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Backscatter Difference Measurements of Cancellous Bone Using an Ultrasonic Imaging System

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Abstract

Backscatter difference measurements may be used to detect changes in bone caused by osteoporosis. The backscatter difference technique measures the power difference between two portions of an ultrasonic backscatter signal. The goal of this study is to evaluate the feasibility of using an ultrasonic imaging system to perform backscatter difference measurements of bone. Ultrasonic images and backscatter signals were acquired from 24 specimens of human cancellous bone. The signals were analyzed in the frequency domain to determine the normalized mean backscatter difference (nMBD) and in the time domain to determine the normalized backscatter amplitude ratio (nBAR). The images were analyzed to determine the normalized pixel value difference (nPVD), which measures the difference in average pixel brightness between regions of interest placed at two different depths in the image. All three parameters were found to increase with bone mineral density. The signal-based parameters, nMBD and nBAR, correlated well with bone mineral density, yielding linear correlation coefficients that ranged from 0.74 to 0.87. The image based parameter, nPVD, performed somewhat less well, yielding correlation coefficients that ranged from 0.42 to 0.81. These results suggest that ultrasonic imaging systems may be used to perform backscatter difference measurements for the purpose of ultrasonic bone assessment.

Keywords

ultrasound; backscatter; cancellous bone; osteoporosis

Introduction

Ultrasonic techniques are being developed to detect changes in bone caused by osteoporosis. Many ultrasonic techniques use a through-transmission approach in which ultrasonic pulses are propagated through a bone such as the calcaneus to measure the ultrasonic attenuation

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and/or speed of sound. Other techniques use an axial transmission approach in which ultrasonic waves are propagated along long bones such as the radius. All of these techniques use separate transmitting and receiving transducers, which limit their ability to access clinically interesting sites such as the hip and spine where approximately two-thirds of osteoporotic fractures occur.¹

Backscatter techniques may provide a better way to access central skeletal sites. Backscatter measurements use a single transducer to transmit ultrasonic pulses into regions of cancellous bone and then to receive the backscattered signal. Scattering occurs as the ultrasonic wave interacts with the trabecular microstructure of the cancellous bone tissue. Backscatter measurements are known to be sensitive to the microstructural characteristics, mechanical properties, density, and tissue composition of cancellous bone.²

Laboratory studies typically use mechanically scanned, single-element transducers to perform backscatter measurements on bone. Clinically, however, it may be desirable to use real-time ultrasonic imaging systems with multielement array transducers. Such systems are used widely for purposes other than bone assessment, accounting for approximately one-fourth of all imaging procedures worldwide.³ It is conceivable that bone assessment measurements could be added to many of these procedures relatively easily and inexpensively, thus increasing the population of people screened for osteoporosis.

A few investigators have used imaging systems to perform *in vivo* backscatter measurements of bone. Wear and Garra used an imaging system with a 2.25 MHz transducer to acquire backscatter signals from the heels of 10 healthy volunteers.⁴ They measured a parameter called “relative ultrasonic backscatter,” and found that this parameter correlated with site matched x-ray bone mineral density (BMD) measurements. Garra et al. used an imaging system with a 2.5 MHz transducer to acquire backscatter signals from the lumbar spine of 9 women.⁵ They processed the signals to analyze the centroid shift of the backscatter spectrum, which they found to correlate moderately well with site matched BMD measurements. Litniewski et al. used an imaging system they developed with a 1.5 MHz transducer to perform backscatter measurements at the heels of 10 women.⁶ Most recently, Conversano et al. used an imaging system with a 3.5 MHz transducer to measure an “osteoporosis score” based on spectral characteristics of backscatter from the lumbar spine of 342 women.⁷

Despite its potential, the clinical application of imaging systems for bone assessment is far from being fully realized. Backscatter measurements of bone still face some significant challenges. Parameters that are based on the power in the backscatter signal may depend on the portion of the backscatter signal that is analyzed, and also on attenuation and reflection losses caused by intervening tissues that lie between the transducer and the ultrasonically interrogated region of bone.⁸⁻¹⁰ Parameters based on the centroid shift and other changes to the backscatter spectrum may have similar limitations associated with intervening tissues.¹¹ The solution to these challenges may come in the form of new backscatter techniques such as backscatter difference techniques that measure the power difference between two gated portions of the same backscatter signal or dual-frequency ultrasound.¹²⁻¹⁷

The goal of the present study is to evaluate the utility of backscatter difference techniques applied to an imaging system for the purpose of ultrasonic bone assessment. Ultrasonic images and ultrasonic signals are acquired *in vitro* from cube shaped specimens of cancellous bone. The ultrasonic signals are analyzed to measure two parameters: the normalized mean backscatter difference (nMBD) and the normalized backscatter amplitude ratio (nBAR). nMBD and nBAR both depend on the power difference between two gated portions of the backscatter signal. Recent studies have identified nMBD as a potentially useful parameter for bone assessment purposes.^{12,16} nBAR is a newly introduced parameter that is similar to nMBD but is based on a time domain analysis of the backscatter signals that is computationally more efficient than a frequency domain analysis. Because many imaging systems do not provide users with easy access to the received ultrasonic signals, an analogous technique is applied directly to the images by measuring the difference in average pixel brightness between two regions of interest (ROIs) located at different depths in the image. The difference is quantified using another newly introduced parameter called the normalized pixel value difference (nPVD).

Materials and Method

Specimen Preparation

A total of 24 cube shaped specimens of cancellous bone were prepared from the distal ends of five human femurs. Donor information is provided in Table 1. A band saw was used to cut the specimens in the shape of cubes with side lengths of 12.5 mm. As shown in Figure 1, the specimens were oriented along the principal anatomic axes of the femur. A water jet was used to remove as much marrow as possible from the intertrabecular spaces. The specimens were placed in physiologic saline solution and stored in refrigeration until the time of testing. Specimens were vacuum degassed prior to all measurements.

Data Acquisition

Image and signal data were acquired using an ultrasonic imaging system (Terason) with a 3 to 7 MHz, 128-element linear array transducer (Model 7L3). Specimens were placed on the bottom of a water filled tank with the transducer supported above the specimen. Settings on the Terason ultrasound system included the following. Image depth was set to 3 cm and the focal length was set to 1.5 cm. The focus was located at the front surface of the specimen. Time gain compensation (which is used to vary the gain at different depths in the image) was set to the same intermediate value for all depths.

Data were acquired with each of the six faces of the specimen (anterior, posterior, medial, lateral, superior, inferior) oriented to face the transducer. As illustrated in Figure 1, data were acquired from two perpendicular scan planes along each of the six orientations for a total of 12 scan planes from each specimen. Figure 2 shows images from three specimens with low, intermediate, and high densities along with three signals from each specimen along the lines indicated in the figure. The vertical scale is not the same for all signals. The horizontal scale of the signals is in units of microseconds with a time increment of 0.05 μ s between points. Some signal clipping is evident in some of the signals, especially near the

front surface of the specimen. Care was taken to avoid clipped portions of the signals during analysis.

Signal Analysis

Signals were analyzed using software developed in LabVIEW 2012. A total of 288 scans (24 specimens, 12 scans per specimen) were analyzed. Each scan consisted of 256 signals total, with approximately one-third of those representing backscatter from the specimen. The backscatter signals from the specimen were analyzed in the frequency domain to determine the nMBD, and in the time domain to determine the nBAR.

nMBD was introduced recently as a new technique for ultrasonic bone assessment.¹² The procedure is described here briefly. Two analysis gates were placed on the signal as shown in Figure 3a. The first gate was delayed from the start of the signal by 4 μ s. This choice avoided portions of the signal near the front surface of the specimen where signal clipping was evident. The two gates had the same width τ_w , and were separated by an amount τ_s . nMBD was determined according to the following equation:

$$\text{nMBD} = \frac{\int_{f_l}^{f_h} (10\log_{10} P_1 - 10\log_{10} P_2) df}{(\tau_w + \tau_s)(f_l - f_h)}, \quad (2)$$

where P_1 and P_2 represent the power in the first and second gates, respectively, and f_l and f_h represent the low and high limits of the frequency range used for analysis, respectively. The normalization term $(\tau_w + \tau_s)$ represents the time between the centers of the gates, and is used to remove the effects of different choices of gate width and gate separation. nMBD was determined for three different choices of gate width ($\tau_w = 1, 1.5$, and 2μ s) and three different choices of gate separation ($\tau_s = 0, 0.5$, and 1μ s). These gate choices were based on the assumption that the speed of sound in human bone is approximately 1550 m/s. Signal to noise considerations also influenced these choices.

The frequencies f_l and f_h were determined for each scan in the following manner. Power spectra from the first gated portion of the backscatter signals from the specimen were averaged to obtain a single power spectrum from which the -6 dB frequency band was determined. The -6 dB frequency band of the second gated portion of the backscatter signals from the specimen was determined in the same way. The intersection of these two frequency bands was defined as the frequency range for analysis. The frequency range varied slightly from scan to scan but was 3 to 5 MHz on average.

The nBAR is determined in the time domain rather than the frequency domain. Time domain techniques may be computationally more efficient than frequency domain techniques, and thus may be better suited to real-time imaging applications. nBAR was determined according to the following equation:

$$\text{nBAR} = \frac{\log_{10}(V_{\text{rms1}}/V_{\text{rms2}})}{(\tau_w + \tau_s)}, \quad (3)$$

where V_{rms1} and V_{rms2} represent the root mean square (rms) voltage values in gates 1 and 2, respectively. nBAR uses the same normalization term ($\tau_w + \tau_s$) used by nMBD. nBAR was determined using the same choices of gate width and gate separation that were used to determine nMBD.

Image Analysis

The Terason system generated 8 bit (256 levels) log-magnitude images that were saved in the tagged image file format (TIFF) format. Images were analyzed with software developed in LabVIEW 2012. The average pixel value was determined for two rectangular ROIs positioned on the image to correspond to the same choices of gate width τ_w and gate separation τ_s that were used for the signal analyses. An image based parameter called nPVD was determined by subtracting the average pixel value in the lower ROI from that of the upper ROI (see Figure 3b) and dividing the result by the normalization term ($\tau_w + \tau_s$).

Bone Mineral Density Measurements

After completion of the ultrasonic measurements, the BMD of the specimens was measured using a dual energy x-ray absorptiometry (DXA) system (Hologic model QDR 87157) running small animal software. At present, DXA is considered to be the standard diagnostic method for osteoporosis.¹⁸ All six sides of each specimen were scanned using a 9.5 by 9.5 mm ROI centered on the specimen. The resulting BMD values were averaged to obtain a single value of BMD for each specimen.

Results

Figure 4 shows nMBD, nBAR, and nPVD plotted as a function of BMD for $\tau_w = 1 \mu s$ and $\tau_s = 1 \mu s$. Each data point in Figure 4a represents the mean value of nMBD for a particular specimen obtained by averaging all measured values of nMBD from all 12 scan planes from that specimen. Error bars represent standard errors of the mean. Data points in Figures 4b and 4c were obtained in a similar fashion for nBAR and nPVD, respectively. All three parameters are found to be increasing functions of density. Different choices of gate width and gate separation produced qualitatively similar results to those presented in Figure 4.

Table 2 reports mean values of nMBD, nBAR, and nPVD averaged over all 24 specimens. The values tend to decrease slightly as the gate width and gate separation are increased. This seems to be associated with placing the center of the second gate (or second ROI in the case of nPVD) more deeply in the specimen. The effect is less pronounced for nMBD than for nBAR and nPVD.

Discussion

Utility of nMBD, nBAR, and nPVD as Bone Assessment Purposes

The clinical utility of the backscatter difference techniques considered in this study can be assessed, in part, by how well the measured ultrasonic parameters correlate with BMD, which is the standard parameter used to diagnose osteoporosis.¹⁸ Linear regression analysis was used to measure the correlation of nMBD, nBAR, and nPVD with BMD. Pearson's R

correlation coefficients are reported in Table 3 for all choices of gate width ($\tau_w = 1, 1.5$, and $2 \mu\text{s}$) and gate separation ($\tau_s = 0, 0.5$, and $1 \mu\text{s}$). For 24 specimens, correlations are highly significant ($p < 0.001$) for $R > 0.63$.

nMBD and nBAR demonstrate highly significant ($p < 0.001$) correlations with BMD for all choices of gate width and gate separation. nMBD appears to produce slightly better correlations with bone mineral density than nBAR, but the difference is not statistically significant. The image-based parameter, nPVD, demonstrates a comparable level of performance for $\tau_w = 1 \mu\text{s}$, but deteriorates as gate width increases (see Table 3).

Comparison with Previous Studies

Of the three ultrasonic parameters considered in this study, nMBD is the only parameter that has been investigated previously. The other two parameters were developed for this study to determine how analogous techniques work when the analysis is performed in the time domain (nBAR) or applied directly to the ultrasound images (nPVD). In one previous study, backscatter measurements were performed on 22 cube shaped specimens of human cancellous bone using a mechanical scanning system and single-element transducers with center frequencies of 2.25, 5, 7.5, and 10 MHz.¹² The backscatter difference parameter nMBD was found to increase approximately linearly with density. Measurements with the 5 MHz transducer yielded correlation coefficients that ranged between 0.89 and 0.91. When averaged over all specimens, the mean value of nMBD ranged between 3.4 and 4.0 dB/ μs with the 5 MHz transducer. These values are similar to values reported in the present study (see Tables 2 and 3). In a separate study, mean backscatter difference (MBD; not normalized for gate width and gate separation) was measured in intact human proximal femurs using a single-element transducer with a 5 MHz center frequency.¹⁶ MBD was found to correlate positively with BMD. Significant correlations also were reported between MBD and bone microstructure.

Role of Attenuation

The ultrasonic attenuation of cancellous bone is known to increase with bone density. Values for the frequency slope of the attenuation coefficient (often referred to as normalized broadband ultrasonic attenuation, or nBUA) typically fall within the range of 10 to 40 dB/cm/MHz for cancellous bone.¹⁹

In this study, all three ultrasonic parameters, nMBD, nBAR, and nPVD, are found to increase with bone mineral density. This is expected because dense specimens of bone are more attenuating than less dense specimens. Greater attenuation leads to a greater power difference between the two gated portions of the backscatter signal or image ROIs (see Figure 3), which causes the parameters to increase with density. Although nMBD, nBAR, and nPVD are sensitive to attenuation, they do not represent actual estimates of ultrasonic attenuation in bone. In principle, however, it is possible to use backscatter signals to estimate attenuation in bone. This has been demonstrated in soft tissues such as the liver²⁰⁻²³ and in bone to a limited extent.⁶ Accurate estimations of attenuation require knowledge of the thickness of the tissue or the speed of sound in the tissue. These may be difficult to determine from backscatter measurements *in vivo*.

Anisotropy

Specimens used in this study were prepared from the distal end of the femur where the trabeculae align approximately along the long axis of the bone. This direction corresponds to the superior-inferior axis of the specimens (see Figure 1). Defining the superior-inferior (SI) axis as the longitudinal direction and the other two axes (anterior-posterior [AP] and medial-lateral [ML]) as the transverse direction, measurements in the transverse direction (perpendicular to the trabeculae) may be different from measurements in the longitudinal direction (parallel to the trabeculae).

As shown in Figure 5, all three parameters considered in this study exhibited a modest anisotropy. The bar graphs in Figure 5 were generated by averaging all measurements from all specimens and all gate choices along either the transverse or longitudinal direction. Error bars represent standard deviations of the means. nMBD, nBAR, and nPVD are all slightly less in the longitudinal direction than in the transverse direction. Statistical analysis using a paired *t* test found the anisotropy to be statistically significant ($p < 0.001$) for all three parameters.

nMBD and nPVD tended to correlate more strongly with bone mineral density (BMD) along the longitudinal direction as compared with the transverse direction. The correlation of nBAR with BMD did not depend on direction. Of the three parameters, nMBD demonstrated the strongest correlation with BMD for measurements along the transverse direction ($R = 0.83$, $\tau_w = 2 \mu\text{s}$, $\tau_s = 0 \mu\text{s}$) and also the longitudinal direction ($R = 0.86$, $\tau_w = 1.5 \mu\text{s}$, $\tau_s = 0.5 \mu\text{s}$).

Limitations

The main limitation of this study is the *in vitro* nature of the measurements. Measurements were performed on cube shaped specimens of cancellous bone in a water filled tank. Extrapolation of the findings to *in vivo* conditions may not be straightforward. Another limitation involves the effects of phase cancellation, which may lead to an underestimation of the power in gated portions of the backscattered signal. Errors associated with phase cancellation effects were not explored in this study. In addition, this study used a commercial system with proprietary technology that generates signals and images in ways not fully disclosed to the user. It is possible that a different imaging system may yield different results. However, the results of the present study for nMBD demonstrate good agreement with results from previous studies that used different measurement systems.^{12,16}

Summary and Conclusion

This study investigates the feasibility of using an ultrasonic imaging system to perform backscatter difference measurements of bone. One of the parameters, nMBD, demonstrated good potential as a bone assessment parameter in two previous studies that used nonimaging systems to perform backscatter measurements.^{12,16} The other two parameters, nBAR and nPVD, are introduced in the present study as parameters that are analogous to nMBD, but performed on signals in the time domain and directly on the images, respectively.

All three parameters are found to be increasing functions of bone density. This is expected as dense specimens of bone are more attenuating than less dense specimens, causing a greater difference between the two gated portions of the backscatter signal (nMBD and nBAR) or image ROIs (nPVD). The signal-based parameters, nMBD and nBAR, correlate well with bone density, yielding linear correlation coefficients that range from 0.74 to 0.87. The image-based parameter, nPVD, performs somewhat less well, yielding correlation coefficients that range from 0.42 to 0.81.

The results of this study suggest that backscatter difference techniques can be applied successfully to ultrasonic imaging systems with multielement array transducers. Thus, it may be feasible to apply backscatter difference techniques to real-time imaging systems for the purpose of detecting changes in bone caused by osteoporosis.

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Figure 1.

Cube shaped specimens of cancellous bone were prepared from the distal end of the femur and oriented along the AP, ML, and SI axes. Ultrasonic measurements were performed along all six axes in two perpendicular scan planes. For example, the scan planes for measurements along the superior or inferior direction were the SI-ML and SI-AP planes as shown. Data were acquired from a total of 12 scan planes per specimen. AP = anterior-posterior; ML = medial-lateral; SI = superior-inferior.

Figure 2.

Images from three cube shaped specimens of bone with low, medium, and high densities. Three signals are shown from each specimen along the lines indicated by A, B, and C in the images. The vertical scale of the signals is not the same for all specimens. The horizontal scale is in units of microseconds with a time increment of 0.05 μ s between points. BMD = bone mineral density.

Figure 3.

(a) Two analysis gates were positioned on the signal to determine the nMBD and the nBAR. The first gate was delayed by 4 μs from the front surface echo. The gates had a width (duration) τ_w and separation τ_s . (b) Rectangular ROIs were used to select equivalent portions of the images to determine the nPVD. nMBD = Normalized mean backscatter difference; nBAR = normalized backscatter amplitude ratio; ROI = regions of interest; nPVD = normalized pixel value difference.

Figure 4.

(a) nMBD, (b) nBAR, and (c) nPVD plotted as a function of BMD for a gate width of $\tau_w = 1 \mu\text{s}$ and gate separation $\tau_s = 1 \mu\text{s}$. Each data point represents the mean of all measurements from all 12 scan planes from a particular specimen. Error bars represent standard errors of the mean. nMBD = normalized mean backscatter difference; nBAR = normalized backscatter amplitude ratio; nPVD = normalized pixel value difference; BMD = bone mineral density.

Figure 5.

Comparison of (a) nMBD, (b) nBAR, and (c) nPVD measured along the longitudinal and transverse directions. These directions correspond to wave propagation approximately parallel and perpendicular to the trabeculae, respectively. Each bar represents the mean of all measurements from all specimens along one of the two directions. Error bars represent standard deviations of the mean. A statistically significant anisotropy is observed for all three parameters. nMBD = normalized mean backscatter difference; nBAR = normalized backscatter amplitude ratio; nPVD = normalized pixel value difference.

Table 1

Donor Information.

Donor ID	Number of Specimens	Age	Gender
1	4	51	Male
2	7	33	Male
3	4	48	Male
4	3	67	Female
5	6	56	Female

Table 2

Mean $\pm$ Standard Deviation (Averaged over All 24 Specimens) for nMBD, nBAR, and nPVD for Different Choices of Gate Width τ_w and Gate Separation τ_s .

τ_s (μ s)	0			0.5			1		
	1	1.5	2	1	1.5	2	1	1.5	2
nMBD (dB/ μ s)	3.40 $\pm$ 0.99	3.37 $\pm$ 0.80	3.29 $\pm$ 0.69	3.36 $\pm$ 0.89	3.31 $\pm$ 0.73	3.27 $\pm$ 0.68	3.35 $\pm$ 0.78	3.26 $\pm$ 0.70	3.21 $\pm$ 0.68
nBAR (μ s ⁻¹)	0.078 $\pm$ 0.020	0.076 $\pm$ 0.015	0.073 $\pm$ 0.012	0.077 $\pm$ 0.017	0.074 $\pm$ 0.013	0.071 $\pm$ 0.012	0.076 $\pm$ 0.014	0.072 $\pm$ 0.012	0.069 $\pm$ 0.012
nPVD (μ s ⁻¹)	18.2 $\pm$ 4.1	17.5 $\pm$ 3.0	16.4 $\pm$ 2.3	17.9 $\pm$ 3.5	16.9 $\pm$ 2.6	15.8 $\pm$ 2.2	17.4 $\pm$ 2.9	16.4 $\pm$ 2.4	15.2 $\pm$ 2.0

nMBD = normalized mean backscatter difference; nBAR = normalized backscatter amplitude ratio; nPVD = normalized pixel value difference.

Table 3

Pearson's R Correlation Coefficients for nMBD, nBAR, and nPVD versus Specimen Density for Different Choices of Gate Width τ_w and Gate Separation τ_s .

	0			0.5			1		
	1	1.5	2	1	1.5	2	1	1.5	2
τ_w (μ s)	0.85	0.84	0.87	0.83	0.86	0.87	0.85	0.87	0.86
nMBD	0.85	0.84	0.87	0.83	0.86	0.87	0.85	0.87	0.86
nBAR	0.75	0.74	0.77	0.74	0.75	0.77	0.76	0.76	0.76
nPVD	0.81	0.69	0.59	0.76	0.65	0.52	0.72	0.59	0.42

nMBD = normalized mean backscatter difference; nBAR = normalized backscatter amplitude ratio; nPVD = normalized pixel value difference.