Published in final edited form as:

Magn Reson Med. 2019 May ; 81(5): 3138–3152. doi:10.1002/mrm.27643.

Simultaneous Proton Resonance Frequency Shift Thermometry and T_1 Measurements Using a Single Reference Variable Flip Angle T_1 Method

Bryant T. Svedin¹, Allison Payne¹, and Dennis L. Parker¹

¹Utah Center for Advanced Imaging Research, University of Utah, Salt Lake City, Utah

Abstract

Purpose: Implement simultaneous proton resonance frequency (PRF) shift and T_1 measurements with equivalent temporal resolution using a single reference variable flip angle (VFA) method. This novel method allows for simultaneous thermometry in both aqueous and fatty tissue.

Methods: This method acquires a single reference image at the lower flip angle and all dynamic images at the higher angle. T_1 is calculated using a single reference VFA method, which accounts for the reference image temperature remaining constant. Monte Carlo simulations determined the optimal dynamic flip angle for combined PRF and T_1 measurements. This method was evaluated in MR guided focused ultrasound heating experiments using a gelatin phantom and human cadaver breasts. In vivo measurement precision was demonstrated in healthy female volunteers under non-heating conditions.

Results: Temperature rise during MRgFUS heating was measured in aqueous tissue with both PRF and T_1 . Both measures show good qualitative agreement in both space and time in aqueous tissue. The T_1 change due to temperature increase was measured in fat, demonstrating the expected temporal response. The dynamic flip angle that produces optimal SNR for PRF measurements is lower than the optimal angle for T_1 measurements, necessitating the selection of a compromise angle.

Conclusion: The single reference VFA method provides a reliable way to simultaneously measure PRF temperature and T_1 change and overcomes PRF's inability to simultaneously monitor temperature in aqueous and adipose tissues. Future work will calibrate T_1 change to temperature enabling real-time temperature in fat, increasing patient safety and treatment efficacy during thermal interventional treatments.

Keywords

MRgFUS; Thermometry; MRTI; T_1 Measurement; VFA; T_1

*Corresponding author: Bryant T. Svedin, Utah Center for Advanced Imaging Research, Department of Radiology and Imaging Sciences, 729 Arapleen Drive, Salt Lake City, Utah, 84108, Phone: (435)232-2788, fax: (801)585-3592, bsvedin@gmail.com.

INTRODUCTION

Magnetic resonance temperature imaging (MRTI) has been used to monitor several kinds of thermal therapies including radiofrequency, microwave, laser and MR-guided focused ultrasound (MRgFUS). MRgFUS has been used to noninvasively treat breast, prostate, liver and brain cancers as well as essential tremor and Parkinson's disease (1–10). In order to ensure treatment safety and efficacy, it is desirable that MRTI be able to monitor the entire heated tissue volume with enough temporal resolution to accurately follow the most rapid temperature changes. The different types of thermal therapy pose different challenges in terms of the needed coverage and acquisition speed. MRgFUS is especially challenging because the ultrasound often traverses a large volume of non-treated tissue before being focused to a point where rapid heating occurs. Thus, ideally, for MRgFUS, MRTI would monitor the focus and the near and far-fields with full coverage and high temporal resolution.

The proton resonance frequency (PRF) shift method has been widely adopted due to its linearity over the temperature range of interest, the constant of proportionality being largely independent of tissue type (except adipose tissue) (11), and its ability to produce temperature maps with the spatial and temporal resolution required to monitor treatments in real time. There have been several successful implementations of fully 3D thermometry methods using the proton resonance frequency (PRF) shift thermometry technique (12–21). Many FUS treatment targets are surrounded by or have adipose tissue in the near field (e.g. breast, abdominal targets). PRF thermometry is unable to monitor temperature changes in adipose tissue, and therefore several alternative methods to monitor temperature changes in adipose tissue have been proposed. These include methods based on relaxation times T_1 and T_2 as well as some hybrid approaches.

T_2 relaxation change with temperature has been used in adipose tissue (22–24). Baron et al (22) showed that the T_2 relaxation time at 1.5 T in pork adipose tissue changes approximately linearly with temperature over the temperature range 25–45 °C. T_2 relaxation changed exponentially at higher temperatures at 1.5 T. Ozhinsky et al (23) showed that T_2 changes at 3 T in pork adipose tissue was approximately linear from 25–70 °C. Baron and Ozhinsky both note that the T_2 change calibration is tissue and imaging protocol specific. The two TE values and whether or not water saturation was used both affected the T_2 change calibration and it was recommended that the same imaging parameters used during calibration be used during monitoring. The spin echo sequence that is required for T_2 relaxation time measurements is not ideal for the PRF shift as phase changes due to temperature are refocused as well. If an asymmetric spin echo is used to restore the PRF shift sensitivity, the dispersion of phase across a voxel might cause errors in the T_2 measurement. Further the method requires much longer repetition times reducing the efficiency of the PRF measurement. For these reasons, the T_2 relaxation changes were monitored with a separate sequence between FUS sonications and could not provide simultaneous monitoring of adipose and aqueous tissue. In addition, each of these T_2 thermometry methods only acquired a single slice, which limits the monitored field of view.

Several methods using the temperature dependence of the T_1 relaxation time have been implemented (25–27). It has been shown that T_1 changes approximately linearly in fat from 10–70 °C (28). Similar to T_2 , the rate of T_1 change with temperature is tissue type dependent. Bohris et al (25) used a saturation recovery turboFLASH sequence whose signal intensity depends on T_1 and the equilibrium magnetization. By comparing a baseline T_1 -weighted image with images acquired during heating and calibrated rates of T_1 change, temperature calculations could be made. However, there are several drawbacks to this method. There is no analytical solution to calculate temperature using this method and an iterative approach is needed. While the signal change with temperature is approximately linear over a small range of temperatures ($T < 20$ °C), making a linear approximation possible, the rate of change for this linear approximation is very dependent on the sequence parameters. The range of linearity can increase with recovery time between saturation and acquisition, but this has the added effect of increasing scan time. Finally, this method was performed in 2D which provides a limited field of view.

Todd et al. (26) and Diakite et al. (27) implemented simultaneous PRF/ T_1 measurement techniques using the variable flip angle (VFA) method to calculate temperature changes. Todd used a 2D spoiled gradient echo (GRE) sequence where the flip angle varied between each image acquisition. The PRF temperature was calculated for each time frame and the T_1 value was calculated by combining two sequential images with the VFA method. This method was then extended by adding multiple echo readouts and combining echo data to improve both PRF and T_1 precision (29). While this method showed promise, it had some serious drawbacks. It only acquired a single 2D slice, limiting the monitoring field of view. The effective temporal footprint of the T_1 measurement was twice the image acquisition time. While it can be possible to obtain accurate VFA T_1 measurements using 2D images with an average slice profile assumption as was done by Todd et al, it is extremely dependent on the flip angle choices (30). The 2D slice profile introduces a significant systematic error in the VFA T_1 calculation making it effectively impossible to get an accurate T_1 value during heating because the T_1 change will quickly cause the flip angles being used to no longer provide accurate T_1 values. Extending beyond 2D, Diakite used a 3D seg-EPI sequence and the VFA method combined with an extended 2-point Dixon to calculate the T_1 value in fat tissue. The imaging sequence alternated between two flip angles every acquisition and alternated the TE every two acquisitions between TE (1st and 2nd) and TE+ (3rd and 4th). Water and fat images were derived for each flip angle with the extended 2-point Dixon using the 1st and 3rd images and the 2nd and 4th images. T_1 values in the fat were calculated from the derived fat images at each flip angle. The PRF temperature was calculated for each image acquisition, but the T_1 value calculation required 4 image acquisition times. The T_1 value could be calculated using a sliding window over four image acquisitions but had a large temporal footprint. A couple of drawbacks for this technique include the very large fat chemical shift in the phase encoding direction (8 mm reported) and the need to achieve steady state through dummy excitations between every image acquisition, which increases overall scan time and lowers scanning efficiency.

Every VFA method requires accurate knowledge of the flip angle and it has been shown that the RF transmit strength can vary significantly throughout the body (31,32). There are several proposed methods to measure the RF transmit inhomogeneity including the double

angle method (33), saturated double-angle method (34), actual flip angle imaging (35), implementing the Bloch-Siegert shift (36) or the 180° signal null (37), and measuring the flip angle of a saturation pulse (38). Each method has different strengths and weaknesses including robustness, data acquisition time, difficulty of implementation, accuracy, and imaging field of view.

In this work, we describe and implement a single reference VFA method to measure T_1 . The proposed method, when combined with a multi-echo pseudo golden angle stack of stars (SOS) acquisition (39) and k-space weighted image contrast (KWIC) reconstruction method (20,21) will allow for rapid simultaneous PRF and T_1 thermometry techniques, providing T_1 images with temporal resolution equivalent to that of the magnitude image. This work presents the theory behind single reference VFA T_1 calculations and the optimal sequence parameters for simultaneous PRF and single reference VFA T_1 , determined using Monte Carlo simulations of noisy signal as a function of flip angle. The new hybrid method is evaluated in MRgFUS experiments using a gelatin phantom, human cadaver breasts, and human volunteers.

THEORY

The original VFA method for measuring T_1 uses the spoiled gradient recalled steady state signal equation

$$S = M_0 \frac{(1 - E_1) \sin(\alpha)}{1 - E_1 \cos(\alpha)} E_2 \quad [1]$$

where $E_1 = \exp(-TR/T_1)$, $E_2 = \exp(-TE/T_2^*)$, M_0 is the equilibrium magnetization, α is the flip angle, TR is the pulse repetition time, TE is the sequence echo time, and T_1 and T_2^* are the longitudinal and observed transverse relaxation times. Equation 1 is derived with the assumption that either $TR \gg T_2^*$ or adequate spoiling is used to ensure that negligible transverse signal remains before subsequent excitations. If these conditions are not met, Equation 1 will not accurately describe the signal and significant errors in T_1 calculation will occur. T_1 is calculated from the linearized form of Equation 1.

$$\frac{S}{\sin(\alpha)} = E_1 \frac{S}{\tan(\alpha)} + M_0(1 - E_1)E_2 \quad [2]$$

The signal from applying two different flip angles (α and β) can be used in Equation 2 to calculate the slope m , which is equal to an estimate of E_1 (E_{1est}).

$$E_{1est} = m = \frac{y_2 - y_1}{x_2 - x_1}, \quad [3]$$

$$y_2 = \frac{s_2}{\sin(\beta)}, y_1 = \frac{s_1}{\sin(\alpha)}, x_2 = \frac{s_2}{\tan(\beta)}, x_1 = \frac{s_1}{\tan(\alpha)}$$

T_1 is then calculated from the slope m using

$$T_{1est} = \frac{-TR}{\ln(m)} \quad [4]$$

The proposed single reference VFA method acquires a single reference image at the lower flip angle α and then acquires dynamic images at the higher flip angle β . The dynamic and reference images are identical in all respects except flip angle. Estimates of T_1 using the original VFA method (T_{1est}) will have a systematic error because the T_1 of the dynamic images will change with temperature, while the reference image is constant. The potential systematic error is shown in Figure 1, where the calculated T_{1est} overestimates the true T_1 as T_1 increases from the baseline value and underestimates the true T_1 as T_1 decreases from the baseline. The actual T_1 of the dynamic images can be calculated with a simple correction. The signals from the reference (S_r) and dynamic images (S_d) are given by

$$S_r = M_0 \frac{(1 - E_1)\sin(\alpha)}{1 - E_1\cos(\alpha)} E_2 \quad S_d = M_0 \frac{(1 - E_{1d})\sin(\beta)}{1 - E_{1d}\cos(\beta)} E_2 \quad [5]$$

where $E_{1d} = \exp(-TR/(T_1 + \Delta T_1))$, and ΔT_1 is the not yet known change in T_1 due to temperature change. Substituting Equation 5 into Equation 3 where $S_d = S_2$ and $S_r = S_1$ yields

$$T_1 + \Delta T_1 = \frac{-TR}{\ln\left(\frac{1 - \gamma}{1 - \gamma\cos(\beta)}\right)} \quad [6]$$

$$\gamma = \frac{1 - E_1}{1 - E_1\cos(\alpha)} \frac{1 - E_{1est}\cos(\alpha)}{1 - E_{1est}\cos(\beta)}$$

Equation 6 requires knowing the baseline T_1 value. The value for E_1 can be calculated using the signal from the reference image (S_r) and the baseline images of the dynamic images (S_d) before the heating begins. The true $T_1 + \Delta T_1$ is calculated by first calculating the E_{1est} , which is incorrect, and then applying the correction in Equation 6 using the baseline E_1 value, the TR and the flip angles used.

METHODS

The single reference VFA method was implemented using a multi-echo pseudo golden angle stack of stars (SOS) acquisition and k-space weighted image contrast (KWIC) reconstruction method (20,21). The method was evaluated with simulations and experiments in phantoms, cadaver breasts, and normal volunteers with sequence parameters given for each set of experiments. All simulations and image reconstructions were done offline using MATLAB (Mathworks, Natick, MA).

Flip Angle Sensitivity Simulations

To simulate the sensitivity of single reference VFA T_1 measurements to noise and to determine the optimal choice of flip angles for the single reference VFA method, noisy measurements were simulated using a Monte Carlo technique for a range of flip angles. It has been shown that the propagation of errors through the VFA T_1 calculation is nonlinear and highly sensitive to flip angle choices (40). The effects of T_2^* decay were ignored and TR was set to 10 ms. The reference steady state signal values were calculated for flip angles from 1 to 90° in 1° increments for $T_1 = 300$ ms using equation 1. Dynamic steady state signal values were calculated for the same flip angles and for T_1 values from 200 to 900 ms in 10 ms increments. White Gaussian noise was added to each reference and dynamic signal value 1000 different times, using MATLAB's wgn function with a noise power level of -58 dBW giving an SNR of approximately 100 at the Ernst angle of the baseline T_1 . T_1 values were calculated for every combination of flip angles using equation 3 and then corrected using 6. The standard deviation (σ_{T_1}) at each flip angle combination was calculated from the 1000 noisy estimates. The PRF temperature standard deviation was determined from the relative SNR defined by the signal vs. flip angle dependence of the spoiled gradient recalled echo (GRE) sequence (Equation [1]).

Flip Angle Correction / B1 Mapping

The B1 mapping method used in this work is based off of the method presented by Chung et al. (38). This method was quantitatively compared to the double angle method (33) providing equivalent results with a mean difference of 0.025. The method uses the ratio between two proton density images, I_{PD} , where one of the images has been pre-saturated by a slice selective pulse, I_{PRE} . The images were acquired with a centric reordered turbo fast low angle shot (turboFLASH) to decrease scan time. The ratio of the two images is related to the nominal flip angle of the saturation pulse, θ_{nom} , by

$$\frac{I_{PRE}}{I_{PD}} = \cos(\kappa(r) \cdot \theta_{nom}) \quad [7]$$

where $\kappa(r)$ is a flip angle scale factor at position r , which by definition is the actual flip angle divided by nominal flip angle. Equation 7 can be rewritten as

$$\kappa(r) = \frac{1}{\theta_{nom}} \cos^{-1} \frac{I_{PRE}}{I_{PD}} \quad [8]$$

The flip angle of the pre-saturation pulse was set to $\theta_{nom} = 60^\circ$ for this work. The data acquisition was started as quickly as possible (10 ms) after the pre-saturation to minimize the effects of T_1 relaxation, which are neglected. A centric k-space reordering also minimizes the effects of T_1 relaxation, which can be minimized further by segmenting the acquisition into multiple “shots”. The original method by Chung acquired a single 2D slice, which could be acquired rapidly in a single shot. We acquired 3D maps which required segmenting the data acquisition to maintain the proton density weighting. Both images were filtered with a Hamming window along the phase encoding direction before reconstruction. The chemical shift between fat and water was minimized by acquiring multiple echoes, each with a high readout bandwidth.

MRgFUS Experiments

Experiments were performed in a Siemens Prisma 3T MRI scanner (Siemens Healthcare, Erlangen, Germany) using the MRI-compatible phased-array transducer (256 elements, 1 MHz frequency, 10cm radius of curvature; Imasonic, Besançon, France and Image Guided Therapy, Pessac, France) from a breast-specific MRgFUS system (41–43) to evaluate the single reference VFA method. Two formalin preserved human cadaver breasts from different donors were positioned such that the ultrasound focus was approximately 3 cm deep in the cadaver breast. The experiment setup is shown in Figure 2. The single reference VFA angle was used in conjunction with a multi-echo linearly rotated stack-of-stars (RSOS) imaging sequence (21,44) with an in-plane pseudo-golden angle increment and reconstructed with a dynamic (KWIC) reconstruction to increase the temporal resolution (20,21). The 3D RSOS imaging volume was prescribed in a sagittal orientation (voxel size = 1.3 mm isotropic; field of view = $208 \times 208 \times 20.8$ mm; matrix = $160 \times 160 \times 16$; 1514 radial projections; TR = 10.5 ms; $TE = 2.46 + 1.23 * n, n=0$ to 5 ms; readout bandwidth = 1200 Hz/pixel). The reference image flip angle was $\alpha = 5^\circ$ and the dynamic images flip angle ($\beta = 15^\circ$) was set to the Ernst angle for the fat tissue. The first cadaver breast was heated with two ultrasound sonications, each in a different location using electronic steering, while imaging with the RSOS sequence. The second cadaver breast was heated with one ultrasound sonication. The ultrasound sonicated a linear pattern composed of four discrete points (each separated by 2 mm, 50 ms per point) at 75 acoustic watts for 30 seconds total. A breast shaped homogenous gelatin phantom (45) was also imaged and sonicated with the same parameters. B1 maps for each phantom were acquired using the method described above (voxel size = 2.6 mm isotropic zero-filled to 1.3 mm isotropic; field of view = $208 \times 208 \times 20.8$ mm; 40 lines per TR; TR = 5000 ms; TE = 1.31 ms readout bandwidth = 1500 Hz/pixel).

In Vivo Breast Non-heating Experiments

Three healthy female volunteers (age range: 22–42 years) were recruited for non-heating experiments. Each volunteer was positioned in a breast-specific MRgFUS system (41–43).

After localization, multi-echo RSOS images were acquired in both the coronal and sagittal orientations while the volunteer was free breathing. The reference and dynamic flip angles for the single reference VFA method were 5° and 15° respectively. The imaging parameters for each dynamic image acquisition and for the reference acquisitions for volunteers 2 & 3 were voxel size = 1.3 mm isotropic; field of view = $208 \times 208 \times 20.8$ mm; matrix = $160 \times 160 \times 16$; 1514 radial projections; TR = 9.34 ms; TE = $2.46 + 1.26 * n, n=0$ to 5 ms; readout bandwidth = 1080 Hz/pixel. The reference acquisition for volunteer 1 had 400 radial projections. B1 maps for each volunteer and orientation were acquired using the same imaging parameters as the phantom data and the method described above. All imaging parameters used in this study are also shown in Supporting Information Table S1. T_1 values and PRF temperatures were calculated for each volunteer with reference flip angle of 5° and dynamic flip angle of 15° . For comparison, T_1 values and PRF temperatures for volunteers 2 and 3 were also calculated with the reference flip angle of 15° and dynamic flip angle of 5° .

Image Reconstruction

Respiration and field drift was corrected using the method described in (20). The gpuNUFFT algorithm (46) was used to reconstruct the non-Cartesian data. The dynamic images were reconstructed using a sliding symmetric KWIC window with 13 central projections and 377 total projections and the sliding window was advanced 13 projections between reconstructions. The effective temporal resolution of the KWIC reconstructed images for the phantom and cadaver breast data was 2.18 s and 1.94 s for the volunteer data. The reference images were reconstructed without a KWIC window using all of the collected data. Separate water and fat images were created using the 3-point Dixon method (47) from the first three echoes for the reference image and each dynamic image. T_1 values were calculated using the single reference VFA method described above using the separated water/fat images and acquired B1 maps. The change in T_1 from a trajectory matched baseline value (20) was calculated for each image. The phase information from each echo were combined using a weighted linear least squares fit and the PRF temperatures were calculated using the trajectory matched baseline described in (20). The change in T_1 is compared to PRF temperature values in aqueous tissue for the phantom data. The standard deviation was calculated for the T_1 and PRF measurements in all data.

RESULTS

The Monte Carlo simulations of the single reference VFA precision are shown in Figure 3 for several values of T_1 . The single reference VFA precision using finer T_1 steps is shown in Supporting Information Video S1. Similar to the standard VFA method, the measurement precision is best when the two flip angles chosen are on opposite sides of the Ernst angle. The precision varies rapidly when varying the smaller flip angle and is relatively forgiving when varying the larger flip angle. The optimal flip angle combination changes with T_1 , but the choice of reference flip angle remained constant. For the simulated scan parameters, the optimal choice of reference flip angle was 5° . As T_1 increases, the optimal choice for the dynamic flip angle approaches but does not go lower than the original baseline Ernst angle. Figure 4 plots the relative SNR as a function of dynamic flip angle for PRF and single reference VFA T_1 measurements. The PRF SNR measurements assume an aqueous tissue T_1

of 800 ms, while the single reference VFA T_1 measurements assume an adipose tissue baseline T_1 of 300 ms and a reference flip angle of 5° was used. Because of these different baseline T_1 values, the optimal dynamic flip angle choices for PRF measurements and single reference VFA T_1 are different and therefore a compromise flip angle must be selected.

Separated water and fat images of the cadaver breasts are shown in Figure 5a,c. The center slice through the B1 maps in the cadaver breasts, used for flip angle correction, are shown in Figure 5b,d. Cadaver breast 1 had a mix of fibroglandular tissue and fat while cadaver breast 2 was comprised primarily of fat. The difference in B1 susceptibility between aqueous and fatty tissue is evident in Figure 5b. While a smooth transition of flip angle from the water tank into the aqueous tissue is observed, the susceptibility difference between the two tissues causes the sharp discontinuity into the fatty tissue. Separated water/fat images and B1 maps through the center slice for each of the three volunteers are shown in Supporting Information Figure S1.

Images of the PRF temperature, the T_1 change in water voxels and the T_1 change in fat voxels for the gelatin phantom and cadaver breasts during ultrasound sonication are shown in Figure 6 at the time of the peak temperature rise. For the left and middle columns, the PRF temperature and T_1 change are masked to only be shown in aqueous voxels. For the right column, the T_1 change is masked to only be shown in fat voxels. Time lapse videos of the sonications in Figure 6 are shown in Supporting Information Video S2. In the first cadaver breast (Figures 6 b and c), the heated region can be seen across the water/fat boundary when combining the PRF and T_1 measurements. In the second cadaver breast (Figure 6d), the T_1 measurement was able to demonstrate a change while the PRF method was unable to detect any change.

Plots of the PRF temperature and T_1 change versus time for a single voxel are shown in Figure 7. The PRF temperature and T_1 change show agreement of the temporal evolution shape in Figure 7a-c. Figure 7d shows the T_1 change in a fat voxel from the second cadaver breast where PRF temperature measurements were not possible due to the lack of aqueous tissue.

Figure 8 gives a point by point comparison of the T_1 change vs. PRF temperature change for the heated region in the gelatin phantom (Figure 8a) and the first cadaver breast (Figure 8b). For Figure 8b, the comparison is made only for the aqueous tissue in the first cadaver breast heated during the first ultrasound sonication. The slope of the T_1 change versus temperature from a linear fit to the data was $42.85 \text{ ms}/^\circ\text{C}$ ($R^2 = 0.81$) for the gelatin and $22.96 \text{ ms}/^\circ\text{C}$ ($R^2 = 0.5$) for the aqueous tissue in the first cadaver breast. There appear to be two T_1 clusters in Figure 8b. This is due to the rapid heating of the ultrasound, limiting the number of measurements acquired during the heating period. This data demonstrates a proof of concept for calibration. A more controlled, slowly varying temperature gradient would provide more evenly distributed T_1 measurements allowing a more accurate calibration. The flip angles were chosen as a compromise between PRF precision in tissue and T_1 precision in fat. The large variability displayed in the Figure 8b PRF vs T_1 values is due to the measurements being in aqueous tissue and did not have the optimal flip angles for either PRF or T_1 .

Images of the average baseline T_1 value and temporal standard deviation during baseline scans for each of the samples are shown in Figure 9. These baseline T_1 values are essential for the corrected measurement, but can be acquired over somewhat longer time periods allowing averaging to reduce measurement error.

Results from the 3 volunteers are shown in Figure 10. Here we display the standard deviation of the T_1 single reference VFA measurements in fatty tissue (a and c) and standard deviation of PRF temperatures in aqueous tissue (b and d) for each of the volunteers with reference flip angle 5° and dynamic flip angle 15° . For comparison, the same measurements for volunteers 2 and 3 using the reference flip angle as 15° and the dynamic flip angle as 5° are shown in Supporting Information Figure S2. The average measured T_1 value for each volunteer in both orientations is shown in Supporting Information Figure S3.

DISCUSSION

This paper describes how simultaneous PRF temperature and T_1 relaxation values can be obtained using a single reference VFA method. To the extent that the T_1 change calibration is accurate, the acquisition of these two values will allow for a simultaneous measurement of temperature in aqueous and adipose tissue. A significant advantage of this method is the fact that the steady state signal remains stable between each dynamic image. Changing flip angles dynamically would require a settling time to reach steady state, especially when changing to the low flip angle, which would increase scan time. Using the same dynamic flip angle allows the T_1 measurement to have the same temporal resolution as the PRF temperature, a major step forward in using dynamic T_1 measurements for MR temperature imaging. The ability for simultaneous 3D thermometry in fat and aqueous tissue using the single reference VFA method will allow the complete monitoring of both the targeted tissue and surrounding aqueous and adipose tissues, increasing both treatment safety and efficacy.

The ability to measure PRF temperature and T_1 was demonstrated during MRgFUS sonications in a gelatin phantom and two cadaver breasts from two separate subjects. The hybrid nature of this technique can be seen in Figure 6 where an ablation region can be seen across the water and fat boundary. This study also demonstrates (Figures 7 & 8) the ability of the PRF temperature and T_1 change to provide equivalent measures within aqueous tissues, where there is good correlation in space and time between both measures. This method was also demonstrated with healthy volunteers in in vivo breast. The in vivo results show that the precision of the measurements depends strongly on the flip angles used. The SOS sequence combined with respiration correction provide robustness to motion. The MRgFUS breast system has a relatively large water volume which adds some considerations, such as water motion and strong water signal, that are not present with other heating modalities.

The presented method was implemented using a rapid image update reconstruction method, which greatly improves upon previous simultaneous techniques (26,27). Indeed, using the standard VFA method with a SOS sequence would be effectively impossible as the acquisition time (without severe artifacts) would be too long and a sliding KWIC window could not be applied across the transition between flip angles. The multi-echo SOS

acquisition with KWIC reconstruction allowed for improved data acquisition for both T_1 and PRF measurements. The SNR for T_1 measurements is improved with shorter TE and the PRF SNR is optimal when $TE = T_2^*$. Acquiring multiple echoes allowed for echo combination of the phase data to improve the PRF measurements and using the shorter TE with water/fat separation for T_1 measurements.

The precision of the T_1 measurement can be optimized with proper choice of flip angles. Using the VFA method to measure T_1 will amplify noise through its nonlinear nature of calculating T_1 (40). Using the standard VFA method, the ideal flip angles will produce signals that are about 71% of the signal at the Ernst angle signal, with one flip angle above and one below the Ernst angle (40). The Monte-Carlo simulations for this single reference VFA method show that the reference flip angle should be the lower flip angle and that the optimal choice for the lower angle gives ~60% of the Ernst angle signal. A more accurate estimate of the percent of the Ernst angle signal could be simulated with much finer flip angle increments or possibly an exact estimate could be derived using the same propagation of errors method employed by (40). The optimal reference flip angle will vary with TR and T_1 of interest. The optimal choice of dynamic flip angle, for the simulated parameters, began at 26° (~85% of Ernst signal) and as T_1 increased it approached the Ernst angle.

Simultaneous measurements of PRF and T_1 need to balance the precision of both measurements (see Figure 4). The PRF temperature is optimal when the chosen flip angle gives the highest SNR in the aqueous tissue, which is at the Ernst angle of the aqueous tissue. In general, aqueous tissue will have a higher T_1 value than adipose tissue, meaning its Ernst angle will be lower than that of adipose tissue. The precision of VFA T_1 measurements is relatively insensitive to changes in the larger flip angle as shown in Figures 3 and 4. In order to balance the precision of the PRF and T_1 measurements, the dynamic flip angle was chosen to be the Ernst angle of the fat tissue before heating. While this will not provide the maximum PRF SNR, it will still give more SNR than the standard VFA method (27). An example aqueous tissue $T_1=800$ ms with $TR=10$ ms will give ~88% of its maximum signal at its Ernst angle. This tradeoff between T_1 precision and PRF precision can be seen by comparing Figure 10 to Supporting Information Figure S2. There is a relatively large spatial variation in the standard deviations of both the T_1 and PRF measurements, which is likely due to proximity to the lungs and receive coils. This spatial variation is expected and has been observed previously (20). When the dynamic flip angle is 5° , the PRF precision is comparable to the previously reported values for multi-echo SOS thermometry (20). In this case, the PRF precision is considerably better but the T_1 precision is worse, as expected from the Monte Carlo simulations. The PRF precision when the dynamic flip angle is 15° is worse and may or may not be acceptable, depending on the thermometry application. The case is opposite for the T_1 measurements. If the PRF precision is most important, then the reference flip angle could be set to the higher angle. It may be possible to calculate T_1 using a similar method with multiple reference flip angles and thus maintain high precision for both T_1 and PRF measurements, but that was not investigated in this work.

The temperature dependence of T_1 has been investigated previously, e.g. (26–29). Unlike the PRF shift, the calibration of T_1 change to temperature is very tissue type dependent. Kuroda et al. (28) showed that the rate of change was different for CH_2 and CH_3 hydrogen groups.

The temperature calibration would change for different percentages of CH₂ and CH₃ mixtures. If the CH₂ and CH₃ groups are separated during water and fat separation, then the temperature could be calculated from their separate T₁ changes. Comparisons of the standard VFA to inversion recovery T₁ measurements have been done previously (27,48) and are generally accepted as equally accurate although VFA provides lower SNR measurements. Calibration of T₁ changes with temperature obtained using this single reference VFA method by comparing against T₁ changes with temperature obtained using gold standard T₁ measurements, e.g. inversion recovery, remains as work to be done.

It has also been shown that irreversible changes to the T₁ value occur after tissue coagulation/death (49) in aqueous tissue voxels. It is possible that a similar effect would be observed in adipose tissue. These effects would cause T₁ temperature measurements obtained using any method to require a variable calibration specifically made for ablated tissue in order to be used as a reliable measure of temperature after ablation. This technique could potentially also serve as a helpful indication that the tissue has been ablated.

While this preliminary study has demonstrated the functionality of this technique, there are several limitations that must be addressed before translating this sequence for clinical use. While the sequence measures a change in T₁ value, this change is not currently calibrated to an increase in temperature, although such a calibration could be performed (28). All reconstruction was performed offline with a significant amount of time required for regridding (21), though much faster reconstructions will be possible on commercial reconstruction computers. Any clinical use would require a reduced reconstruction time in order to meet real-time monitoring conditions. Also, the flip angles used in this study were chosen based on the T₁ values of cadaver breast aqueous and adipose tissue, which was lower than the T₁ values of in vivo breast due to temperature differences, degassing of the cadaver breast and biological factors such as perfusion and overall blood volume. The measured T₁ values in aqueous tissue are noisier than in adipose tissue, Supporting Information Figure S3, but this is to be expected as the two flip angles are not the optimal choices for measuring higher T₁ values.

While the proposed single reference VFA method is inherently independent of the acquisition sequence and reconstruction method, the acquisition method used here addresses several factors that any such method must take into consideration when configuring the acquisition sequence. A small fat/water chemical shift is desirable, the T₁ precision is increased with short TE, and PRF measurement precision is optimal when TE=T₂^{*}, which creates conflicting optimization as discussed above. Different acquisition parameters may be desirable depending on the patient specific breast composition or monitoring application. Depending on the imaged anatomy, respiratory motion can be a concern. As long as all motion is outside the imaged field of view, the respiratory motion will induce oscillatory field shifts which can cause significant artifacts such as ghosting in a 3D seg-EPI sequence (17) and blurring in a SOS sequence (20). It has been shown that these artifacts can be corrected to an extent using FID phase navigators (17) and a self-navigated phase correction (20), which was used in this study. Similar to other thermometry sequences, the acquisition time should be short enough to capture the dynamics of the temperature change. An accurate

B_1 map is needed in order to calculate accurate T_1 values, and the pulse sequence must be a 3D acquisition because of the slice profile effects for VFA T_1 measurements (30).

As implemented, the proposed single reference VFA method was limited to acquiring multiple echoes with very high bandwidth to reduce the fat/water chemical shift while at the same time retaining a reasonable SNR. With current gradients, the method was limited to about 1mm isotropic resolution. To achieve high temporal resolution, the method required a relatively short TR, further limiting the maximum flip angle that could be used as well as the ultimate SNR that could be attained. Finally, the method requires time to acquire the accurate B_1 map and initial reference images. All of these limitations can and will be addressed in future studies.

CONCLUSIONS

This work has provided the theoretical background and experimental implementation for a simultaneous PRF and T_1 thermometry method using a single reference VFA technique. This single reference VFA method provides a reliable way to simultaneously measure PRF temperature in water and T_1 change in fat tissue. Results were demonstrated in two cadaver breasts and in three healthy volunteer breasts. To the extent that the T_1 change calibration is accurate, this technique could overcome the inability of PRF methods to simultaneously monitor the temperature in aqueous and adipose tissues and increase patient safety and treatment efficacy by providing accurate, real time temperature measurements in fat, which are currently difficult or unavailable. This is an advantage for interventional treatments in inhomogeneous tissue types containing large amounts of adipose tissue such as the breast or abdominal targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support: NIH R01 CA172787, R01 EB013433, R01 CA224141, S10OD018482, Siemens Medical Solutions

REFERENCES

1. Kennedy JE, Ter Haar GR, Cranston D. High intensity focused ultrasound: surgery of the future? *Br J Radiol* 2003;76(909):590–599. [PubMed: 14500272]
2. Stafford RJ, Hazle JD. Magnetic resonance temperature imaging for focused ultrasound surgery: a review. *Top Magn Reson Imaging* 2006;17(3):153–163. [PubMed: 17414072]
3. Tempny CM, McDannold NJ, Hynynen K, Jolesz FA. Focused ultrasound surgery in oncology: overview and principles. *Radiology* 2011;259(1):39–56. [PubMed: 21436096]
4. Schlesinger D, Benedict S, Diederich C, Gedroyc W, Klibanov A, Larner J. MR-guided focused ultrasound surgery, present and future. *Med Phys* 2013;40(8):080901. [PubMed: 23927296]
5. Gallay MN, Moser D, Rossi F, Pourtehrani P, Magara AE, Kowalski M, Arnold A, Jeanmonod D. Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J Ther Ultrasound* 2016;4:5. [PubMed: 26877873]

6. Jolesz FA. MRI-guided focused ultrasound surgery. *Annu Rev Med* 2009;60:417–430. [PubMed: 19630579]
7. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery* 2010;66(2):323–332; discussion 332. [PubMed: 20087132]
8. Medel R, Monteith SJ, Elias WJ, Eames M, Snell J, Sheehan JP, Wintermark M, Jolesz FA, Kassell NF. Magnetic resonance-guided focused ultrasound surgery: Part 2: A review of current and future applications. *Neurosurgery* 2012;71(4):755–763. [PubMed: 22791029]
9. Weintraub D, Elias WJ. The emerging role of transcranial magnetic resonance imaging-guided focused ultrasound in functional neurosurgery. *Mov Disord* 2016.
10. Magara A, Buhler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D. First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound* 2014;2:11. [PubMed: 25512869]
11. Peters RD, Hinks RS, Henkelman RM. Ex vivo tissue-type independence in proton-resonance frequency shift MR thermometry. *Magn Reson Med* 1998;40(3):454–459. [PubMed: 9727949]
12. Enholm JK, Kohler MO, Quesson B, Mougenot C, Moonen CT, Sokka SD. Improved volumetric MR-HIFU ablation by robust binary feedback control. *IEEE Trans Biomed Eng* 2010;57(1):103–113. [PubMed: 19846364]
13. Fielden S, Zhao L, Miller W, Feng X, Wintermark M, Pauly KB, Meyer C. Spiral-based 3D MR thermometry. *Journal of Therapeutic Ultrasound* 2015;3(1):P18.
14. Kohler MO, Mougenot C, Quesson B, Enholm J, Le Bail B, Laurent C, Moonen CT, Enholm GJ. Volumetric HIFU ablation under 3D guidance of rapid MRI thermometry. *Med Phys* 2009;36(8):3521–3535. [PubMed: 19746786]
15. Marx M, Ghanouni P, Butts Pauly K. Specialized volumetric thermometry for improved guidance of MRgFUS in brain. *Magn Reson Med* 2017;78(2):508–517. [PubMed: 27699844]
16. Marx M, Plata J, Pauly KB. Toward volumetric MR thermometry with the MASTER sequence. *IEEE Trans Med Imaging* 2015;34(1):148–155. [PubMed: 25163055]
17. Svedin BT, Payne A, Parker DL. Respiration artifact correction in three-dimensional proton resonance frequency MR thermometry using phase navigators. *Magn Reson Med* 2016;76(1):206–213. [PubMed: 26272108]
18. Todd N, Vyas U, de Bever J, Payne A, Parker DL. Reconstruction of fully three-dimensional high spatial and temporal resolution MR temperature maps for retrospective applications. *Magn Reson Med* 2012;67(3):724–730. [PubMed: 21702066]
19. Jonathan SV, Grissom WA. Volumetric MRI thermometry using a three-dimensional stack-of-stars echo-planar imaging pulse sequence. *Magn Reson Med* 2017.
20. Svedin BT, Payne A, Bolster BD, Jr., Parker DL. Multiecho pseudo-golden angle stack of stars thermometry with high spatial and temporal resolution using k-space weighted image contrast. *Magn Reson Med* 2017.
21. Svedin BT, Dillon CR, Parker DL. Effect of k-space-weighted image contrast and ultrasound focus size on the accuracy of proton resonance frequency thermometry. *Magn Reson Med* 2018.
22. Baron P, Ries M, Deckers R, de Greef M, Tanttu J, Kohler M, Viergever MA, Moonen CT, Bartels LW. In vivo T2-based MR thermometry in adipose tissue layers for high-intensity focused ultrasound near-field monitoring. *Magn Reson Med* 2014;72(4):1057–1064. [PubMed: 24259459]
23. Ozhinsky E, Kohi MP, Ghanouni P, Rieke V. T2-based temperature monitoring in abdominal fat during MR-guided focused ultrasound treatment of patients with uterine fibroids. *Journal of Therapeutic Ultrasound* 2015;3:15. [PubMed: 26366288]
24. Winter PM, Lanier M, Partanen A, Dumoulin C. Initial investigation of a novel noninvasive weight loss therapy using MRI-Guided high intensity focused ultrasound (MR-HIFU) of visceral fat. *Magn Reson Med* 2016;76(1):282–289. [PubMed: 26284310]
25. Bohris C, Schreiber WG, Jenne J, Simiantonakis I, Rastert R, Zabel HJ, Huber P, Bader R, Brix G. Quantitative MR temperature monitoring of high-intensity focused ultrasound therapy. *Magn Reson Imaging* 1999;17(4):603–610. [PubMed: 10231187]

26. Todd N, Diakite M, Payne A, Parker DL. Hybrid proton resonance frequency/T1 technique for simultaneous temperature monitoring in adipose and aqueous tissues. *Magn Reson Med* 2013;69(1):62–70. [PubMed: 22392856]
27. Diakite M, Odeen H, Todd N, Payne A, Parker DL. Toward real-time temperature monitoring in fat and aqueous tissue during magnetic resonance-guided high-intensity focused ultrasound using a three-dimensional proton resonance frequency T1 method. *Magn Reson Med* 2014;72(1):178–187. [PubMed: 23901014]
28. Kuroda K, Iwabuchi T, Obara M, Honda M, Saito K, Imai Y. Temperature dependence of relaxation times in proton components of fatty acids. *Magn Reson Med Sci* 2011;10(3):177–183. [PubMed: 21960000]
29. Todd N, Diakite M, Payne A, Parker DL. In vivo evaluation of multi-echo hybrid PRF/T1 approach for temperature monitoring during breast MR-guided focused ultrasound surgery treatments. *Magn Reson Med* 2013.
30. Svedin BT, Parker DL. Technical Note: The effect of 2D excitation profile on T1 measurement accuracy using the variable flip angle method with an average flip angle assumption. *Med Phys* 2017;44(11):5930–5937. [PubMed: 28796308]
31. Sung K, Daniel BL, Hargreaves BA. Transmit B1+ field inhomogeneity and T1 estimation errors in breast DCE-MRI at 3 tesla. *J Magn Reson Imaging* 2013;38(2):454–459. [PubMed: 23292822]
32. Sung K, Nayak KS. Measurement and characterization of RF nonuniformity over the heart at 3T using body coil transmission. *J Magn Reson Imaging* 2008;27(3):643–648. [PubMed: 18306272]
33. Insko EK, Bolinger L. Mapping of the Radiofrequency Field. *Journal of Magnetic Resonance, Series A* 1993;103(1):82–85.
34. Cunningham CH, Pauly JM, Nayak KS. Saturated double-angle method for rapid B1+ mapping. *Magn Reson Med* 2006;55(6):1326–1333. [PubMed: 16683260]
35. Yarnykh VL. Actual flip-angle imaging in the pulsed steady state: a method for rapid three-dimensional mapping of the transmitted radiofrequency field. *Magn Reson Med* 2007;57(1):192–200. [PubMed: 17191242]
36. Sacolick LI, Wiesinger F, Hancu I, Vogel MW. B1 mapping by Bloch-Siegert shift. *Magn Reson Med* 2010;63(5):1315–1322. [PubMed: 20432302]
37. Dowell NG, Tofts PS. Fast, accurate, and precise mapping of the RF field in vivo using the 180 degrees signal null. *Magn Reson Med* 2007;58(3):622–630. [PubMed: 17763355]
38. Chung S, Kim D, Breton E, Axel L. Rapid B(1)(+) Mapping Using a Pre-Conditioning RF Pulse with TurboFLASH readout. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine* 2010;64(2):439–446.
39. Block KT, Chandarana H, Milla S, Bruno M, Mulholland T, Fatterpekar G, Hagiwara M, Grimm R, Geppert C, Kiefer B, Sodickson DK. Towards Routine Clinical Use of Radial Stack-of-Stars 3D Gradient-Echo Sequences for Reducing Motion Sensitivity. *J Korean Soc Magn Reson Med* 2014;18(2):87–106.
40. Schabel MC, Morrell GR. Uncertainty in T(1) mapping using the variable flip angle method with two flip angles. *Phys Med Biol* 2009;54(1):N1–8. [PubMed: 19060359]
41. Payne A, Merrill R, Minalga E, Vyas U, de Bever J, Todd N, Hadley R, Dumont E, Neumayer L, Christensen D, Roemer R, Parker D. Design and characterization of a laterally mounted phased-array transducer breast-specific MRgHIFU device with integrated 11-channel receiver array. *Med Phys* 2012;39(3):1552–1560. [PubMed: 22380387]
42. Payne A, Todd N, Minalga E, Wang Y, Diakite M, Hadley R, Merrill R, Factor R, Neumayer L, Parker DL. In vivo evaluation of a breast-specific magnetic resonance guided focused ultrasound system in a goat udder model. *Med Phys* 2013;40(7):073302. [PubMed: 23822456]
43. Minalga E, Payne A, Merrill R, Todd N, Vijayakumar S, Kholmovski E, Parker DL, Hadley JR. An 11-channel radio frequency phased array coil for magnetic resonance guided high-intensity focused ultrasound of the breast. *Magn Reson Med* 2013;69(1):295–302. [PubMed: 22431301]
44. Zhou Z, Han F, Yan L, Wang DJ, Hu P. Golden-ratio rotated stack-of-stars acquisition for improved volumetric MRI. *Magn Reson Med* 2017.

45. Farrer AI, Odeen H, de Bever J, Coats B, Parker DL, Payne A, Christensen DA. Characterization and evaluation of tissue-mimicking gelatin phantoms for use with MRgFUS. *J Ther Ultrasound* 2015;3:9. [PubMed: 26146557]
46. Knoll F, Scharzl A, Diwoký C, Sodickson D. gpuNUFFT - An Open-Source GPU Library for 3D Gridding with Direct Matlab Interface. *Proc Intl Soc Mag Reson Med* 2014:4297.
47. Glover GH, Schneider E. Three-point Dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magn Reson Med* 1991;18(2):371–383. [PubMed: 2046518]
48. Deoni SC. High-resolution T1 mapping of the brain at 3T with driven equilibrium single pulse observation of T1 with high-speed incorporation of RF field inhomogeneities (DESPOT1-HIFI). *J Magn Reson Imaging* 2007;26(4):1106–1111. [PubMed: 17896356]
49. Diakite M, Payne A, Todd N, Parker DL. Irreversible change in the T1 temperature dependence with thermal dose using the proton resonance frequency-T1 technique. *Magn Reson Med* 2013;69(4):1122–1130. [PubMed: 22576265]

Figure 1.

Measured T_1 versus true T_1 using the single reference VFA method without correction (solid blue) and with correction (dashed red) using Equation 6. Baseline T_1 was 700 ms. Reference flip angle $\alpha=5^\circ$ and dynamic flip angle $\beta=35^\circ$.

Figure 2.

Experiment setup for a) the first and b) the second ultrasound heatings in the first cadaver breast. c) Experiment setup for the second cadaver breast. The ultrasound transducer is outlined with the blue line at the bottom of each image and the approximate ultrasound propagation envelope is shown with the red lines. The yellow ovals are the approximate locations for each of the electronically steered focal locations.

Figure 3.

Standard deviation of the T_1 measurement as a percent of $T_1 + T_1$ for each flip angle combination using the single reference VFA method for a baseline T_1 of 300 ms and $TR = 10$ ms for a) $T_1 = 0$ ms, b) $T_1 = 100$ ms, c) $T_1 = 200$ ms and d) $T_1 = 300$ ms. The white x is the smoothed estimate of the flip angle choices that give the minimum standard deviation. Supporting Information Video S1 shows the standard deviation change in smaller T_1 increments.

Figure 4.

Relative SNR of PRF temperature measurements (black) and T_1 measurements (red) as a function of dynamic flip angle. The reference flip angle was set to 5°. Relative T_1 SNR is equal to the standard deviation divided by $T_1 + T_1$ and then normalized to the maximum value of $T_1 = 0$ ms. T_1 for PRF was 800 ms and for T_1 SNR, baseline T_1 was 300 ms.

Figure 5.
a,c) Separated water (left) and fat (right) images of the a) first and c) second cadaver breasts.
b,d) B1 map acquired using the pre-saturation pulse technique for the b) first and d) second cadaver breasts.

Figure 6.

Images of the peak temperature time point for a) the gelatin phantom b) the first sonication trajectory and c) the second sonication trajectory in the first cadaver breast and d) the second sonication trajectory in the second cadaver breast. Left) PRF temperature maps in aqueous tissue. Middle) T₁ change in aqueous tissue voxels. Right) T₁ change in adipose tissue voxels.

Figure 7.

PRF temperature (°C, black) and T₁ change (ms, red) versus time in each model. a) The same voxel in the gelatin phantom. b) The same aqueous tissue voxel from the first ultrasound sonication in the first cadaver breast. c) Neighboring voxels across the water/fat boundary from the second ultrasound sonication in the first cadaver breast where the PRF values are from the aqueous voxel and the T₁ change is from the fat voxel. d) A fat tissue voxel in the second cadaver breast. Due to the fat content of the breast, PRF temperature measurement was not possible.

Figure 8.

PRF temperature versus T₁ change within the heated aqueous tissue in a) the gelatin phantom and b) the first cadaver breast during the first ultrasound sonication.

Figure 9.

Average T_1 value during baseline dynamic scans for the a) gelatin phantom, b) 1st cadaver breast and c) 2nd cadaver breast. Standard deviation of T_1 value as a percent of average value during baseline dynamic scans for the d) gelatin phantom, e) 1st cadaver breast and f) 2nd cadaver breast.

Figure 10.

Results of healthy volunteer scans for sagittal (a-b) and coronal (c-d) orientations for Volunteers 1 (left), 2 (middle) and 3 (right). a,c) Images of the standard deviation of T_1 measurements in adipose tissue as a percent of baseline value. b,d) Images of the standard deviation of PRF temperature ($^{\circ}\text{C}$) in aqueous tissue.