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Validation of Quantitative Bound and Pore Water Imaging in Cortical Bone

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Abstract

Purpose—To implement and validate a previously proposed ultra-short echo time (UTE) method for measuring collagen-bound and pore water concentrations in bone based on their T_2 differences.

Methods—Clinically compatible UTE image sequences for quantitative T_2 -based bound and pore water imaging in bone were implemented and validated on a 3T human scanner and a 4.7T small bore system. Bound and pore water images were generating using T_2 -selective adiabatic pulses. In both cases, the magnetization preparation was integrated into a 3D UTE acquisition, with 16 radial spokes acquired per preparation. Images were acquired from human cadaveric femoral mid-shafts, from which isolated bone samples were subsequently extracted for non-imaging analysis using T_2 spectroscopic measurements.

Results—A strong correlation was found between imaging-derived concentrations of bound and pore water and those determined from the isolated bone samples.

Conclusion—These studies demonstrate the translation of previously developed approaches for distinguishing bound and pore water from human cortical bone using practical human MRI constraints of gradient performance and RF power deposition.

Keywords

bone; UTE; adiabatic; bound water; pore water

INTRODUCTION

Recent studies showed that ^1H NMR signals with short T_2 ($\approx 400 \mu\text{s}$) correspond primarily to collagen-bound water and those with longer T_2 components ($1 \text{ ms} - 1 \text{ s}$) correspond primarily to pore water (1–4). These bound and pore water measures correlate to mechanical properties of bone, including yield stress, peak stress, and pre-yield or elastic toughness (5–8). In particular, bones with a greater concentration of bound water and a lower concentration of pore water have higher values of peak stress, yield stress, and pre-yield toughness. These results suggest that appropriate MRI methods that robustly distinguish and quantitatively measure bound- and pore-water concentrations in cortical bone may offer a viable methodology for predicting fracture risk. In particular, they can assess the contribution of the bone tissue to fracture resistance in addition to the structural contribution already provided by conventional MRI or X-ray computed tomography. This is potentially quite useful since clinical assessment of areal bone mineral density by dual-energy X-ray absorptiometry does not necessarily capture all the deleterious effects of aging and certain diseases (type 2 diabetes, chronic kidney disease) on fracture risk (9,10).

Bi-exponential analysis of T_2^* signal decays has shown correlations between the fitted components amplitudes and the bound and pore water concentrations (7,11–13). This approach requires noise-sensitive non-linear regression and may be limited at high static field strengths by the similarity of T_2^* of bound and pore water (3,4,14). An alternative approach uses T_2 -selective adiabatic radiofrequency (RF) pulses over a broad enough resonance bandwidth to effectively distinguish bound- and pore-water signals (14). Specifically, playing two consecutive broad-bandwidth adiabatic full passage pulses will drive short T_2 magnetization (bound water) to saturation while rotating long T_2 magnetization (pore water) through 360° , leaving it essentially unaffected. This approach is referred to as the Double Adiabatic Full Passage (DAFP). To image bound water, a similar approach uses one adiabatic full passage pulse followed by an appropriate delay to invert and null pore water magnetization while the bound water magnetization experiences a saturation-recovery process. This approach is referred to as the Adiabatic Inversion Recovery (AIR). Presented here are demonstrations and validations of DAFP and AIR methods of imaging bound- and pore-water of human cadaver bones, using clinically practical parameters, on both a 4.7T small-bore and a 3.0T human system.

METHODS

The Vanderbilt Donor Program supplied human femurs from 3 cadaveric donors, two males and one female, mean age 77 years. Mid-shaft sections of each bone were cut to $\approx 80 \text{ mm}$ in length. Images of the femur mid-shafts along with a CuSO_4 -doped 10% $\text{H}_2\text{O}/90\% \text{D}_2\text{O}$ phantom (in a 10 mm NMR tube adjacent to the bone) were acquired using the DAFP and AIR sequences, detailed below, with $96 \times 96 \times 96 \text{ mm}^3$ field of view and a nominal

isotropic resolution of 1.5 mm. After imaging, cylindrical cortical bone samples (4–9 mm length, 6 mm diameter) were cored from four radial locations near the middle of the mid-shaft. These samples, along with a long- T_2 water sample of known volume, were used to provide reference values of bound and pore water concentrations using a previously described CPMG protocol (14) at 4.7 T. Imaging at 3T was performed on a Philips Ingenia (Best, NL) using their dStream Knee 8ch receive coil and the body coil for signal transmission. Measurements at 4.7 T were performed on an Agilent Direct Drive (Santa Clara, CA) using an in-house built 63-mm diameter low-proton birdcage style coil for whole bone imaging and an in-house built 20 mm diameter low-proton loop-gap style RF coil for CPMG measurements on isolated bone specimen (15).

Pulse Sequences

Figure 1 shows sequence diagrams of the DAFP and AIR sequences. In all cases, the following sequence parameters were used: radial sampling of k-space with 83 points at 250 kHz receiver bandwidth, acquisition time per spoke = 332 μ s; a post-acquisition spoiler gradient 1.74 ms duration and 31 mT/m amplitude; repetition time per spoke (TR_A) = 3.18 ms; number of spokes per shot (N_S) = 16; total number of spokes = 8192; RF excitation pulse width = 115 μ s. The radial spokes were distributed evenly over the k-space sphere (16). A variable flip angle schedule was used for excitations in order to generate approximately constant transverse magnetization for all 16 spokes (17), with an initial prescribed flip angle, $\theta_1 = 12.5^\circ$, and effective total flip angle, $\theta_E = 60^\circ$ (i.e., longitudinal magnetization is reduced by $\cos(\theta_E)$ by the combination of all 16 excitations). In all cases, the effective echo time (TE), as measured from the center of the RF excitation pulse to the start of acquisition, was 105.5 μ s (4.7T) and 127.5 μ s (3.0T).

The AIR sequence used a sequence repetition time (TR) = 300 ms, $TI = 90$ ms/85ms (4.7T/3T), and a 10-ms duration, 3.5 kHz bandwidth, 8th ordered hyperbolic secant (HS8) pulse (18) as the preparation pulse. The DAFP sequence used $TR = 400$ ms, $TD = 5$ ms, and two consecutive HS8 pulses (20 ms total duration). The maximum gradient amplitudes and slew rates of the human system were also used on the 4.7T. The TR values for each sequence were dictated by FDA-defined RF power deposition limits on the 3.0T scanner. On the 4.7T system, one excitation provided sufficient signal, resulting in scan times of $\approx 3 \frac{1}{2}$ min and $\approx 2 \frac{1}{2}$ min for DAFP and AIR, respectively. On the 3.0T system, lower signal-to-noise ratio (SNR) dictated 4 averaged excitations ($\approx 13 \frac{1}{2}$ min) for DAFP and 6 averaged excitations ($\approx 20 \frac{1}{2}$ min) for AIR to achieve SNR comparable to 4.7T.

In addition, a conventional UTE (CUTE) image was acquired for each bone at 3.0T and 4.7T, and at 4.7T a B_1 map was also acquired. The CUTE acquisition used $TR/TE = 2.5$ ms/62.5 μ s and a 25 μ s duration, 6° flip excitation pulse. The B_1 mapping was performed by the Bloch-Siegert method (19) with a multi-slice spin echo acquisition. Ten axial slices (3 mm thick/5 mm gap) spanned the length of the bone. The B_1 measured in the water phantom of each slice was used to determine the actual flip angle seen in each slice for analysis of AIR and DAFP data (see below). Variation of $|B_1|$ within the slice was independently determined to be $< 2.5\%$ for the coil used on the 4.7T. On the 3.0T, the body RF coil was used for

transmission and was independently determined to vary in $|B_1|$ by $< 4.5\%$ over the entire bone volume, so no B_1 mapping was necessary.

Data Analysis

All data were analyzed using MATLAB (Natick, MA). Images were reconstructed using standard trajectory mapping, density compensation, and gridding methods (20). Bound and Pore water concentrations were computed on a voxel-by-voxel basis, as described below, then regions of interest (ROIs) were defined at the approximate locations from which the cylindrical bone samples were taken. The signal equations for DAFP and AIR measurements in cortical bone are shown below (note the correction in Eq [1], compared with a previous report (14)):

$$S_{\text{DAFP}} \approx S_0^{\text{pw}} \beta^{\text{pw}} \sin \theta_1 \frac{(\alpha^{\text{pw}})^2 (1 - e^{-R_1^{\text{pw}} \text{TR}})}{1 - (\alpha^{\text{pw}})^2 e^{-R_1^{\text{pw}} \text{TR}} \cos \theta_E} e^{-R_2^{*\text{pw}} \text{TE}}, \quad [1]$$

and

$$S_{\text{AIR}} \approx S_0^{\text{bw}} \beta^{\text{bw}} \sin \theta_1 \frac{1 - (1 - \alpha^{\text{bw}}) e^{-R_1^{\text{bw}} \text{TI}} - \alpha^{\text{bw}} e^{-R_1^{\text{bw}} \text{TR}}}{1 - \alpha^{\text{bw}} e^{-R_1^{\text{bw}} \text{TR}} \cos \theta_E} e^{-R_2^{*\text{bw}} \text{TE}}, \quad [2]$$

where α is the inversion efficiency of the AFP pulse, β is the signal loss due to relaxation-induced blurring, S_0 is proportional to water concentration, and superscripts pw and bw indicate pore water and bound water, respectively. Replacing pw or bw with ref , provides the signal equations for the reference marker for each sequence. At 4.7T, previously obtained values were used for inversion efficiency (α), R_1 , and R_2^* of bound water, pore water, and the reference marker (14): $\alpha^{\text{bw/pw/ref}} = 0.09/-0.78/-0.83$, $1/R_1^{\text{bw/pw/ref}} = 357 \text{ ms}/551 \text{ ms}/13 \text{ ms}$, $1/R_2^{*\text{bw/pw/ref}} = 290 \text{ } \mu\text{s}/1280 \text{ } \mu\text{s}/13 \text{ ms}$. At 3.0T, R_1^{pw} was estimated from one bone using a saturation-recovery fast spin echo acquisition, and R_1^{bw} was estimated to change similarly from 4.7T as did R_1^{pw} . R_2^* values at 3.0T were used as measured by Du et al. for ex vivo human cortical bone (12). Because R_2 values were assumed to be nearly B_0 independent, the same α values were used at 3.0T as were previously measured at 4.7T. A summary of parameter values used at 3.0T were $\alpha^{\text{bw/pw/ref}} = 0.09/-0.78/-0.83$, $1/R_1^{\text{bw/pw/ref}} = 290 \text{ ms}/450 \text{ ms}/10 \text{ ms}$, $1/R_2^{*\text{bw/pw/ref}} = 350 \text{ } \mu\text{s}/2600 \text{ } \mu\text{s}/10 \text{ ms}$. The blurring-induced signal loss values were empirically estimated by simulating the effect of blurring using the known bone geometry for each bone (see Appendix for more details). Individual β values were found for each ROI and bone, but mean estimates used to create images were $\beta^{\text{bw/pw}} = 0.77/0.97$ at 3.0 T and $0.74/0.93$ at 4.7 T. In both cases, β^{ref} was defined = 1.0. Thus, given the observed bone signals S_{DAFP} and S_{AIR} , the equilibrium signals, S_0^{pw} and S_0^{bw} were computed from each bone ROI or voxel using Eq [1] and [2]. These relative measures of proton density were then converted into absolute units of $\text{mol } ^1\text{H}/\text{L}_{\text{bone}}$ by comparison to corresponding values of S_0^{ref} , which were known to reflect $111.1 \text{ mol } ^1\text{H}/\text{L}_{\text{H}_2\text{O}}$.

The non-imaging data from the extracted cortical bone samples were analyzed by fitting CPMG echo amplitudes to a broad range of decaying exponential functions by non-negative least squares criteria subject to a minimum curvature constraint, resulting in a T_2 -spectrum

for each sample (3,21). The integrated T_2 spectrum amplitude over various domains provided signal amplitude measures for bound water ($100 \mu\text{s} < T_2 < 1 \text{ ms}$), pore water ($1 \text{ ms} < T_2 < 1 \text{ s}$) and reference sample ($T_2 > 1 \text{ s}$). The bound and pore water signals amplitudes were then converted into units of $\text{mol } ^1\text{H}/\text{L}_{\text{bone}}$ by comparison with the reference signal amplitude and known volumes of the bone and reference samples, and the known proton concentration of water, as above.

RESULTS

Figure 2 shows approximately the same slice taken from 3D bound- and pore-water images of one bone at 3T and 4.7T. The gray scale images are CUTE images; color overlaid images are the bound or pore water concentration maps generated from the respective method. The DAFP image shows consistently a higher concentration of pore water in the posterior section of the femur, which agrees with previous findings (6,22), and in general there is an apparent negative correlation between the spatial distribution of bound and pore water, as expected. The signal to noise ratio (SNR) of DAFP/AIR images were $\sim 27/\sim 22$ at 4.7T and $\sim 26/\sim 28$ at

3.0T, defined as $\text{SNR} = \mu_S / \left(\mu_N / \sqrt{\pi/2} \right)$, where μ_S and μ_N are mean signal in a region of cortical bone and background noise, respectively. (At 3.0T, the background of the AIR images showed significant signal from the foam used to hold the bone samples, so for this μ_N measure one scan was repeated with a larger FOV but equal voxel size and receiver bandwidth.) The RF coil used at 3.0T is suitable for wrist and lower leg imaging, so these SNR values should be predictive of in vivo scans of the radius and tibia.

Figure 3 shows a representative T_2 spectrum from an extracted cortical bone sample, with the bound water, pore water, and water marker signals labeled. Figure 4 shows linear correlations between bound/pore water concentrations measures from the extracted samples and those from the AIR and DAFP images at approximate locations of the extracted bone samples (shown by red squares on inset image). Coefficients of determination for pore water concentrations were $r^2 = 0.41$ at 3T and $r^2 = 0.94$ at 4.7T; for bound water concentrations they were $r^2 = 0.76$ at 3T and $r^2 = 0.55$ at 4.7T.

DISCUSSION

The magnetization preparations used in the AIR and DAFP pulse sequences were previously demonstrated to effectively distinguish bound and pore water signals in isolated human cortical bone samples (14). Presented here is the translation of these methods into clinically practical MRI protocols, and the quantitative evaluation of these MRI protocols on human cadaver bones at 3.0 and 4.7 T. The results suggest that the AIR and DAFP methods are effective for quantitative imaging of bound and pore water, respectively, but there are numerous factors that may affect their performance and utility.

First, in contrast to previous non-localized studies of isolated bone samples, the imaging protocols presented here required accelerated acquisition to achieve scan times amenable to human studies. Power deposition from the AFP pulses set the lower limit on TR, so additional acceleration was achieved by acquiring $N_S = 16$ radial spokes in k-space per TR

period, similar to a conventional MP-RAGE protocol (23). The 3D radial trajectory sampled the k-space origin with every radial spoke, so accurate quantitation of image intensity required a variable excitation flip angle schedule that generated approximately the same amplitude of transverse magnetization for each spoke (17). Increasing N_S requires reduced flip angles, resulting in $\text{SNR} \propto 1/\sqrt{N_S}$, so the choice of N_S depends on the SNR and scan time requirements. The choice of N_S may also affect signal accuracy, because each spoke experiences slightly different magnetization preparation. For the AIR sequence, each of the N_S spokes is acquired at a different TI and, therefore, includes a varying amount of non-nulled pore water signal. As long as the net pore water signal across the N_S spokes is zero, this is not a problem, but increasing N_S will likely result in greater net pore water signal. For the DAFP sequence, the recovery of bound water magnetization will grow with each spoke, so $N_S \times \text{TR}_A$ should be kept small compared to T1 of bound water.

In addition accelerated acquisition, practical use of the AIR and DAFP protocols depends upon having good estimates of a number of parameters in the signal equations, Eq [1] and [2]. As done here for scans on the 4.7T, it is relatively quick and easy to map B_1 , thereby providing good estimates of θ_1 and θ_E on a case-by-case basis. However, estimates of bound- and pore-water relaxation rates may not be readily acquired during a clinical protocol, so good population estimates are needed. The values used here and in a previous study (14) of a small sample of cadaver bones have been sufficient to demonstrate efficacy of the AIR and DAFP methods, but it is likely that errors in these values underlie the systematic deviations between the imaging and CPMG measures seen in Fig 4. Given the parameters used in this work, an error of 10% in R_1 results in a 5/8% error of DAFP/AIR signal, while a 10% error in R_2^* gives a 1/4% error of DAFP/AIR signal. Further, it may not be suitable to describe R_1 and R_2^* with scalar values. In particular, pore water likely consists of a relatively broad spectrum of T_1 values due to the variation in pore sizes within the bone (2,3), which likely explains why TI must be empirically set to null the net pore water magnetization rather than by calculation from the estimated R_1^{pw} (14).

Two parameters that are known but require special attention for accurate AIR and DAFP measures are TE and receiver bandwidth. Although it is common to define TE from the end of the RF excitation pulse, the effect of relaxation during the RF pulse must be incorporated to ensure accurate measures. For hard pulse 3D UTE, as used here, transverse relaxation can be effectively accounted for by measuring TE from the middle of the RF pulse rather than the end (24). Accounting for transverse relaxation during the acquisition is a somewhat more complicated problem. Because the bound water T_2^* is similar to the acquisition duration (332 μs), its relatively broad point spread function results in an underestimation of bound water signal compared to signal from the long T_2 water reference (25, 26). In the present studies, as noted in the METHODS, the bound and pore water signal losses was empirically estimated, which resulted in the $\beta^{\text{bw/pw/ref}} = 0.77/0.97/1.0$ at 3.0 T and $0.74/0.93/1.0$ at 4.7 T. See the Appendix for calculation details.

CONCLUSION

These studies demonstrate the translation of previously developed approaches for distinguishing bound and pore water from human cortical bone. The methods, referred to AIR and DAFP here, were implemented as part of 3D UTE pulse sequences, subject to the practical human MRI constraints of gradient performance and RF power deposition. The results showed good correlation between these imaging measures of bound and pore water and those determined by previously established non-localized CPMG measures.

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APPENDIX

Signal Amplitude Correction for Blurring

Because the relaxation times of bound and pore water are similar to the acquisition duration, it is necessary to account for the effect transverse relaxation during the acquisition on image signal amplitude. Relaxation during acquisition broadens the image-domain point spread function, which can blur a significant amount of signal out of voxel or ROI, and ramp sampling exacerbates the problem because the signal decays more rapidly in k-space. For the 3D bone imaging in this paper, the samples are roughly invariant in the direction of the long axis of the bone, so the blurring effect can be neglected in that direction. Also, because the k-space sampling is radial, the point spread function can be solved in 1D (25,26), then applied in the 2D plane corresponding to the axial view of the bone (Fig 2).

For a known image geometry, $T_2^*(s)$, and k-space trajectory, the signal attenuation can be numerically estimated as follows: *i*) a masked 2D bone image, $s(\mathbf{r})$ (bone signal = 1, all other signal equals 0) is Fourier transformed to produce the k-space signal, $S(\mathbf{k})$; *ii*), the effect of T_2^* decay during acquisition is imparted by multiplying $S(\mathbf{k})$ by $H(\mathbf{k})$, derived below; *iii*) the resulting apodized signal is inverse Fourier transformed to produce a blurred image, $s_b(\mathbf{r})$; and *iv*) the signal loss term, β , is then computed on a voxel-by-voxel basis as $\beta = s_b(\mathbf{r})/s(\mathbf{r})$.

The apodizing function, $H(\mathbf{k})$, is derived for a 2D radial acquisition as follows. The signal decay during acquisition as a function of time is

$$h(t) = e^{-\frac{t}{T_2^*}}, \quad [\text{A1}]$$

and k is a function of t by the relationship:

$$|k(t)| = \frac{\gamma}{2\pi} \int_0^t g(t') dt', \quad [\text{A2}]$$

where γ is the gyromagnetic ratio and $g(t)$ is the gradient waveform. Assume that $g(t)$ increases linearly at constant slew rate up to max gradient amplitude, G , at time $t = t_0$, then,

$$|k(t)| = \begin{cases} \frac{\lambda}{2\pi} \frac{G t^2}{2t_0} & t < t_0 \\ \frac{\lambda}{2\pi} G \left(t - \frac{t_0}{2}\right) & t \geq t_0 \end{cases} \quad [\text{A3}]$$

Let $k_0 = k(t_0) = \frac{\gamma}{2\pi} G t_0$, then

$$t = \begin{cases} \sqrt{\frac{4\pi t_0 |k|}{\gamma G}} & k < k_0 \\ \frac{2\pi |k|}{\gamma G} + \frac{t_0}{2} & k \geq k_0 \end{cases}, \quad [\text{A4}]$$

Substituting [A4] into [A1] give the apodizing function in k-space

$$H(\mathbf{k}) = \begin{cases} e^{\sqrt{\frac{4\pi |k|}{\gamma G}} / T_2^*} & |k| < k_0 \\ e^{\left[\frac{2\pi |k|}{\gamma G} + \frac{t_0}{2}\right] / T_2^*} & |k| \geq k_0 \end{cases} \quad [\text{A5}]$$

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Figure 1.

The 3D-UTE pulse sequence used. The PREP pulse is a double HS8 pulse for DAFP and a single HS8 pulse for AIR. The time delay between the end of the preparation pulse and the start of data acquisition is TD. The effective inversion-recovery time $TI = TD + TR_A \times N_S/2$, where N_S radial spokes are acquired with period TR_A during every TR period.

Figure 2. Imaging results from 3 T (top) and 4.7 T (bottom) of the DAFP and AIR sequences showing three cardinal planes of pore and bound water maps. Note the negative correlation between bound and pore water throughout the bone volume and the higher concentration of pore water in the posterior section of the femur.

Figure 3.

A representative T_2 spectrum from the CPMG measurements of the cored samples of cortical bone showing signals from bound water, pore water, and the water marker. The amount of bound and pore water was converted into units of mol $^1\text{H/L}$ based on the known size and concentration of the water marker.

Figure 4.

Concentrations from CPMG measurements versus DAFP and AIR results at approximate ROI locations from 3 T and 4.7T images of a) bound water and b) pore water. Both 3 T and 4.7 T imaging measurements showed strong linear correlations with CPMG measurements.