition, the results presented here offer additional substantiation for the utility of the cylinder model for predicting aspects of backscattering from cancellous bone and reinforce a previous study of the frequency dependence of backscatter.

Several models have been proposed to predict ultrasonic backscatter from bone. In addition to the Faran cylinder model, two weak scattering models (which assume small disparities in acoustic properties between trabecular material and marrow) have been demonstrated to explain certain important experimental observations [40, 42]. In comparison to the cylinder model, these approaches have the advantage of allowing for more flexible geometries of the scattering medium. This is useful as trabecular bone contains plate-like structures in addition to rod-like trabeculae. In addition, trabeculae are not perfectly straight (as assumed in the cylinder model) but are actually somewhat curved and jagged. In defense of the cylinder model however, cylinder-like objects do contribute a substantial portion of the scattering. Moreover, only those plate-like structures oriented approximately perpendicular to the ultrasound propagation direction can measurably affect backscattering. Finally, plates are comparatively rare in bones from older subjects, upon which the data from the studies mentioned above are based. The main advantages of the cylinder model is that (1) it places no restrictions on the degree of disparity of acoustic properties between the trabecular medium and marrow, and (2) it allows for the propagation within trabeculae of shear waves, which have been demonstrated to propagate in cortical bone [56]. However, in view of the complexity of the problem of scattering from cancellous bone, all existing models, including the cylinder model, are somewhat simplistic.

The autocorrelation model (one of the weak scattering models mentioned above) has also been demonstrated to be useful for the prediction of mean trabecular thickness from cancellous bone [71]. In addition, Laugier *et al.* [71] reported a squared correlation coefficient between mean trabecular thickness measured from micro computed tomography and that computed by applying the autocorrelation model to backscatter data of approximately 0.5. This is close to the value reported here (0.4) using the cylinder model instead of the autocorrelation model. So regardless of what modeling method is utilized, it seems likely that 40 – 50 % of variations in backscatter may be attributed to variations in mean trabecular thickness.

Nicholson and Bouxsein [72] have reported measurements of ultrasonic *attenuation* in human trabecular bone to be proportional to mean trabecular thickness to the 3.2 power. This

value is very close to the approximate cubic dependence of *backscattering* on Tb.Th reported in the present study. If scattering is the primary source of attenuation in cancellous bone, then these two results are very compatible. If, on the other hand, absorption is the primary source of attenuation, then these similar exponents would merely be coincidental.

In summary, the results presented here (1) reinforce previous studies that offered validation for the Faran cylinder model for prediction of scattering properties of cancellous bone, and (2) provide additional evidence for the potential diagnostic utility of the backscatter measurement.

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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 has become interested in applications with bone in the late 1990's as FDA's regulatory interest in bone sonometry has increased.

He is a senior member of IEEE and the American Institute of Ultrasound in Medicine. He is a member of IEEE Ultrasonics Society, IEEE Signal Processing Society, IEEE Engineering in Medicine and Biology Society, AIUM Technical Standards Committee, American Society for Bone and Mineral Research, and the American Society for Testing of Materials. He was elected Vice-Chairperson of the AIUM Basic Science and Instrumentation Section in 2002. He is an Associate Editor, IEEE Transactions on Ultrasonics, Ferroelectrics, & Frequency Control. He is an Adjunct Professor of Radiology at Georgetown University.

Andres Laib graduated from the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland, with an MSc in Physics in 1994, where he stayed on to do his Ph.D. in Medical Physics, finishing in 1999. After spending a year as a post-doctoral fellow at the Magnetic Resonance Science Center at the University of California at San Francisco on the assessment of trabecular bone structure with MicroCT and MRI, he joined SCANCO Medical in the year 2000, where he is still employed today.

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Figure 1. MicroCT reconstruction of a volume of interest from a calcaneus sample. This is a subset of the total acquired data set from one sample.

Figure 2.
Intensity of backscatter from a cylindrical scatterer as a function of trabecular thickness (Tb.Th) for several choices for trabecular bone material parameters, density (ρ) and longitudinal velocity (c_l).

Figure 3. Measurements of backscatter coefficients at 500 kHz for the 43 human calcaneus samples versus mean trabecular thickness (Tb.Th) assessed using microCT.

Table 1.

Morphometric parameters for human calcaneus. Tb.Sp stands for mean trabecular separation. Tb.Th stands for mean trabecular thickness (which is the same as mean trabecular diameter, d) [48].

Reference	n	Tb.Sp (microns) mean $\pm$ std. dev. (range)	Tb.Th (d) (microns) mean $\pm$ std. dev. (range)
Hausler <i>et al.</i> [46]	15	630 $\pm$ 110	120 $\pm$ 10
Trebecz and Natali, [16]	20	-	145 $\pm$ 33 (99 – 228)
Ulrich <i>et al.</i> , [47]	60	684 $\pm$ 109 (456 – 982)	127 $\pm$ 17 (102 – 169)

Table 2.

Material properties of bone and bone-like substances. &: Extrapolated (to zero porosity) from bulk measurements over a range of porosities. (Porosity is the ratio of the volume occupied by pores to the total volume of the sample). #: Assuming $\rho = 1.96$ gm/cc

Reference	Substance	c_l (m/s)	c_s (m/s)	ρ (g/cc)	ν
Hosokawa & Otani, [49]	Bovine cancellous bone	3800	2000	1.95	0.32
Anderson <i>et al.</i> , [50]	Hydroxyapatite	6790			0.28
Luo <i>et al.</i> , [39]	Cortical bone	2900	1303	1.85	
Gong <i>et al.</i> , [51]	Bovine cancellous bone			1.93	
Lang <i>et al.</i> , [52]	Bovine cortical bone			1.96	0.32
Williams [53]	Bovine cancellous bone	3800 &			
Rho <i>et al.</i> , [54]	Bovine cancellous bone	2898±85			
Ashman <i>et al.</i> , [55]	Human cancellous bone	2639–2754		1.73–1.80	
-	Bovine cancellous bone	2501		1.74	
Grenoble <i>et al.</i> , [56] #	Powdered human femur	3917	2020		0.33
-	Fresh bovine femur	4890	2495		0.34
-	Hydroxyapatite (mineral)	5565	4765		0.27
-	Hydroxyapatite (synth.)	5628	4818		0.28