Published in final edited form as:

Magn Reson Med. 2016 September ; 76(3): 803–813. doi:10.1002/mrm.25971.

Evaluation of a Three-Dimensional MR Acoustic Radiation Force Imaging Pulse Sequence Using a Novel Unbalanced Bipolar Motion Encoding Gradient

Joshua T. de Bever^{1,*}, Henrik Odéen², Nick Todd², Alexis I. Farrer³, and Dennis L. Parker⁴

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

²Department of Physics, Utah Center for Advanced Imaging Research, University of Utah, Salt Lake City, Utah, USA

³Department of Bioengineering, Utah Center for Advanced Imaging Research, University of Utah, Salt Lake City, Utah, USA

⁴Department of Radiology, Utah Center for Advanced Imaging Research, University of Utah, Salt Lake City, Utah, USA

Abstract

Purpose—MR guided focused ultrasound procedures require accurate focal spot localization in three dimensions. This study presents a three-dimensional (3D) pulse sequence for acoustic radiation force imaging (ARFI) that efficiently localizes the focal spot by means of ultrasound induced tissue displacement over a large field-of-view.

Methods—A novel unbalanced bipolar motion encoding gradient was implemented to maximize time available for motion encoding, reduce echo times, and allow for longer echo train lengths. Two advanced features, k_z reduction factor (KZRF) and k_z -level interleaving, were implemented to reduce tissue heating. Studies in gelatin phantoms compared the location of peak displacement and temperature measured by 3D MR thermometry. MR-ARFI induced tissue heating was evaluated through a parametric study of sequence parameters and MR thermometry measurements during repeated application of ARFI sonication patterns. Sequence performance was characterized in the presence of respiration and tissue inhomogeneity.

Results—The location of peak displacement and temperature rise agreed within 0.2 ± 0.1 mm and 0.5 ± 0.3 mm in the transverse and longitudinal direction, respectively. The 3D displacement maps were acquired safely, and the KZRF and k_z -level interleaving features reduced tissue heating by 51%. High quality displacement maps were obtained despite respiration and tissue inhomogeneities.

Conclusion—This sequence provides a safe, accurate, and simple approach to localizing the focal spot in three dimensions with a single scan.

*Correspondence to: Joshua T. de Bever, Ph.D., School of Computing, Utah Center for Advanced Imaging Research, University of Utah, Address: 729 Arapleen Drive, Salt Lake City, UT, 84108. jdebever@cs.utah.edu.

Keywords

MRI; acoustic radiation force; ARFI; 3D; three-dimensional; focused ultrasound

Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) is a promising noninvasive technology with wide ranging applications for the treatment of cancer (1–3), localized drug-delivery (4–6), neuromodulation (7,8), and blood–brain barrier opening (9–11). Two critical aspects of successfully using MRgFUS for any application are accurate positioning of the ultrasound (US) focal spot and ensuring high quality focusing when the beam propagates through an aberrating tissue environment. Aberrations caused, for example, by tissue inhomogeneity in the breast (12,13) or by tissue-bone (14) interfaces could lead to inadvertent damage to nontargeted tissues.

One clinically implemented approach to localizing the focal spot is to perform low power interrogation pulses while measuring the resulting temperature distribution by means of MR proton resonance frequency (PRF) shift thermometry. Because many such interrogation pulses may be required during a single treatment, unintended tissue damage may occur. Furthermore, the PRF thermometry method is ineffective in fat, which would be problematic for therapies in organs such as breast. Tissue displacement caused by focused ultrasound can be measured using MR-ARFI, and this technique can localize the focal spot in two-dimensions (2D) (15–17). Because MR-ARFI techniques use short ultrasound bursts on the order of 1–20 ms with low duty cycles (1–10%), minimal tissue heating is induced making 2D MR-ARFI a safe alternative to low power interrogation pulses. Because MR-ARFI uses motion encoding gradients (MEG) that produce a phase difference proportional to the tissue's displacement, MR-ARFI is not susceptible to the same issues as PRF thermometry and can measure displacement in any tissue type, including fat (18).

Several methods for performing MR-ARFI have been presented using both spin-echo (SE) and gradient echo (GRE) pulse sequences, and several MEG schemes have been used including: (i) Repeated unipolar (16,19), (ii) Bipolar gradients (17,20,21) (often repeated on both sides of the refocusing radiofrequency (RF) pulse in SE sequences), (iii) Alternating bipolar gradients (22), and (iv) Tripolar gradients (23). In addition to beam localization, variations of these encoding schemes have been used to apply MR-ARFI for phase aberration correction (23–27), and tissue property determination (16,20), but have done so with 2D imaging only. While 2D imaging is fast, the small displacements being measured (on the order of micrometers) sometimes require many averages to improve the signal-to-noise ratio (SNR). Additionally, the 2D measurement plane is placed before the location of the focus is known and may not capture the maximum displacement. Furthermore, energy deposited outside the 2D field-of-view (FOV) could provide insight into the quality of the focus. Multiple slice 2D MR-ARFI could improve the localization of the focal spot, but the voxel grid cannot be retrospectively shifted along the slice direction with 2D data. For equal acquisition durations, the improvement in SNR achieved by averaging multiple 2D datasets is equivalent to the inherent signal averaging of a 3D acquisition; however, the 3D scheme

will provide the benefit of contiguous slices where the voxel spacing can be made arbitrarily small in all three dimensions using zero-filled interpolation. Measuring the displacement field in a large 3D FOV would simplify and improve the accuracy of beam localization, improve knowledge of how intervening tissues affect beam quality, and achieve similar imaging times to an averaged 2D acquisition. For the purpose of phase aberration correction, it is also possible that the increased information content provided by a 3D displacement field would improve the resulting focus or reduce the number of scans required to perform the optimization process.

This study presents a method for performing 3D MR-ARFI with special attention paid to reducing imaging time and maintaining safe levels of tissue heating ($< 6^{\circ}\text{C}$). Several unique features are presented including: (i) an unbalanced bipolar motion encoding gradient waveform that allows for shorter echo times (TE) and higher echo train lengths (ETL) than a repeated motion encoding gradient waveform; (ii) a configurable k_z reduction factor (KZRF) which reduces the number of US pulses required by firing only during the acquisition of a central subset of the k_z partitions; and (iii) interleaving of the US-ON and US-OFF images at the k_z partition level which reduces the effective duty cycle (DC), and resulting tissue heating, by approximately half. This work also presents a detailed safety analysis for both repeated ARFI measurements, and a parametric study of the trade-offs among sequence parameters that influence imaging time and tissue heating over a single measurement. Finally, the sequence's sensitivity to susceptibility changes due to motion outside the FOV, and the effect of tissue inhomogeneities, were evaluated for breast applications.

Methods

Sequence Overview

A 3D SE segmented echo-planar imaging (EPI) pulse sequence was modified to include an unbalanced bipolar MEG and optional flyback readout (Fig. 1a). The areas of MEG lobe, A1, and crusher gradient lobe, A2, are user specified, and the area of the second MEG lobe is set to $A1 + A2$ to ensure the 0th order gradient moment sums to zero. All sequence evaluations were performed on a Siemens 3 Tesla (T) Tim Trio MRI (Erlangen, Germany). An optical trigger output from the MRI pulse sequence synchronizes the firing of an ultrasound burst with the second lobe of the MEG. Two types of images are required for each displacement map; (i) images with no US bursts ([OFF] images), and (ii) images with US bursts ([ON] images). In the default mode, all lines of k-space for an [OFF] image are acquired followed by all lines for an [ON] image (ME2 mode), and each k_z partition is filled before proceeding to the next partition. However, the 3D SE unbalanced bipolar ARFI sequence presented here has two additional features that enhance safety. First, the KZRF parameter reduces the number of ultrasound pulses delivered while acquiring [ON] images by firing only during a central subset of the k_z partitions. Second, instead of acquiring all k-space lines for an [OFF] image followed by all k-space lines for an [ON] (ME2 mode), acquisition of an [OFF] image can be interleaved with an [ON] image at the k_z partition level (KZ2 mode). In KZ2 mode, one echo train's k-space lines are acquired for each partition of the [OFF] image followed by the same set of lines for each partition of the [ON] image. For example, when interleaving [OFF] and [ON] images that each require 28 k_z

partitions using KZ2 mode, the first 28 TRs will be acquired without US bursts, followed by 28 TRs with US. Thus, a cooling period will be interleaved that is of equal duration to the interval of applied US pulses. This reduces the effective (average) duty cycle by 50% compared with ME2 mode. Like ME2 mode, setting KZRF < 1 will further increase the cooling duration. For example, if KZRF = 0.64, then only 18 of 28 k_z partitions will be acquired with US for the [ON] image, resulting in no US pulses for first 38 TRs, followed by 18 TRs with US.

Focal Spot Localization with 3D MR-ARFI

A study in a tissue mimicking phantom (28) was performed to evaluate the ability of 3D MR-ARFI to predict the location heated during a continuous-wave sonication measured by 3D PRF thermometry. A gelatin phantom was constructed in-house from powder (Vyse Gelatin Co., Schiller Park, IL), and was at room temperature when testing began. The phantom was positioned approximately 10 cm (Fig. 1b) above a 256-element phased-array transducer (Imasonic, Besançon, France) operating at 1 MHz (focal distance of 13 cm, aperture diameter of 14.5 cm, full-width-at-half-maximum $2 \times 2 \times 8$ mm, f-number = 0.90). The transducer was driven by electronics and software by Image Guided Therapy (Pessac, France), and a deionized and degassed water bath coupled the phantom to the transducer. A single loop RF receive-only coil was positioned around the phantom approximately 3 cm from the bottom. The 3D ARFI maps were acquired with MR parameters given in Table 1 using ME2 mode and KZRF = 0.64 (US on during 18/28 k_z partitions). Diffusion-related signal loss is summarized by the b-value parameter. This sequence configuration resulted in a b-value of 30 s/mm² which is similar to b-values reported by other investigators using the repeated bipolar MEG (15,18,19). In all tests, the motion encoding was performed along the slice direction of the imaging volume, and the slices were oriented perpendicular to the transducer face. For each ARFI dataset in ME2 mode, three images were acquired in [OFF], [ON], [OFF] order. The two [OFF] images were averaged, and the phase difference maps were computed from the complex subtraction between the [ON] and average [OFF] image. While not strictly necessary, averaging the two [OFF] images is a simple method for correcting linear field changes that may occur during image acquisition. The measured phase difference, ϕ , was converted to an effective displacement, D_{eff} , representing a weighted-average displacement over the encoding interval, t_{enc} , using:

$$\Delta D_{eff} = \frac{\Delta \phi}{2\pi \int_0^{t_{enc}} G_{MEG}(t) \delta t} \quad [1]$$

where γ is the proton gyromagnetic ratio, and G_{MEG} is the motion encoding gradient amplitude. This study set $MEG_{amp} = 30$ mT/m, $t_{enc} = 10$ ms, and total acquisition time = 168 s for an [OFF][ON][OFF] ARFI map. Holding the ultrasound power constant, 3D ARFI maps were acquired while electronically steering the focal spot to four locations (US_x , US_y , US_z): (0, 0, 0) mm, (6, 0, 0) mm, (12, 0, 0) mm, and (0, 0, 8) mm.

Temperature distributions resulting from continuous-wave heating at the same four electronically steered focal spot locations were measured using a 3D GRE segmented EPI

PRF thermometry sequence with flyback readout. Temperature imaging parameters are shown in Table 1.

The k-space data for both temperature and ARFI data-sets was filtered along k_z using Matlab's (Mathworks Inc, Natick, MA) *tukeywin()* function ($R = 0.85$) to suppress Gibbs ringing artifact. The Tukey filter smoothly transitions the edges of k-space to zero with a raised cosine, similar to a Hann filter, but allows for a user configurable unfiltered center region. The k-space data was also zero-fill-interpolated to $0.2 \times 0.2 \times 0.33$ mm voxel spacing to mitigate partial volume effects.

MR-ARFI and MR temperature measurements were repeated three times at each focal zone location. For each measurement, a “center of mass” (COM) location was computed over a $9 \times 9 \times 9$ voxel region surrounding the maximum value by means of:

$$\text{COM}(\vec{r}) = \frac{\sum_{i=1}^n v_i(\vec{r}_i) \cdot \vec{r}_i}{\sum_{i=1}^n v_i(\vec{r}_i)} \quad [2]$$

where $\vec{r}_i$ is the position of each voxel and v_i is the associated displacement/temperature rise. The three temperature-COM positions for each focal position were averaged and used as the reference point for comparison to the displacement-COM locations. The average temperature-COM at (0,0,0) was used as the global reference point when comparing desired and achieved beam deflection. ARFI's ability to predict the location of heating was quantified by computing the average and standard deviation of the position difference between the ARFI-COM and the reference temperature-COM for each focal zone position.

Heating Induced by 3D MR-ARFI

Three-dimensional imaging generally requires more phase encoding steps than 2D imaging, and while the primary penalty of this is increased imaging time, for 3D MR-ARFI this also increases tissue heating due to the increased number of US pulses delivered. To safely perform MR-ARFI, the induced temperature rise should be limited to 6°C both to avoid the accumulation of Thermal Dose (29) and to satisfy FDA limits on Thermal Index (30). Tissue heating induced during the acquisition of 3D MR-ARFI was investigated in two studies.

First, an evaluation of the trade-offs among sequence parameters affecting tissue heating was performed. This study considered acquiring a single ARFI measurement in ME2 mode with the FOV and resolution used to acquire the experimental 3D ARFI maps in the previous section. Parameters studied that affect tissue heating included: number of US pulses, ETL, KZRF, repetition time (TR), and DC. EPI helps achieve practical imaging times and reduces the number of US pulses required to attain a 3D MR-ARFI map. However, longer ETLs can increase ghosting artifacts and increase TE, both of which diminish image quality and SNR. Using this sequence's KZRF feature, the number of US pulses can be reduced without changing the ETL by setting $\text{KZRF} < 1$. This reduces the spatial resolution of the displacement maps along the k_z direction (while maintaining full resolution of the anatomical images); however, these high frequency components may not be necessary to

resolve the ARFI peak because the broadest dimension of the beam is also along k_z . The number of US pulses, N_{US} , required for a given ETL and KZRF are given by:

$$N_{US} = \frac{N_y N_z}{ETL} \times KZRF \quad [3]$$

where N_y and N_z are the number of 3D phase encoding steps required for a given FOV and resolution. For the fixed FOV and resolution studied, $N_y = 90$ and $N_z = 28$. The number of US pulses required for a single US-ON 3D MR-ARFI image was computed using Eq. [3] with ETL ranging from 1 to 15 and for three KZRFs: [1.00, 0.64, 0.50]. The imaging time to acquire a single measurement of a 3D MR-ARFI sequence, t_{Acq} , was computed using Eq. [4].

$$t_{Acq} = \frac{N_y N_z}{ETL} \times TR \quad [4]$$

Impractically long configurations (>60 s per measurement) were excluded. A set of experiments were performed in the gelatin phantom to quantify the temperature rise induced as a function of the number of ARFI ultrasound pulses applied. A 3D PRF thermometry sequence measured temperature rise (parameters in Table 1) while the ultrasound generator ran preprogrammed sonication patterns equivalent to those produced by running the 3D ARFI sequence with TRs of 100, 200, 400 ms. During acquisition of the [ON] image in ME2 mode, the TR, US-pulse duration (US_{dur}) and DC are related by:

$$DC_{ME2} = \frac{US_{dur}}{TR} \times 100 \quad [5]$$

US power and US_{dur} were held constant (55 W and 10 ms, respectively), resulting in DCs of 10%, 5%, and 2.5% when the time between US pulses (i.e., TR) was 100, 200, and 400 ms, respectively. For each DC heating experiment, the maximum temperature rise at each time frame was used as the heating due to the number of US pulses delivered up to that point. A double exponential curve was fitted to the temperature data for each DC by means of least-squared error minimization. The fitted curves evaluate how much heating would occur for an arbitrary number of US pulses at a given DC.

The procedure above evaluated heating caused by ARFI for a single measurement. A final safety analysis explored the safety of performing multiple 3D ARFI measurements repeatedly for 11 min. Heating resulting from preprogrammed sonication patterns was measured using 3D PRF temperature imaging (see Table 1 for scan parameters). The sonication patterns replicated a 3D ARFI acquisition in ME2 mode with KZRF = 1.0 (280 US shots) and KZRF = 0.64 (180 US shots), and a 3D ARFI acquisition in KZ2 mode with KZRF = 1.0 (280 US shots) and KZRF = 0.64 (180 US shots).

Evaluation of KZ2 Mode and KZRF

KZ2 mode differs from ME2 mode both in the order of acquiring k_z partitions, and in the interleaving of [ON] and [OFF] images (see Sequence Overview). Similarly, the KZRF reduces the number of k_z partitions acquired with US enabled. Two experiments investigated the impact of these features on the displacement profiles measured. The same phantom was used as in the previous sections, but the experiments were run in a separate session. Because the phantom's starting temperature was different, the magnitude of displacement cannot be compared with the results of the previous sections. In the first experiment, 3D ARFI displacement maps were acquired in KZ2 mode with KZRF = 0.64 and compared with 3D ARFI maps acquired in ME2 mode with KZRF = 1.0 and 0.64. No k-space filtering was applied to the ME2 displacement map with KZRF = 1.0. Because KZ2 mode interleaves acquisition of k-space lines for [OFF] and [ON] images, the total acquisition time for a single ARFI map was $2 \times 56 \text{ s} = 112 \text{ s}$, in contrast to the [OFF][ON][OFF] reconstruction of ME2 mode acquired in 168 s.

In the second experiment, the width of the displacement profiles along the US-x and US-z directions were measured for 3D ARFI measurements acquired with KZRF = 1.0, 0.86, 0.64, 0.50, 0.35, and 0.21. The full-width at 70% max was computed through the location of peak displacement.

Sensitivity to Motion Induced Susceptibility Changes

While FUS systems can be designed to constrain bulk tissue motion (7,31,32), motion of tissue outside the FOV, caused for example by respiration, can cause susceptibility changes that induce errors within the imaging volume. The sensitivity of this sequence to such effects was evaluated using a human volunteer laying prone on top of a breast-shaped gelatin phantom. The phantom was positioned in a breast specific MRgFUS system with 940 kHz 256-channel phased-array transducer (Imasonic, Besançon, France) and integrated 11-channel receive-only RF coil (31). Signal from the water bath was suppressed by adding manganese chloride to shorten its T2. The volunteer was asked to breathe freely while ARFI maps were acquired safely in the phantom. The ARFI imaging volume was oriented obliquely so that the slice direction was perpendicular to the transducer face (see Table 1 for sequence parameters).

Ex Vivo Cadaver Breast

The sequence was further tested in a cadaver breast to evaluate performance in a realistic inhomogeneous tissue environment. The cadaver breast was secured to a plastic plate and suspended above the same breast specific MRgFUS system described previously. The 3D ARFI maps were acquired in ME2 mode (KZRF = 1) with fat saturation to reduce chemical shift artifact. See Table 1 for detailed sequence parameters.

Results

Focal Spot Localization with 3D MR-ARFI

A representative 3D displacement pattern measured by the SE Unbalanced-Bipolar MR-ARFI sequence while firing at the geometric focus is shown in Figure 2. Slices longitudinal

to the beam through the point of maximum displacement when electronically steering the beam from (0, 0, 0) to (6, 0, 0), (12, 0, 0), and (0, 0, 8) mm are shown in Figure 3 along with the corresponding 3D temperature maps. The actual beam deflection for each electronically steered location from the global (0, 0, 0) reference position is illustrated in Figure 4. The average difference between the location of the displacement-COM and the reference temperature location along the (US-x, US-y, US-z) was $(0.0, 0.2, 0.5) \pm (0.0, 0.1, 0.3)$ mm. The maximum difference between the displacement-COM and the reference temperature-COM occurred for the (0, 0, 8) mm focal zone position where a 1 mm difference along US-z was observed. The difference between the COM locations for displacement and temperature were all within one measurement voxel (before zero-filling). The displacement standard deviation in a background region (i.e., away from the peak displacement) ranged from 0.3–0.6 mm. A reduction in the magnitude of displacement and temperature rise was observed as the beam was electronically steered away from (0,0,0). When steering to (6, 0, 0), (12, 0, 0), and (0,0,8) mm the average displacement was reduced by 39%, 53%, 12% and temperature rise was reduced by 31%, 51%, 12%.

Heating Induced by 3D MR-ARFI

Figure 5 summarizes the critical sequence parameters and their effects on tissue heating. In Figure 5a the imaging time required for several TR and ETL combinations is shown. For a given combination of ETL and TR, it is possible to look up the corresponding number of US pulses required in Figure 5b for various KZRFs. For example, with ETL = 9, TR = 200 ms, and KZRF = 1.0, Figure 5a shows that acquisition time = 56 s while Figure 5b indicates 280 US pulses would be required. In ME2 mode, a TR of 200 ms corresponds to a 5% DC, and according to Figure 5c, which shows tissue heating as a function of the number of US pulses, acquiring a 3D ARFI map with this configuration would violate the 6°C safety limit by inducing a 6.2°C temperature rise. However, by reducing KZRF to 0.64 (such that only 18 of the 28 k_z partitions are acquired with US), the number of US pulses decreases to 180 and induced tissue heating is reduced to 5.6°C. The KZ2 mode reduces the average duty cycle by half (to 2.5%), which in this case would limit the induced temperature rise to 3.1°C.

The temperature rise induced by 3D ARFI when acquiring multiple measurements repeatedly is shown in Figure 6. Using ME2 mode with KZRF = 1.0, the safety threshold is breached while acquiring the second volumetric ARFI map. By setting KZRF = 0.64, the maximum temperature after six complete 3D ARFI measurements is reduced to 5.6°C (below the safety threshold). Using KZ2 mode, the maximum temperature reached was 5.2°C and 3.6°C for KZRF = 1.0 and 0.64, respectively. Compared with the 7.4°C temperature rise attained by ME2 with KZRF = 1.0, KZ2 with KZRF = 0.64 reduced heating by 51%.

Evaluation of KZ2 Mode and KZRF

The displacement profiles measured by ME2 and KZ2 modes produced distinct peaks with displacement magnitudes agreeing within 5% (Figs. 7a,b). The measured displacement profile width decreases at a rate of 2.4 mm/KZRF along US-x, and 6.0 mm/KZRF along US-z (Fig. 7c). Using a KZRF of 0.64 versus 1.0 increased the width of the US-x/US-z profiles by 0.86/2.2 mm, but also reduced tissue heating. ME2 and KZ2 with KZRF = 0.64 reduced

the peak temperature rise to 4.8°C and 2.7°C, respectively (Fig. 6), while producing peak locations that agreed with ME2 with KZRF = 1.0 to within 0.4 mm for US-x and 0.7 mm for US-z.

Sensitivity to Motion Induced Susceptibility Changes

3D ARFI maps acquired using the breast specific MRgFUS system with the human volunteer free-breathing on top of the breast shaped gelatin phantom (Figs. 8a–c) demonstrated a clearly defined focal spot with 8 µm peak displacement. The displacement standard deviation in a region away from the peak displacement was 0.3 µm.

Ex Vivo Cadaver Breast

The transducer and slice orientations relative to the cadaver breast are shown in Figure 9a, and slices transverse and longitudinal to the US beam through the 3D displacement volume are shown in Figures 9b,c. A peak displacement of 21 µm was measured and the standard deviation of the displacement in a region away from the focus was 0.7 µm.

Discussion

This study has presented and evaluated a new 3D SE MR-ARFI pulse sequence, and has demonstrated that this method can safely and accurately localize the ultrasound focus and expected point of peak temperature increase in three dimensions with a single scan. The results in Figures 3 and 4 show that the difference between the COM location of displacement and temperature was on average 0.2 ± 0.1 mm along US-x, and 0.5 ± 0.3 mm along US-z. Some of this error is likely due to differing distortions that impact the GRE PRF temperature and SE MR-ARFI sequences. Overall however, this demonstrates that 3D ARFI can localize the focal spot in all three dimensions in a single scan, and that the displacement COM location is a good predictor of the location of heating. Because this sequence uses a full 3D acquisition, voxel spacing can be made arbitrarily small in all three dimensions using zero-filled interpolation. While zero-filling does not improve the fundamental resolution of the image, it does reduce errors introduced by partial volume effects, and thus a 3D acquisition is advantageous for localizing the focal spot. This is especially pertinent in the case of ARFI where the profile has a sharp peak along the beam's transverse directions, or if larger voxels are used to improve scan time and/or FOV coverage.

The sequence parameter map in Figure 5 indicates that the induced temperature rise for a single 3D ARFI measurement in ME2 mode at a 2.5% DC will reach a steady state of 3.5°C. Thus MR-ARFI could be performed safely without violating the 6.0°C safety threshold for any practical set of imaging parameters studied. However, the parameter map also indicates that at the 5.0% and 10% DCs it becomes important to consider the number of US shots delivered as the 6°C threshold is violated after 236 and 80 shots, respectively. For the imaging volume tested, ETLs of 5 are impractical either because the imaging time is too long (> 60 s) or because the number of US shots required results in significant tissue heating. On the other hand, as the ETL is increased there are diminishing returns in regard to imaging time and tissue heating. Higher ETLs can also increase ghosting artifacts and TE,

which degrade image quality and SNR. For the studies in the paper, we found that ETLs in the range of 7–11 strike a balance between image quality, imaging time, and safety.

Using the parameter map shown in Figure 5 led to the selection of ETL = 9 and KZRF = 0.64 for ME2 mode. This mitigated tissue heating concerns by reducing the induced temperature rise from 6.2°C (KZRF = 1.0) to 5.6°C (KZRF = 0.64). While this also reduces the effective resolution of the 3D ARFI maps along the US-z direction, generally FUS transducers have an ellipsoid shaped focal zone with one dimension being elongated, and this reduces the spatial resolution requirements along that dimension. While the width of the displacement profile did increase by 0.86/2.2 mm along US-x/US-z when reducing KZRF from 1.0 to 0.64 (Fig. 7c), the maximum difference in focal position remained within 0.4 mm and 0.7 mm along the US-x and US-z directions, respectively. This indicates that the high frequency components did not contribute significantly to the localization of the focal spot, and thus acquiring them with US on unnecessarily heats the tissue. These results suggest that the KZRF could be further decreased (reducing tissue heating), without hampering the ability to localize the focal spot. Furthermore, the higher k_z spatial frequencies were acquired (albeit without US), so the magnitude images needed for correlation of the MR-ARFI maps with patient anatomy would retain their full prescribed resolution.

Additional reductions in tissue heating were achieved by enabling the k_z partition-interleaving feature, KZ2. Using this mode with KZRF = 0.64 reduced tissue heating for a single measurement to 2.7°C, and limited tissue heating over six consecutive measurements to 3.6°C (Fig. 6). Compared with ME2 mode with KZRF = 1.0, the combined effect of KZ2 and KZRF = 0.64 reduced tissue heating by 51% (Fig. 6) while producing equally useful displacement profiles. Thus, repeated ARFI measurements can be safely acquired using KZ2 mode with KZRF = 1 or ME2 mode with KZRF = 0.64. As a final note on safety, these measurements represent a worst case scenario as the phantom is not perfused and tissue perfusion accelerates tissue cooling.

The 3D ARFI sequence acquired high quality 3D displacement maps using a breast specific MRgFUS system in a breast-shaped phantom positioned below a free-breathing volunteer (Fig. 8). Susceptibility changes induced by respiration did not cause significant artifact, and suppression of the water signal with manganese chloride was effective. The standard deviation of the background displacement was 0.3 μm which is comparable to the 0.3–0.6 μm standard deviation found in the cylindrical phantom studies. Because the breast MRgFUS system has multiple RF coils and used a slightly larger voxel size, the values are not directly comparable, but does indicate that the respiration motion did not have a large impact on noise. Background displacement noise did increase to 0.7 μm in the inhomogeneous cadaver breast study in Figure 9, but a localized peak of 21 μm was measured that would readily allow for focal spot localization.

The cadaver breast study demonstrated that 3D ARFI maps could be attained in a realistic inhomogeneous tissue environment. Fat saturation was used to minimize chemical shift artifact; however, there still existed sufficient water signal to acquire high quality displacement maps. It is hypothesized that this is due to decomposition of the tissue and may

not be typical of in vivo scenarios. Without fat saturation, the fat shift in these studies would have ranged from approximately 10–15 mm due to the lower bandwidth of the EPI sequence in the phase encoding direction. It has been shown that displacement can be measured in fat using a 2D ARFI sequence with a non-EPI readout and without fat saturation (18). Chemical shift impacts 2D techniques as well, though the shifts may be smaller depending on the readout bandwidth selected. One solution for performing ARFI in fat for both 2D and 3D techniques may be to use water suppression and center the acquisition frequency on fat, or alternatively, use a Dixon fat-water separation technique (33). A related concern is that of sensitivity to field inhomogeneity which may be accentuated by the MRgFUS hardware. Each MRgFUS system will impact the achievable field homogeneity in differing ways and is a critical part of a system's design. This work has demonstrated the acquisition of high fidelity ARFI maps in two different MRgFUS systems, and thus serves as a proof of concept for the 3D technique. A multislice 2D approach could also be used, though care must be taken to ensure safety is maintained as the time between US bursts will be reduced by the number of slices (15). Using a single-shot readout would mitigate the safety concerns, but may come at the expense of increased geometric distortion and sensitivity to chemical shift artifact. This sequence represents a middle ground in sensitivity to fat shift and field inhomogeneities; 2D single line readout strategies will be more robust while single-shot readouts will be more sensitive.

As with all 3D acquisition schemes, this sequence is sensitive to bulk motion which will significantly degrade image quality if it occurs in the FOV. Motion of peripheral objects may still generate susceptibility changes in the imaging volume, however, the studies presented here (Fig. 8) found these were a secondary concern. Increased robustness to all types of motion may be achieved by adding a phase navigator to perform correction during image reconstruction. 2D ARFI techniques have advantages when bulk motion is a concern, or when tens or hundreds of displacement maps must be acquired very quickly for performing phase aberration correction. Nevertheless, many applications exist where the SNR efficiency of the 3D technique can safely provide much more information in a reasonable time frame. For example, 3D ARFI could be beneficial for applications such as focal spot localization in organs where bulk motion can be constrained such as in the breast and brain.

The choice of motion encoding gradient proved to be beneficial in reducing imaging time and tissue heating. Other common motion encoding strategies use repeated bipolar gradients pulses on either side of the 180° pulse (for SE sequences), single bipolar pulses with alternating polarity (for GRE sequences), or tripolar pulses. The repeated bipolar approach increases the TE and/or limits the ETLs that can be used, which increases imaging time in a 3D acquisition and increases tissue heating due to repeated application of US bursts. A single bipolar approach helps reduce TE, but if an alternating polarity gradient encoding is used, such that there is no US-OFF image, then the number of US pulses is doubled which would increase tissue heating. Tripolar gradients have the benefit of producing more self-canceling eddy currents but increase the risk that the tissue is still displaced during the 3rd gradient lobe thus incorrectly subtracting motion encoding phase. The unbalanced bipolar MEG gains time efficiency by combining the motion encoding and crusher gradient moments allowing the US to be on for a maximum amount of time. Because there is only one MEG (before the 180° pulse), motion encoding does not compete for time with the EPI

readout after the 180° pulse, allowing for shorter TE's and longer ETLs. In comparison to repeated bipolar gradients, the unbalanced design can increase the ETL by 3 (with flyback) to 6 (without flyback) for the same TE. This reduces both imaging time and tissue heating, and could also be applied to 2D acquisitions.

In future, it may be possible to further reduce the tissue heating and acquisition time by integrating existing k-space undersampling techniques (34–36) into this 3D ARFI sequence. This could be beneficial for applications that require a large FOV to avoid phase wrap. Additional investigation into the use of 3D MR-ARFI for the purpose of phase aberration correction would also be beneficial as the 3D displacement field provides significantly more information with which to perform correction.

Conclusions

A 3D SE pulse sequence using a novel unbalanced bipolar motion encoding gradient was presented and shown to safely measure displacement due to acoustic radiation force over a large FOV and at high resolution in reasonable scan times. Comparisons to 3D PRF temperature imaging showed that 3D ARFI accurately localized the ultrasound focal spot in three dimensions using a single scan. This makes 3D ARFI a useful alternative to low-power heating localization methods. The ability to cover a large FOV increases the likelihood that the peak displacement is captured, and that the desired focal location is verified before potentially harmful heating is attempted. Advanced sequence features, such as k_z reduction factor and k_z partition level interleaving, were tested and shown to reduce tissue heating by up to 51% without affecting the accuracy of beam localization.

Acknowledgments

The authors gratefully acknowledge the input and guidance of Dr. Allison Payne.

References

1. Furusawa H, Namba K, Thomsen S, Akiyama F, Bendet A, Tanaka C, Yasuda Y, Nakahara H. Magnetic resonance-guided focused ultrasound surgery of breast cancer: reliability and effectiveness. *J Am Coll Surg*. 2006; 203:54–63. [PubMed: 16798487]
2. Sommer G, Bouley D, Gill H, Daniel B, Pauly KB, Diederich C. Focal ablation of prostate cancer: four roles for magnetic resonance imaging guidance. *Can J Urol*. 2013; 20:6672–6681. [PubMed: 23587506]
3. Kim Y, Bae DS, Kim BG, Lee JW, Kim TJ. A faster nonsurgical solution very large fibroid tumors yielded to a new ablation strategy. *Am J Obstet Gynecol*. 2011; 205:292.e1–e5. [PubMed: 22071069]
4. Kneidl B, Peller M, Winter G, Lindner LH, Hossann M. Thermosensitive liposomal drug delivery systems: state of the art review. *Int J Nanomedicine*. 2014; 9:4387–4398. [PubMed: 25258529]
5. Rapoport N, Nam KH, Gupta R, et al. Ultrasound-mediated tumor imaging and nanotherapy using drug loaded, block copolymer stabilized perfluorocarbon nanoemulsions. *J Control Release*. 2011; 153:4–15. [PubMed: 21277919]
6. Frenkel V, Etherington A, Greene M, Quijano J, Xie J, Hunter F, Dromi S, Li KCP. Delivery of liposomal doxorubicin (Doxil) in a breast cancer tumor model: investigation of potential enhancement by pulsed-high intensity focused ultrasound exposure. *Acad Radiol*. 2006; 13:469–479. [PubMed: 16554227]

7. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med.* 2013; 369:640–648. [PubMed: 23944301]
8. Suffredini G, Levy LM. MR-guided focused ultrasound: applications to essential tremor and other neurologic conditions. *AJNR Am J Neuroradiol.* 2014; 35:829–831. [PubMed: 24200903]
9. McDannold N, Arvanitis CD, Vykhodtseva N, Livingstone MS. Temporary disruption of the blood-brain barrier by use of ultrasound and microbubbles: safety and efficacy evaluation in rhesus macaques. *Cancer Res.* 2012; 72:3652–3663. [PubMed: 22552291]
10. O'Reilly MA, Hynynen K. Ultrasound enhanced drug delivery to the brain and central nervous system. *Int J Hyperthermia.* 2012; 28:386–396.
11. Hynynen K, McDannold N, Vykhodtseva N, Raymond S, Weissleder R, Jolesz FA, Sheikov N. Focal disruption of the blood-brain barrier due to 260-kHz ultrasound bursts: a method for molecular imaging and targeted drug delivery. *J Neurosurg.* 2006; 105:445–454. [PubMed: 16961141]
12. Mougnot C, Tillander M, Koskela J, Köhler MO, Moonen C, Ries M. High intensity focused ultrasound with large aperture transducers: a MRI based focal point correction for tissue heterogeneity. *Med Phys.* 2012; 39:1936–1945. [PubMed: 22482615]
13. Freiburger PD, Sullivan DC, LeBlanc BH, Smith SW, Trahey GE. Two dimensional ultrasonic beam distortion in the breast: in vivo measurements and effects. *Ultrason Imaging.* 1992; 14:398–414. [PubMed: 1296342]
14. Hynynen K, DeYoung D. Temperature elevation at muscle-bone interface during scanned, focused ultrasound hyperthermia. *Int J Hyper-thermia.* 1988; 4:267–279.
15. Kaye EA, Chen J, Pauly KB. Rapid MR-ARFI method for focal spot localization during focused ultrasound therapy. *Magn Reson Med.* 2011; 65:738–743. [PubMed: 21337406]
16. McDannold N, Maier SE. Magnetic resonance acoustic radiation force imaging. *Med Phys.* 2008; 35:3748–3758. [PubMed: 18777934]
17. Holbrook A. In vivo MR acoustic radiation force imaging in the porcine liver. *Med Phys.* 2011; 38:5081–5089. [PubMed: 21978053]
18. Bitton RR, Kaye E, Dirbas FM, Daniel BL, Pauly KB. Toward MR-guided high intensity focused ultrasound for presurgical localization: focused ultrasound lesions in cadaveric breast tissue. *J Magn Reson Imaging.* 2012; 35:1089–1097. [PubMed: 22170814]
19. Kaye EA, Pauly KB. Adapting MRI acoustic radiation force imaging for in vivo human brain focused ultrasound applications. *Magn Reson Med.* 2013; 69:724–733. [PubMed: 22555751]
20. Souchon R, Salomir R, Beuf O, Milot L, Grenier D, Lyonnet D, Chapelon JY, Rouvière O. Transient MR elastography (t-MRE) using ultrasound radiation force: theory, safety, and initial experiments in vitro. *Magn Reson Med.* 2008; 60:871–881. [PubMed: 18816871]
21. Chen J, Watkins R, Pauly KB. Optimization of encoding gradients for MR-ARFI. *Magn Reson Med.* 2010; 63:1050–1058. [PubMed: 20373406]
22. Auboiroux V, Viallon M, Roland J, et al. ARFI-prepared MRgHIFU in liver: simultaneous mapping of ARFI-displacement and temperature elevation, using a fast GRE-EPI sequence. *Magn Reson Med.* 2012; 68:932–946. [PubMed: 22246646]
23. Hertzberg Y, Volovick A, Zur Y, Medan Y, Vitek S, Navon G. Ultrasound focusing using magnetic resonance acoustic radiation force imaging: application to ultrasound transcranial therapy. *Med Phys.* 2010; 37:2934–2942.
24. Kyriakou A, Neufeld E, Werner B, Paulides MM, Szekely G, Kuster N. A review of numerical and experimental compensation techniques for skull-induced phase aberrations in transcranial focused ultrasound. *Int J Hyperthermia.* 2014; 30:36–46. [PubMed: 24325307]
25. Marsac L, Chauvet D, Larrat B, Pernot M, Robert B, Fink M, Boch AL, Aubry JF, Tanter M. MR-guided adaptive focusing of therapeutic ultrasound beams in the human head. *Med Phys.* 2012; 39:1141–1149. [PubMed: 22320825]
26. Vyas U, Kaye E, Pauly KB. Transcranial phase aberration correction using beam simulations and MR-ARFI. *Med Phys.* 2014; 41:032901. [PubMed: 24593740]
27. Larrat B, Pernot M, Montaldo G, Fink M, Tanter M. MR-guided adaptive focusing of ultrasound. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2010; 57:1734–1737. [PubMed: 20704061]

28. Farrer AI, Odéen 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]
29. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol*. 1984; 10:787–800.
30. Anon Guidance for industry and FDA staff - information for manufacturers seeking marketing clearance of diagnostic ultrasound systems and transducers. Washington, DC: U.S. Department of Health and Human Services, Food and Drug Administration; Radiological Devices Branch, Office of Device Evaluation; Division of Solid and Fluid Mechanics, Office of Science and Engineering Laboratories; 2008.
31. Payne A, Merrill R, Minalga E, et al. Design and characterization of a laterally mounted phased-array transducer breast-specific MRgHIFU device with integrated 11-channel receiver array. *Med Phys*. 2012; 39:1552–1560. [PubMed: 22380387]
32. 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; 66:323–332. discussion 332. [PubMed: 20087132]
33. Glover GH, Schneider E. Three-point dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magn Reson Med*. 1991; 18:371–383. [PubMed: 2046518]
34. Todd N, Prakash J, Odéen H, de Bever J, Payne A, Yalavarthy P, Parker DL. Toward real-time availability of 3D temperature maps created with temporally constrained reconstruction. *Magn Reson Med*. 2014; 71:1394–1404. [PubMed: 23670981]
35. Odéen H, Todd N, Diakite M, Minalga E, Payne A, Parker DL. Sampling strategies for subsampled segmented EPI PRF thermometry in MR guided high intensity focused ultrasound. *Med Phys*. 2014; 41:092301. [PubMed: 25186406]
36. Gaur P, Grissom WA. Accelerated MRI thermometry by direct estimation of temperature from undersampled k-space data. *Magn Reson Med*. 2015; 73:1914–1925. [PubMed: 24935053]

Fig. 1.

a: Pulse sequence diagram for the unbalanced-bipolar spin-echo ARFI sequence. $G_s/G_p/G_r$ are the slice encode, phase encode, and readout gradients, respectively. **b:** Phantom experiment setup. Phased array transducer approximately 10 cm below gelatin phantom. Geometric focus penetrates approximately 3 cm into the phantom.

Fig. 2.

The 3D ARFI volume measured at geometric focus with ME2 mode. **a:** Cut away view of 3D displacement map. **b:** Slice transverse to US beam through maximum displacement. **c,d:** Slices longitudinal to US beam through maximum displacement.

Fig. 3.

Comparison of 3D ARFI (in ME2 mode) and 3D temperature patterns while electronically steering to multiple positions. Slices are longitudinal to US beam propagation and cut through maximum displacement/temperature. While the 3D ARFI patterns are generally broader than the 3D temperature patterns, the average difference between the displacement center-of-mass location and the reference temperature center-of-mass location is 0.2 mm in directions perpendicular to the beam, and 0.5 mm in the longitudinal direction. The 3D ARFI maps captured the expected beam tilting and decreased displacement associated with electronic steering in addition to the near-field effects.

Fig. 4.

Line profiles through the images shown in Figure 3. **a:** Transverse profiles through maximum displacement (top) and maximum temperature (bottom) as beam is electronically steered to from (0, 0, 0) mm (black) to (6, 0, 0) mm, (medium gray) and (12, 0, 0) mm (light gray). **b:** Profiles along longitudinal line through maximum displacement (top) and temperature (bottom) as beam is steered from (0,0,0) mm (black) to (0, 0, 8) mm (light gray). Numbers above lines in (a) and (b) indicate the peak location relative to the global temperature reference point that defines (0, 0, 0).

Fig. 5.

Parametric study of the effect of imaging parameters on tissue heating for a single ARFI measurement. **a:** Imaging time, calculated from Equation (4), as a function of ETL for TR = 400, 200, and 100 ms. **b:** Number of ultrasound pulses delivered (Eq. [3]) as a function of ETL and KZRF = 1.0, 0.64, and 0.5. **c:** Tissue heating as a function of number of US pulses for duty cycle = 10.0%, 5.0%, and 2.5%. Curves are the result of double-exponential fits to experimentally measured tissue heating data with the ultrasound pulse duration kept constant at 10 ms. The dashed line in (c) indicates the 6°C safety limit on induced tissue heating.

Fig. 6.

Temperature rise induced by the repeated acquisition of 3D ARFI measurements. The KZRF is indicated by the number after the acquisition mode name. For example ME2:1.0 indicates ME2 mode run with KZRF = 1.0. ME2:1.0 exceeds the safety threshold of 6°C, while ME2:0.64 is safe for the entire acquisition duration. In all cases, KZ2 mode produces the least temperature rise and never exceeds the 6°C safety threshold.

Fig. 7.

Comparison of displacement profiles measured by ME2 and KZ2 acquisition modes and multiple KZRFs. **a:** Displacement profiles along the US-x direction. **b:** displacement profiles along the US-z direction. ME2:1.0 has US on during all k_z partitions (KZRF = 1.0) and no k-space filtering. ME2:0.64 has US on during 18/28 k_z partitions (KZRF = 0.64) and filtering along k_z . KZ2:0.64 has k_z interleaving mode enabled with KZRF = 0.64 and k_z filtering. The location of the peaks in the plane perpendicular to the beam agree within 0.4 mm. A small amount of profile broadening results from setting KZRF = 0.64. Along US-z, ME2:1.0 results in a sharper peak though some Gibbs ringing phenomenon is observed due to the elimination of k_z filtering. ME2:0.64 and KZ2:0.64 show broader beam profiles along US-z, but their peak locations agree with the ME2:1.0 peak location within 0.7 mm. **c:** Beam width measured by ME2 mode as a function of KZRF. The full width at 70% max is reported along the US-x and US-z directions with corresponding linear fits. Reducing the number of k_z partitions acquired with US broadens the measured displacement profile but reduces tissue heating.

Fig. 8.

Sequence test with respiration motion outside the field-of-view. **a:** Anatomical image showing human volunteer on top of a gelatin breast phantom and breast specific MRgFUS device. Approximate transducer orientation shown by red curve. ARFI imaging volume was oriented so the slice direction was perpendicular to the transducer face (green line). The human volunteer was asked to breathe freely while acquiring the ARFI images **b:** Slice transverse to the beam through maximum displacement. **c:** Profile through maximum displacement along the patient LR direction (US-y).

Fig. 9.

The 3D displacement maps in cadaver breast. **a:** Cadaver breast positioned on top of breast specific MRgFUS system. Green and red lines indicate slice orientations of following subfigures. **b:** Slice transverse to US beam. **c:** Slice longitudinal to US beam.

Table 1

Summary of Imaging Parameters for Each Experiment

	Experiment 1 Displacement vs temperature		Experiment 2 Heating due to ARFI – single 3D GRE-PRF		Experiment 3 Heating due to ARFI – repeated 3D GRE-PRF		Experiment 4 ME2 vs KZ2 & KZRF 3D SE-ARFI		Experiment 5 Breast phantom + volunteer 3D SE-ARFI		Experiment 6 Cadaver breast 3D SE-ARFI	
	3D SE-ARFI	3D GRE-PRF										
Resolution [mm]	$1.2 \times 1.2 \times 2.0$	$1.2 \times 1.2 \times 2.0$	$1.2 \times 1.2 \times 2.0$		$1.2 \times 1.2 \times 2.0$		$1.2 \times 1.2 \times 2.0$		$2.0 \times 2.0 \times 2.0$		$2.0 \times 2.0 \times 3.0$	
FOV [mm]	$192 \times 108 \times 48$	$192 \times 108 \times 48$	$192 \times 108 \times 28$		$192 \times 108 \times 20$		$192 \times 108 \times 48$		$256 \times 144 \times 56$		$256 \times 196 \times 36$	
Slice OS	4	4	4		2		4		4		2	
ETL	9	9	9		9		9		9		7	
# US Shots	180	1	750 - 3000		1080 - 1680		59 - 280		164		196	
TR/TE [ms]	200/52	33/15	23/11		33/15		200/52		200/45		250/53	
BW [Hz/Pixel]	744	744	744		744		744		737		751	
Flip Angle [°]	90	30	20		30		90		90		90	
MEG _{amp} [mT/m]	30	-	-		-		30		20		28	
Acquisition Time [s]	56.0	9.24	4.14		2.77		56		57.6		49	
US Power [W]	55	8.8	55		55		55		66		33	
US Duration	10 ms	27.72 s	10 ms		10 ms		10 ms		10 ms		10 ms	

Slice OS = number of oversampling slices acquired; ETL = echo train length; FOV = field-of-view; # US Shots = number of ultrasound bursts emitted; TR = repetition time; TE = echo time. BW = bandwidth per pixel; MEG_{amp} = motion encoding gradient amplitude.