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In vivo evaluation of multi-echo hybrid PRF/T1 approach for temperature monitoring during breast MRgFUS treatments

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Abstract

Purpose—To evaluate the precision of *in vivo* temperature measurements in adipose and glandular breast tissue using a multi-echo hybrid PRF/T1 pulse sequence.

Methods—A high bandwidth, multi-echo hybrid PRF/T1 sequence is developed for monitoring temperature changes simultaneously in fat- and water-based tissues. The multiple echoes are combined with the optimal weightings for magnitude and phase images, allowing for precise measurement of both T1 and the proton resonance frequency (PRF) shift. The sequence was tested during *in vivo* imaging of 10 healthy volunteers in a breast specific MR-guided focused ultrasound (MRgFUS) system and also during FUS heating of excised breast adipose tissue.

Results—The *in vivo* results indicate that the sequence can measure PRF temperatures with 1.25×1.25×3.5 mm resolution, 1.9 second temporal resolution and 1.0 °C temperature precision, and can measure T1 values with 3.75×3.75×3.5 mm resolution, 3.8 second temporal resolution and 2.5 to 4.8 % precision. The excised tissue heating experiments demonstrate the sequence's ability to monitor temperature changes simultaneously in water- and fat-base tissues.

Conclusion—The addition of a high bandwidth, multi-echo readout to the hybrid PRF/T1 sequence improves the precision of each measurement, providing a sequence that will be beneficial to several MR-guided thermal therapies.

Keywords

MR Thermometry; Temperature; Constrained Reconstruction; HIFU

Introduction

Simultaneous measurement of the proton resonant frequency (PRF) shift and the longitudinal relaxation time, T1, may prove useful in monitoring and evaluating MR-guided thermal therapies. These procedures are currently carried out under PRF guidance only, and while PRF is an indispensable tool for measuring temperature changes in water-based tissues, T1 measurements can provide additional and complementary information during the treatment. Investigators have shown that T1 measurements can be used to monitor

temperature changes in fat-based tissues (1-2), assess concentration of contrast-tagged particles released during targeted drug delivery (3), and help determine the onset of tissue thermal damage (4). For these reasons, several groups have proposed an approach to simultaneous PRF and T1 imaging that uses a gradient echo pulse sequence run at alternating flip angles (1-3). The PRF measurements are extracted from the image phase and the T1 values are calculated using a variable flip angle (VFA) approach (5-6).

The primary challenge in these hybrid PRF/T1 approaches is to satisfy the conflicting demands of fast scan times and precise PRF and T1 measurements. Fast imaging requires a short TR, which is suboptimal for both PRF and T1 precision, and the VFA method for measuring T1 uses flip angles away from the Ernst angle, which degrades the PRF precision. However, the most difficult trade-off comes in the choice of the sequence echo time (TE), as the PRF precision is optimized when the TE is set equal to the T2* value of the tissue (7), but the T1 precision is optimized when TE is as short as possible (5,8).

An approach to solving this problem is presented here, where we have extended our previously published hybrid PRF/T1 sequence (2) by adding a high bandwidth multi-echo readout to acquire several images at different TEs within the same TR period. The magnitudes and phases from the multi-echo data are combined into single images using optimal weightings for each. In this way, both the short-TE information needed for high T1 precision and the longer-TE information needed for high PRF precision are acquired in one scan. The method is evaluated during in vivo breast imaging of 10 healthy volunteers in a breast-specific MRgFUS treatment system (9) and during FUS heating of a breast-mimicking phantom consisting of ex vivo pork muscle and excised human breast adipose tissue.

Methods

Multi-Echo Hybrid PRF/T1 Sequence

The multi-echo hybrid PRF/T1 sequence presented here is a 2-D gradient echo sequence that uses a high bandwidth multi-echo readout and alternates between excitation at two different flip angles every time frame. A flyback gradient is used between echoes to ensure that all readout lines are read in the same direction in k-space and therefore any off-resonance signal is shifted in the same direction in image space. If multiple receive coils are used, the

complex data, C_k , from the N_c coils is combined as $\sum_{k=1}^{N_c} \frac{1}{\sigma_k^2} C_k \frac{c_{k,ref}^*}{|c_{k,ref}|}$, where σ_k^2 is the noise variance of the k^{th} coil and $c_{k,ref}$ is a complex baseline image for the k^{th} coil. The magnitude images acquired within one scan at different TEs are combined using a weighting for the j^{th} echo time of $\exp(-2 \cdot TE_j / T2^*)$ and normalized by $\sum_{j=1}^{N_e} \exp(-2 \cdot TE_j / T2^*)$, where N_e is the number of echoes. The phase images are similarly combined with weightings of $TE_j^2 \cdot \exp(-2 \cdot TE_j / T2^*)$ and normalized by $\sum_{j=1}^{N_e} TE_j^2 \cdot \exp(-2 \cdot TE_j / T2^*)$. The PRF temperature maps are calculated at every time frame from the combined phase image using a standard phase difference method (10-11). The T1 maps are calculated at every time frame from the combined magnitude images using the VFA method with one minor modification due to the fact that a dynamically changing T1 is being measured. When reconstructing the

T1 map for time frame, t_i , magnitude images from frames t_{i-1} , t_i , t_{i+1} are used, with the data from frames t_{i-1} and t_{i+1} averaged to give an estimate of what the magnitude at that flip angle would be at frame t_i . This averaging induces a one-frame lag in the T1 map availability and reduces the temporal resolution by approximately a factor of two, but prevents calculation errors that arise from the fact that T1, T2*, and M0 are all changing with temperature and affect the magnitude data used in the VFA calculation.

Simulation results shown in Figure 1 demonstrate the advantages of using a multi-echo readout with the hybrid PRF/T1 sequence. The steady state signal equation for a spoiled gradient echo sequence was simulated with the following parameters: TR = 50 ms; TE's = 2.5, 5.0, ... 50 ms; 2 flip angles chosen for optimal T1 precision (8); T2* = 30 ms; T1 = 350 ms for T1 calculations (to mimic adipose tissue); T1 = 900 ms for PRF calculations (to mimic muscle tissue); Gaussian random noise added to both real and imaginary signal components; M0 and noise levels set to give a signal-to-noise ratio (SNR) of 50 for T1 = 350 ms and TE = 0 ms. The black lines in Figures 1A and 1B show the T1 precision and PRF temperature precision as a function of echo time when data from only one echo is used. The red lines show the corresponding precision values when all data up to and including the particular TE is combined with the above weights and used for the T1 and PRF calculations. As expected in the single echo case, the precision vs TE curves show conflicting requirements for T1 and PRF, and the best that can be done is to select a compromise value for the TE. However, when all echoes are acquired and used, the precision results progressively improve as more data is added. In this case, choosing to acquire as many echoes as the TR will allow gives the optimal outcome, although there are diminishing returns as TE approaches the value of the tissue T2*.

Experiments

The first set of experiments consisted of *in vivo* breast imaging with the hybrid PRF/T1 sequence on ten healthy female volunteers in a breast-specific MRgFUS treatment system (age range 18 to 77 years; mean age 36 $\pm$ 17 years). All patients were positioned prone on the MRgFUS treatment table with one breast suspended in the water-filled treatment cylinder. A tensioning device is attached to the breast to provide motion stability and counteract buoyancy. The 2D imaging plane was positioned in an oblique coronal orientation, aligned to be parallel with the axis of the ultrasound beam. Initial imaging that would be done as a pre-treatment step included acquiring Three-point Dixon images for fat/water separation (12-13), and acquiring a series of 10 hybrid PRF/T1 images at different flip angles for flip angle optimization and calibration (2). The imaging time for these pre-treatment scans is less than two minutes. Next, the "treatment" imaging consisted of a dynamic series of 100 hybrid PRF/T1 images that were acquired with the optimal flip angles and the patient breathing freely, however no FUS heating was applied at any time. Sequence parameters were: one 2D slice; 160 $\times$ 160 mm FOV; 1.25 $\times$ 1.25 $\times$ 3.5 mm resolution; TR = 20 ms; TE's = 2.5, 5.25, ... 16.25 ms; two flip angles of 20° and 45° (for volunteers 2, 3, 4, 5, and 10) or 15° and 50° (for remaining volunteers); bandwidth = 810 Hz/pixel; 6/8 partial phase Fourier; 1.92 sec/scan. The flip angles were chosen such that the magnitude signals were approximately 70% of the Ernst angle magnitude signal.

The second set of experiments consisted of FUS heating of a breast-mimicking phantom in the breast-specific MRgFUS treatment system. Ex vivo pork muscle and excised human breast adipose tissue were placed in a breast-shaped ultrasound-transparent mold. The focus of the ultrasound was targeted near the interface of the two tissue types in order to induce heating in each. For one of the experiments, a fiber optic probe was inserted in the adipose tissue to obtain an independent measurement of temperature to compare against the T1-based temperature measurement. The ultrasound focus was targeted in the muscle and the heat was allowed to diffuse into the adipose tissue, however some direct heating of the probe was still observed as a 1.4 °C measurement spike when the ultrasound was turned on and off. This offset was removed from the probe temperature data. The same imaging steps were done as described for the in vivo experiments with the same imaging parameters used as well. The setups for both experiment sets are shown in Figure 2.

Image analysis was done by first using the Three-point Dixon data to create fat-only and water-only masks such that the T1 calculations were done only in voxels with greater than 75% fat content and the PRF temperatures calculations done only in voxels with greater than 75% water content. In order to correct for phase errors due to breathing, the PRF temperature maps for the in vivo imaging experiments were reconstructed using an atlas-based method with the first 50 image frames used for the atlas (14). The region used to pick the best-matched atlas image for the current image was around the periphery of the breast and did not include the 6×6 water-based ROI over which the Table 1 data was calculated. The PRF temperature maps were reconstructed using a standard complex phase subtraction for the *ex vivo* FUS heating experiments. In order to reduce the effects of approach to steady state caused by the alternating flip angles, a Tukey window with width parameter 0.25 was applied to the k-space data (15). A 3×3 mean filter was applied to the T1 data for noise reduction. Precision maps for the in vivo experiments were calculated by taking a voxel-by-voxel standard deviation over all time frames for the T1 and PRF temperature values. Combined PRF/T1 temperature maps for the ex vivo FUS heating experiments were created by calculating the PRF temperatures in the pork muscle and converting the T1 measurements in the excised breast adipose tissue using a temperature coefficient of 8.0 ms/°C. This temperature coefficient is based on the average result of four calibration experiments using four different samples of excised breast adipose tissue. Note that the spread in the T1 temperature coefficient across the four samples was approximately ± 2 ms/°C, which could add a systematic bias of up to $\pm 25\%$ for the T1 temperature measurement.

Results

Magnitude images from the multi-echo hybrid PRF/T1 sequence are shown in Figure 3A for each of the ten volunteers. The multi-echo data has been optimally combined into one image. Figure 3B shows the magnitude image from each separate echo for volunteer #3. In these images, the adipose tissue appears brighter and the variation in tissue inhomogeneity across patients can be seen. The precision results from four representative volunteers are shown in Figure 4, displaying one mostly fatty breast (#4), one mostly glandular tissue breast (#7), and two mixed content breasts (#1 and #6). For each case, the Dixon images show the fat/water separation, and the T1 precision and PRF temperature precision are

shown for the adipose tissue and glandular tissue, respectively. The precision of each measurement is fairly homogenous over the breast, with the exceptions that the precision of each can be worse near tissue boundaries and the PRF temperature precision is worse near the chest wall.

Table 1 summarizes the precision results for all ten volunteers, where the values reported are the mean and standard deviation of the precision over a 6×6 voxel region of interest in the respective tissue types. For comparison, precision values are also reported for the cases of the data being reconstructed using only the first echo (which would provide optimal precision for T1 measurements obtained with a single-echo sequence) and using only the last echo (optimal precision for PRF temperature measurements obtained with a single-echo sequence). When the data is combined, the T1 precision values range from $\pm 2.5\%$ to $\pm 4.8\%$, which corresponds to a temperature precision of $\pm 1.3\text{ }^{\circ}\text{C}$ to $\pm 2.4\text{ }^{\circ}\text{C}$ (by converting the $8.0\text{ ms}/^{\circ}\text{C}$ temperature coefficient to $2.0\text{ }^{\circ}\text{C}/\%$). The T1 precision values for volunteer #7 were treated as an outlier due to the fact that this volunteer only had a very thin layer of adipose tissue on the periphery of the breast. The combined PRF precision values remain very close to $\pm 1.0\text{ }^{\circ}\text{C}$ for all cases, with the exception of volunteer #8 who can be seen to have a breast composition that is almost entirely adipose tissue. For the case of only using the shortest echo time, the T1 precision values are only slightly worse, but the PRF precision is significantly worse. Conversely, the T1 precision values are significantly degraded for the single long echo case, while the PRF precision values are only slightly worse. The extremely poor T1 precision values for the long echo case seen in volunteers 3, 7, and 9 are due to susceptibility effects at tissue boundaries that reduced the signal at this echo time to almost the noise level.

The results from the three separate FUS heating experiments are shown in Figure 5. The ultrasound acoustic power and duration for each heating run is noted in the figure. The Dixon images show the fat/water separation and the combined PRF/T1 temperature maps are from the peak of heating. Plots of temperature over time are shown for one voxel within the heated region from the muscle (PRF temperature) and one voxel from the excised breast adipose tissue (T1-based temperature). The voxels plotted for each tissue type are denoted with white arrows on the Dixon images. For Sample #1, the fiber optic probe temperatures are plotted in black. The tip of the probe was located with a high resolution scan and the voxel for the T1-based temperature was selected to be as close as possible. In each case, the combined PRF/T1 temperature map demonstrates the ability to simultaneously monitor temperature rises in both muscle and adipose tissue. The T1-based temperatures from sample #1 follow the fiber optic temperatures reasonably well, although with a slight underestimation.

Discussion

This paper has demonstrated a high-bandwidth multi-echo hybrid PRF/T1 approach for simultaneous PRF temperature and T1 measurements. The sequence was evaluated for the application of breast tumor ablation treatments. Testing was performed during dynamic breast imaging of volunteers in a dedicated breast MRgFUS system and during FUS heating of excised breast adipose tissue. For such procedures, the ultrasound focus, where the

temperatures are changing most rapidly in space and time, is targeted in the aqueous tissue of the tumor and therefore monitored with the PRF measurements. The spatiotemporal resolution and precision of the PRF measurements achieved during the in vivo testing would be adequate to accurately track the temperature evolution of an MRgFUS treatment. The addition of the T1 measurements is meant to improve the safety of the treatment by monitoring any potential temperature rises in the adipose tissue. Temperature rises occurring in the ultrasound near- or far-fields are more diffuse and slow and therefore do not require as high spatiotemporal resolution. For heating in adipose tissue that occurs at the margin of the tumor, it may be desirable to leave the data unfiltered and trade lower precision for higher spatial resolution.

The addition of a high bandwidth multi-echo readout is designed to improve the precision of both the PRF and T1 measurements. This approach acquires both the short-TE information needed for precise T1 measurements and the long-TE information needed for precise PRF measurements, and combines the data using optimal weightings for both the image magnitude and phase. The improvement in measurement precision can be seen in results presented in Table 1. The average precision values over all volunteers for the single short-TE and long-TE cases were $\pm 3.8^{\circ}\text{C}$ and $\pm 1.8^{\circ}\text{C}$, respectively, for the PRF measurements, and $\pm 4.0\%$ and $\pm 10.0\%$, respectively, for the T1 measurements (excluding outlier values). Using the multi-echo approach, these values were improved to $\pm 1.3^{\circ}\text{C}$ and $\pm 3.5\%$. The multi-echo approach therefore overcomes the problem of having to choose a compromise value for TE that degrades one or both of the PRF and T1 measurements. Depending on the application, this improvement can be used for more precise measurements or traded for higher spatiotemporal resolution.

It is known that the VFA approach for measuring T1 is susceptible to systematic errors from a number of sources, including the spatial distribution of the achieved flip angle, the shape of the 2D slice profile, the extent to which the signal has reached spoiled steady state, and, in this case, the fact that T1, T2*, and M0 are all changing between measurements due to the heating. The effects of these problems on the accuracy of the T1 measurement and strategies for addressing them have been presented in previous publications (2, 3). In this work, care was taken to obtain T1 measurements as accurately as possible by performing the pre- and post-processing steps described in the Methods section. It should also be noted that the temperature dependencies of M0, T1, and T2* have the net effect of reducing the gradient echo signal magnitude as temperature increases and therefore the T1 measurement precision will be temperature dependent to some degree. Despite these shortcomings, the VFA approach has been chosen due to its ability to rapidly acquire T1 measurements and temperature sensitive image phase.

A minor drawback to the current implementation is that it provides only a single 2D slice for monitoring the treatment. Previous implementations of the hybrid PRF/T1 sequence have used a single echo time 3D approach, but this requires a segmented-EPI readout to achieve reasonable temporal resolution (4). The incorporation of a segmented-EPI readout limits both the shortest possible TE that can be acquired and the total number of TE's that can be acquired before the signal has decayed. To improve coverage, the current 2D implementation could be extended to an interleaved multi-slice approach. A longer TR

would be used to accommodate the extra slices and data undersampling with parallel imaging or compressed sensing reconstruction could also be implemented to recover temporal resolution.

We have not compared the current implementation to the alternative of acquiring a single echo at low bandwidth. Such an acquisition would likely be more efficient because data could be continuously sampled, whereas in the current implementation data is not sampled during the flyback or ramp portions of the readout gradient. The drawback to a single low bandwidth acquisition is that chemical shift artifacts become amplified. In the case of the breast, where the adipose and glandular tissue is mixed together in complicated fashion, this would lead to many regions where fat and water signals become overlapped.

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Figure 1.

Plots of T1 and PRF precision as a function of echo time. The black lines show the T1 and PRF precision values when using data from only a single echo. The red lines show the same precision values when using data from all echoes up to and including the current echo.

Figure 2.

Experimental set up in the breast-specific MRgFUS system. An example volunteer from the in vivo imaging is shown in A) and B), displaying the breast in the treatment cylinder, the tensioning device on the breast, the position of the transducer, and the imaging plane used for the hybrid PRF/T1 sequence. Ex vivo FUS heating experiments, shown in C) and D), were designed to mimic the in vivo set up. Excised human breast fat and ex vivo pork muscle were inserted in a breast-shaped mold with the ultrasound focus targeted at the fat/muscle interface.

Figure 3.

A) Images from the hybrid PRF/T1 sequence for each of the 10 volunteers where the magnitudes have been optimally combined. B) Images from volunteer #3 showing the magnitude image at each of the six echo times.

Figure 4.

Example results from four of the volunteers. The first two columns show the Dixon water and fat images, the third column shows maps of the T1 precision for all fat-based voxels, and the fourth column shows maps of the PRF temperature precision for all water-based voxels.

Figure 5.

Results from the ex vivo FUS heating experiments. The first two columns show the Dixon water and fat images, the third column shows the combined PRF/T1 temperature map at the peak of heating, where the T1 measurements have been converted to temperature change, and the fourth column shows single-voxel plots of the PRF-based temperature rise in the pork muscle and the T1-based temperature rise in the excised adipose breast tissue. The white arrows on the Dixon images indicate the location of the voxels plotted.

Table 1

Precision values for T1 measurements and PRF temperatures. The values are reported as a mean and standard deviation of the precision values from a 6×6 ROI in the respective tissue types. The first two columns use the optimally combined image data from all six echoes. The middle two columns only use data from the first echo time, which would give the optimal T1 precision for a single echo acquisition. The last two columns only use data from the last echo time, which would give the optimal PRF precision for a single echo acquisition. Note that for some volunteers an ROI smaller than 6×6 had to be used due to the limited amount of a particular tissue type.

Volunteer	T1 Precision (%) All Echoes Used	PRF Precision (°C) All Echoes Used	T1 Precision (%) Only TE = 2.5 ms	PRF Precision (°C) Only TE = 2.5 ms	T1 Precision (%) Only TE = 16.25 ms	PRF Precision (°C) Only TE = 16.25 ms
#1	2.7 +/- 0.3	1.1 +/- 0.2	3.5 +/- 0.3	3.5 +/- 0.4	6.4 +/- 0.6	1.2 +/- 0.2
#2	2.5 +/- 0.6	1.0 +/- 0.1	2.6 +/- 0.2	3.1 +/- 0.4	8.3 +/- 2.8	2.0 +/- 0.2
#3	4.7 +/- 2.7	0.9 +/- 0.1	4.5 +/- 1.3	3.5 +/- 0.3	41 +/- 71	1.2 +/- 0.1
#4	3.0 +/- 0.3	0.9 +/- 0.3	3.8 +/- 0.5	2.6 +/- 0.8	7.2 +/- 1.2	1.4 +/- 0.7
#5	3.6 +/- 0.7	1.2 +/- 0.4	4.2 +/- 0.5	2.9 +/- 0.4	15.1 +/- 7.7	1.7 +/- 0.6
#6	3.5 +/- 0.7	1.1 +/- 0.2	3.8 +/- 0.5	3.0 +/- 0.4	10.2 +/- 2.8	1.5 +/- 0.3
#7	9.7 +/- 1.7 *	1.1 +/- 0.1	8.6 +/- 1.2	3.7 +/- 0.6	230 +/- 480	1.5 +/- 0.2
#8	4.8 +/- 0.2	2.8 +/- 1.1	5.2 +/- 0.4	6.5 +/- 2.2	8.5 +/- 1.2	3.8 +/- 1.6
#9	3.4 +/- 0.6	1.0 +/- 0.1	4.0 +/- 0.5	4.6 +/- 0.6	45 +/- 78	1.5 +/- 0.2
#10	3.6 +/- 0.5	1.4 +/- 0.2	4.2 +/- 0.3	4.5 +/- 0.8	14.4 +/- 5.2	2.0 +/- 0.6

* For volunteer #7 there was not enough adipose tissue to apply the 3×3 mean filter to the T1 measurements.