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Assessment of acute thermal damage volumes in muscle using magnetization-prepared 3D T2-weighted imaging following MRI-guided high-intensity focused ultrasound therapy

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Abstract

Purpose—To evaluate magnetization-prepared 3D T2-weighted MR imaging measurements of acute tissue changes produced during ablative MR-HIFU exposures.

Methods—A clinical MR-HIFU system (3T) was used to generate thermal lesions (n=24) in the skeletal muscles of three pigs. T1-weighted, 2D T2-weighted, and magnetization-prepared 3D T2-weighted sequences were acquired before and after therapy to evaluate tissue changes following ablation. Tissues were harvested shortly after imaging, fixed in formalin, and gross-sectioned. Select lesions were processed into whole-mount sections. Lesion dimensions for each imaging sequence (length, width) and for gross sections (diameter of lesion core and rim) were assessed by three physicists. Contrast-to-background ratio between lesions and surrounding muscle was compared.

Results—Lesion dimensions on T1 and 2D T2-weighted imaging sequences were well correlated (R^2 approximately 0.7). The contrast-to-background ratio between lesion and surrounding muscle was 7.4 ± 2.4 for the magnetization-prepared sequence versus 1.7 ± 0.5 for a conventional 2D T2-weighted acquisition, and 7.0 ± 2.9 for a contrast-enhanced T1-weighted sequence. Compared with diameter measured on gross pathology, all imaging sequences over-estimated the lesion core by 22–33%, and under-estimated the lesion rim by 6–13%.

Conclusion—After MR-HIFU exposures, measurements of the acute thermal damage patterns in muscle using a magnetization-prepared 3D T2-weighted imaging sequence correlate with 2D T2-weighted and contrast-enhanced T1-weighted imaging, and all agree well with histology. The

magnetization-prepared sequence offers positive tissue contrast and does not require IV contrast agents, and may provide a noninvasive imaging evaluation of the region of acute thermal injury at multiple times during HIFU procedures.

Keywords

MRI; HIFU; high-intensity focused ultrasound; thermal ablation; preclinical

INTRODUCTION

MRI-guided high-intensity focused ultrasound (MR-HIFU) therapy is a non-invasive image-guided method for tissue ablation, with clinical applications in uterus, bone, prostate, brain, breast, and liver (1). Currently the volume of coagulated tissue produced by thermal therapy is assessed by the absence of uptake of a gadolinium-based contrast agent (GBCA) on contrast enhanced T1-weighted (CET1) scans, and is referred to as the non-perfused volume (NPV). In clinical studies of uterine fibroid ablation, NPV has been correlated with treatment outcome and symptom relief (2). In transurethral ultrasound ablation of prostate (3), and laser photocoagulation of breast (4) and brain (5), the NPV correlates with the histological ablated volume.

While assessment of NPV is a powerful imaging surrogate of thermal coagulation, it has some disadvantages. First, the technique requires the administration of a GBCA, which can be a challenge in compromised patients. Second, there are concerns over the administration of HIFU exposures immediately after GBCA. Although thermal ablation produced by HIFU does not result in dissociation of gadolinium from its chelates *in vivo*, it does trap the contrast agent in the ablated tissue for several hours (6). Entrapment of gadolinium in coagulated tissue makes subsequent assessment of coagulated tissue more difficult, and administration of GBCA between HIFU exposures can influence the accuracy of MR thermometry due to magnetic susceptibility effects (7). Therefore, contrast-enhanced assessment of NPV is normally limited to a final evaluation with no further sonications performed in that HIFU session. Third, a confounding factor in the use of NPV to measure thermal damage is transient disruption of blood flow (8) resulting in non-enhancing tissue which is indistinguishable from coagulated tissue. Finally, NPV measures a tissue volume with locally decreased signal intensity due to lack of GBCA uptake, potentially masking other variations in underlying tissue response within the treated region. Ideally, a method of tissue damage assessment would provide positive imaging contrast in regions where thermal damage has occurred.

A variety of magnetic resonance methods have been studied for imaging the effects of thermal damage in tissue based on endogenous contrast (9). However, visualization of acute thermal injury immediately after ablative treatment is complicated by the variety of cellular, vascular, and inflammatory responses that occur within and at the periphery of thermal lesions (10). While T2 (11, 12), T1 (13), diffusion (14), magnetization transfer (15), and elastography (16) have all demonstrated promise, they are not widely adopted due to variability in lesion conspicuity between subjects, between acquisition parameters, between tissue types, or within heterogeneous tumors (9). Multiparametric approaches may perform

better than individual sequences (17–19), but additional acquisitions increase the total scan time, and automated calculations to predict tissue viability must be clinically validated. Whereas CET1 consistently depicts thermal damage as a well-defined hypo-intense region with an enhancing rim, there are no robust techniques that use intrinsic contrast to visualize thermal damage across all tissue types.

A method for thermal damage assessment based on endogenous tissue contrast is preferable, since it could be applied multiple times during the course of a treatment to monitor the progression of the thermal damage volume. In a recent study, it was observed that thermal lesions produced with MR-HIFU were clearly visualized in the skeletal muscle immediately following targeted nerve ablations using a magnetization-prepared 3D T2-weighted MR imaging sequence designed for MR neurography (20). This sequence is referred to as 3D nerve-sheath signal increase with inked rest-tissue rare imaging (SHINKEI) (21). The SHINKEI acquisition was developed to visualize nerve tissue using a combination of flow-suppressing diffusion gradients, along with fat suppression and T2-based background signal suppression to improve the contrast and visualization of nerve tissue. The rationale for investigating this sequence in this preclinical study is that it combines acquisition strategies that enhance the signal of tissue components affected by thermal ablation while suppressing others.

The purpose of this study was to evaluate this magnetization-prepared 3D T2-weighted MR imaging sequence designed for MR neurography in its ability to measure the acute tissue changes produced during ablative exposures encountered in HIFU therapy.

MATERIALS AND METHODS

Swine Model

Animal experiments were approved by the Institutional Animal Care and Use Committee at University of Texas Southwestern Medical Center. This study conformed to the National Institutes of Health's PHS Policy on the Humane Care and Use of Laboratory Animals, and with the Animal Welfare Act and Guidelines enforced by the USDA. Three female Yorkshire pigs weighing 57–76 kg (Change of Pace, Aubrey, TX) were used. The animals were intubated for general anesthesia with 2.0–3.5% isoflurane delivered by mechanical ventilation (10–15 ml/kg, 15–20 breaths per minute). A 22-gauge angiocatheter was placed in the marginal ear vein for the delivery of intravenous contrast agents. Both hind legs were carefully shaved, chemically depilated, cleaned, and inspected to avoid air or skin defects that might interfere with ultrasound beam propagation. To ensure the appropriate depth of anesthesia, heart rate and oxygen saturation were monitored using an MR-compatible physiological monitor (Nonin 8600V with 10 m fiber-optic cable, Plymouth, MN). A circulating water blanket (Gaymar TP-500, Orchard Park, NY) was used to maintain core body temperature, and rectal temperature was monitored using MR-compatible fiber optic probes (Neoptix Inc, Quebec, Canada).

HIFU Setup

Ultrasound exposures were performed using a clinical MR-HIFU system (Sonalleve V2, Philips Medical Systems, Vantaa, Finland), integrated into a 3T MR scanner (Ingenia, Philips Healthcare, Best, The Netherlands). The HIFU system contains a 14 cm diameter, 256-element phased array focused ultrasound transducer. Through electronic steering of the acoustic focus along concentric circular paths, the system can generate exposures with diameters varying from 2 to 16 mm (22).

Animals were placed on the MR-HIFU tabletop on their side, providing an acoustic path from the HIFU transducer into the deep thigh muscle through a 15 mm thick acoustically transparent gel pad (Aquasonic, Parker Laboratories, Fairfield, NJ). MR signal was received using the five-element coil array of the MR-HIFU system. A T1-weighted MR image used for treatment planning is shown in Figure 1, Panel A, which depicts the positioning of the animal and the location of the ultrasound transducer.

HIFU Exposures

Ultrasound exposures were delivered to 5–6 discrete locations in each thigh with the intent of generating isolated regions of thermal coagulation in homogeneous muscle without overlap of thermal effects or tissue damage. At each location, a single treatment cell was sonicated. Cell sizes ranged from 4 mm to 16 mm in order to produce a range of ablation volumes. The exposure time for continuous-wave feedback-controlled sonications (23) at acoustic powers of 200–280 W and a frequency of 1.2 MHz ranged from 10.9 to 36.1 seconds for the 4 mm cells, to between 49.4 and 67.4 seconds for the largest 16 mm cells. Exposure edges were spaced more than 12 mm apart, and a wait period of at least 5 minutes was observed for tissue cooling. In total, ultrasound exposures were performed at 29 different locations in three pigs (six legs) with diameters of 4 (n=6), 8 (n=9), 12 (n=9), and 16 (n=5) millimeters.

MR Imaging

At each target location, 3D T1-weighted fast field echo (FFE) planning images were reviewed to ensure that there was a suitable acoustic path to the target location, and that the planned ablation volume would not interfere with surrounding tissue structures. Prior to the delivery of ultrasound to the target volume, a series of baseline MR images were acquired including pre-contrast water-only T1-weighted FFE images using multiple-echo two-point Dixon (mDixon) water-fat separation (24), water-only 2D mDixon turbo spin-echo (TSE) T2-weighted images, and 3D isotropic SHINKEI images. The acquisition parameters for these imaging sequences are given in Table 1. The same sequences were acquired after the exposures to evaluate changes in imaging appearance following thermal ablation. Post-treatment contrast-enhanced T1-weighted images were acquired last, approximately 30 minutes after the last sonication, and with k0 acquired 6 to 10 minutes after intravenous injection of GBCA (Gadavist 0.1 mmol/kg, Bayer Healthcare Pharmaceuticals, Wayne, NJ).

To monitor and control heating during the ultrasound exposures, multi-planar MR temperature mapping was performed using the proton resonance frequency shift technique (25). The water-selective segmented echo-planar imaging acquisition included six image

planes, with three slices transverse to the ultrasound beam at the acoustic focus, one along the ultrasound beam at the focus, one freely positioned in the near field at the skin-muscle interface, and one freely positioned in the far field typically 2–4 cm beyond the focus. The MR thermometry acquisition had a temporal resolution of 2.6 seconds for all six slices and a spatial resolution of $2 \times 2 \times 7$ mm (22).

SHINKEI Imaging Sequence

The SHINKEI sequence is based on a magnetization-prepared 3D TSE with variable refocusing flip angles. The magnetization preparation uses the improved motion-sensitization driven equilibrium (iMSDE) sequence for blood signal suppression (26) combined with a spectrally selective adiabatic inversion recovery (SPAIR) pulse for fat suppression. The SHINKEI sequence was originally developed for peripheral nerve imaging (21) by simultaneously suppressing fat and blood vessel signal, and using a long effective echo time to enhance the relatively long T2 of nerves with respect to muscle for improved nerve conspicuity (27). In this study, we used SHINKEI to enhance the conspicuity of thermal damage, which also has a prolonged T2 due to edema accumulation. Additionally, the 50 ms T2 preparation time of the iMSDE suppresses muscle signal and further accentuates the visualization of prolonged T2 species present both in nerve pathologies and edema in thermal damage. In both applications, suppressing bright signal from fat provides clear contrast for the tissue of interest. Finally, 3D TSE with variable refocusing flip angles provides isotropic 1.25 mm voxel resolution and adequate signal-to-noise ratio (SNR) for identifying nerves (or thermal damage) in a reasonable scan time.

Histology

Approximately 30 minutes following the last ultrasound exposure, anesthetized animals were humanely euthanized (Euthasol®, 100 mg/kg, IV). A portion of muscle containing all the coagulated tissue was excised, and fixed in 10% neutral buffered formalin for at least 14 days to allow penetration of fixative through the large sample. After fixation, the tissue samples were manually sectioned transverse to the ultrasound beam direction into 4–5 mm thick slices, and were photographed using a telecentric lens to measure the dimensions of the coagulated regions. The cut tissue slices were then processed into paraffin embedded blocks. A heavy duty sliding microtome (Leica SM2500) was used to produce 5 µm thick whole-mount tissue sections with dimensions of approximately 5×5 inches. The tissue sections were mounted on 5×7 inch glass slides and stained with hematoxylin and eosin (H&E). The stained slides were then scanned at a resolution equivalent to 20× magnification, using a whole-mount slide scanner (TISSUEScope 4000, Huron Technologies, Waterloo, Canada). The scanned images were analyzed using image-viewing software designed for digital histology (Sedeen Viewer, Pathcore Inc, Toronto, Canada). The digitized H&E sections were reviewed by two pathologists (JW and DB, 3 and 30 years of experience) to evaluate zones of tissue damage. The histological features within the center, periphery, and outside the region of thermal damage were evaluated and compared with the MR images of the same regions.

Image Analysis

The contrast-to-background ratios (CBR) between each lesion and nearby non-treated regions-of-interest (ROI) in muscle were calculated from the mean ROI pixel intensities as:

$$CBR = \frac{\text{mean}(\text{lesion}) - \text{mean}(\text{muscle})}{\text{standard deviation}(\text{muscle})} \quad (\text{Eq. 1})$$

The largest diameter and length of each of the individual thermal lesions were measured independently on each image type by three operators (JN, RMS, and RC, with 6, 10, and 20 years of experience) using measurement tools in the MR-HIFU treatment planning software. To obtain histological lesion diameters, ROIs of the lesions were selected from photographs of fixed tissue blocks, and the maximum diameter of each ROI was calculated using MATLAB (version 8.3; Mathworks, Natick, MA, USA). For each lesion, three operators (CB, RS, and RC, with 6, 10, and 20 years of experience) contoured two zones: the inner core of coagulative necrosis (Zone C), and the outer peripheral rim of structural vacuolation and edema (Zone R) (28, 29). Example contours are shown in Figure 1, Panel B.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism (Version 5, GraphPad Software, Inc.). CBRs were compared between image types using repeated measures one-way ANOVA with Tukey Honest Significant Differences adjustment. An adjusted p value less than 0.05 was considered significant. Lesion dimensions measured on MR images were compared between imaging sequences by their mean difference and 95% limits of agreement, the slope of their linear regression, and their coefficient of determination. Histological and imaging-derived lesion diameters were compared using Bland-Altman analysis of mean difference and 95% limits of agreement.

RESULTS

MRI Appearance of HIFU Ablation Volumes

Regions of thermal damage of varying size were produced following sonication, as seen in Figure 1, using exposures of varying acoustic power and diameter of beam steering. Figure 1 also shows the nature of the imaging information collected across six individual regions of thermal damage generated with the HIFU system in skeletal muscle. Panel C shows the four measurements made with MRI. The top left subpanel shows thermal dose contours of 240 (white lines) and 30 (orange lines) cumulative equivalent minutes at 43°C (CEM43) overlaid on a T1-weighted planning image, representing the predicted boundaries of 100% necrosis and subtle thermal damage, respectively (22, 30). The top right subpanel shows a contrast enhanced T1-weighted image in which the regions of thermal damage appear as non-enhancing areas. The bottom left subpanel depicts the appearance of the thermal damage regions on a 2D T2-weighted TSE image, and the bottom right subpanel shows the same locations with a SHINKEI acquisition. Contrast agent was only administered for the CET1 image. Panel B shows a gross section of muscle after 15 days of fixation in formalin, sliced approximately co-planar to the image acquisitions. The individual regions of thermal

damage are apparent, as well as concentric zones within each lesion. The contrast-enhanced T1 and the SHINKEI images offered the best visualization of the regions of tissue damage. With CET1, damage has negative contrast, while with SHINKEI the contrast was positive.

The contrast-to-background ratios between regions of thermal damage and normal muscle were calculated for the 3D SHINKEI, 2D T2-weighted, and contrast-enhanced T1-weighted images across 29 individual HIFU exposures of varying diameter and power (Figure 2). The CBR for contrast-enhanced T1-weighted imaging was 7.0 ± 2.9 , significantly higher than the ratio for the 2D T2-weighted sequence, 1.7 ± 0.5 (adjusted $p < 10^{-6}$). The high CBR for contrast-enhanced imaging illustrates why it is widely used to identify thermal damage regions after HIFU treatments. The SHINKEI acquisition achieved a contrast to background ratio of 7.4 ± 2.4 , also significantly higher than T2 (adjusted $p < 10^{-6}$), but not significantly different from contrast-enhanced imaging (adjusted $p = 0.84$), and with positive rather than negative contrast.

The diameters and lengths of the thermal damage regions identified with each of the three imaging acquisitions are compared in Figure 3. The best agreement is between the 2D T2-weighted and SHINKEI acquisitions for both lesion diameter and length. In both cases, the 95% confidence interval encompasses unity, which is expected since the SHINKEI sequence is a T2-weighted acquisition and is based on similar underlying information. Both of these sequences show a slightly lower than unity relationship with the contrast-enhanced T1-weighted measurements for lesion diameter, mostly due to a few outliers which are discussed later. All of the measurements are strongly correlated, with the strongest agreement between the 2D T2-weighted and SHINKEI sequences.

The diameters of the thermal damage regions measured on images versus the gross tissue sections are compared in Figure 4. All three imaging sequences overestimate the maximum dimensions of the inner core of coagulative thermal damage, with a positive mean difference of 2.4 to 3.8 mm. They all underestimate the dimensions of the peripheral rim, with a negative mean difference of -0.9 to -2.3 mm. There is a smaller spread of differences for the 2D T2-weighted and SHINKEI acquisitions than the contrast-enhanced sequence, indicating a more reproducible agreement.

In two cases, there were large disagreements in the appearance of thermal damage regions between contrast-enhanced and SHINKEI imaging (Figure 5). These two lesions correspond to the outliers in Figure 3. Both of these exposures were close to the femur, and while the SHINKEI image showed the expected circular appearance, the contrast-enhanced images suggested that damage extended to the bone. Closer analysis of image-planes superior and inferior to the one shown indicated that the additional damage indicated on the contrast-enhanced image was likely related to damage to a vessel resulting in reduced downstream contrast enhancement.

Histology

Figure 6 shows H&E staining of one region of thermal damage sectioned longitudinally along the muscle fibers, while Figure 7 shows another lesion in transverse section. Microscopic examination of the thermal lesions revealed hypercontraction and variegated

appearance of muscle fibers with evidence of contraction band-like necrosis (i.e. coagulative necrosis) in the center of the lesions (Figure 6B, 7B). The peripheral region of the lesions demonstrates separation of the individual muscle fibers compatible with edema, consistent with increased vascular permeability and extravasation of fluid from vessels into the interstitial connective tissue (Figure 6C, 7C). Although there were apparent rings of thermal damage in some of the larger thermal damage regions on the gross tissue specimens, histological evaluation did not reveal any underlying differences in the nature of tissue damage.

Figure 8 shows an H&E stained section corresponding to the right-middle lesion in Figure 1. In the 10× view (right), a region of vascular congestion is apparent within the lesion. This indicates that although the vessels have increased permeability to fluids, there are no extravasated erythrocytes, and thus, no hemorrhage.

DISCUSSION

In this study, acute thermal damage following HIFU ablation in muscle was assessed using an iMSDE-prepared 3D T2-weighted TSE sequence (SHINKEI). The results demonstrate that the contrast-to-background ratio (CBR) for SHINKEI was equivalent to that of contrast-enhanced T1-weighted imaging, and was positive in appearance rather than negative. Lesion dimensions correlated strongly between 2D T2-weighted, SHINKEI and contrast-enhanced images, and had good agreement with gross histology. Conventional 2D T2-weighted imaging showed the highest correlation to SHINKEI imaging, but the CBR of SHINKEI was significantly higher. Based on these results, the SHINKEI acquisition appears to be a promising non-contrast method for detection and delineation of thermal ablation in muscle tissue during the treatment.

Clinically, post-treatment contrast-enhanced T1-weighted imaging is widely used to visualize the acute effects of thermally induced vascular collapse and peripheral hyperemia (2, 31). The pattern observed in CET1 images has been validated against histopathology (28, 32, 33), and explained based on pharmacokinetic parameters calculated from dynamic contrast enhanced MRI (DCE-MRI) (29). The non-enhancing central core of coagulative necrosis on CET1 exhibits a low transfer constant (k_{trans}) and low extravascular extracellular volume fraction (v_e), while low k_{trans} and elevated v_e in the enhancing rim suggest structural disruption, vascular congestion, and hemorrhage. The surrounding tissue has high k_{trans} and high v_e , indicative of edema, inflammation, and increased vascular permeability. CET1 images acquired immediately after gadolinium injection depict only a non-enhancing core, while acquisitions after a delay of 4–20 minutes (as in our study) depict the typically reported non-enhancing core with growing peripheral enhancement, and even longer delays exhibit complete lesion enhancement with decreasing CBR (33).

Endogenous MR contrast mechanisms are sensitive to vascular changes, cellular membrane damage, and protein denaturation, but competing effects reduce their contrast appearance and reproducibility with respect to CET1. On T2-weighted images, thermal lesions have a core that is variably hyperintense (22, 34) or hypointense (35, 36), possibly due to contradictory contributions from membrane disruption and hemorrhage. Edema and

inflammation in the lesion periphery appear as a bright rim, increasing in conspicuity and diameter over several days (35, 37). Native T1-weighted images also have a zonal appearance that matches histology but has lower contrast (34). Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping depict a mix of increased ADC due to disruption of cell membranes, and decreased ADC due to cell swelling and vascular shutdown (14, 17, 38, 39). Intravoxel incoherent motion (IVIM) estimates tissue perfusion in addition to diffusion, and may improve specificity (40). Protein denaturation, a cause of thermally induced cell death, has been detected using magnetization transfer, amide proton transfer, and T1 ρ techniques (15, 18, 19). Irreversible protein damage also causes increased tissue stiffness detectable using magnetic resonance elastography (16), but sublethal heating has a contradictory effect, and the method depends on the ability to apply imaging-synchronized mechanical waves to the tissue of interest. Finally, when a time series of MR temperature maps is available, the delivered thermal dose can be calculated (30). Thermal dose thresholds of 30 and 240 CEM43 have been associated with histopathological evidence of edema and coagulative necrosis, respectively (22). However, the accuracy of summed thermal dose over a series of exposures is hindered by gradual displacements due to tissue swelling or patient motion, and changes in baseline temperature.

The primary advantage of the SHINKEI sequence is its ability to visualize thermal ablation in tissue with clear positive contrast, without the use of exogenous contrast agents. This enables repeated interrogation of the target volume during a treatment to evaluate the evolution of the overall thermal damage pattern. This capability is important for longer treatments with multiple exposures since slow changes in tissue volume, swelling, or patient shifts, can reduce the accuracy of thermometry-based thermal damage predictions. Based on assessments of the thermal damage volume, the treatment plan could be altered to achieve a desired treatment volume. Finally, the availability of a sequence based on endogenous tissue contrast could expand the use of ablative treatments to patients with contraindications to GBCA.

The three imaging methods studied here over-estimated the diameter of the inner core of coagulative thermal damage identified on gross histology by 2.4 mm (22%), 2.5 mm (23%), and 3.8 mm (33%) for T2, SHINKEI, and CET1, respectively. Imaging under-estimated the outer rim of structural damage and edema by -2.3 mm (-13%), -2.2 mm (-13%), and -0.9 mm (-6%). Similar discrepancies have been reported previously (28, 34), but could be a systematic error based on how the boundaries of thermal damage were chosen by the observers. Shrinkage of the muscle specimen due to formalin fixation may also explain the differences. The H&E stained sections depicted a similar zonal appearance of the thermal lesions with a core of coagulative necrosis, surrounded by a thin rim of vasogenic edema. Interestingly, the appearance of circular zones within the completely coagulated lesion core on gross sections did not correspond to any visible features on the H&E stained sections. Further staining for structural characteristics of muscle fiber might elucidate the nature of these optical differences.

Among the principal limitations of this study was that the method was only evaluated in muscle, which has a short T2. This produced a low background signal intensity on the SHINKEI images, which may have contributed to the high contrast-to-background ratio

observed, and is not representative of pathologic lesions. Further evaluation in diseased tissues such as uterine fibroids is justified since there will be a more heterogeneous background signal intensity. Another limitation is that SHINKEI was developed for large field of view, high-resolution imaging of nerves, and was not optimized for detection of ablation or scan time. SHINKEI was chosen because it was a convenient magnetization-prepared T2-weighted sequence with which our group had familiarity for nerve imaging. Nonetheless, these results motivate clinical investigation of this class of MR sequences to optimize the capability for thermal damage assessment in pathological tissue, as well as the translational issue of reducing resolution to achieve an appropriate scan time for ablation monitoring. The number of animals was small, but only two of 29 exposures identified major differences in the appearance of the contrast-enhanced T1-weighted images and the SHINKEI images, and these were in areas where histology was unavailable. Therefore, we were unable to determine which sequence provided an accurate assessment of thermal damage, or if they provided complementary information. Further study of these differences is recommended since they have important clinical implications for MRI-guided ablation treatments. Finally, this study would have benefited by also evaluating the conspicuity of thermal lesions on diffusion-weighted imaging, which has shown promise in other studies but suffers from distortion and lower resolution.

In conclusion, this preclinical study demonstrates that magnetization-prepared 3D T2-weighted sequences offer a convenient non-contrast method for visualizing thermal damage in muscle tissue during HIFU treatment, based on endogenous tissue contrast.

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Figure 1.

Panel A: Axial T1-weighted treatment planning image of the animal on its left side, with overlays of the transducer, beam path, and thermometry slice locations. Panel B: Photograph of thermal lesions in formalin-fixed pig thigh. Histological contours of core (C) and rim (R) are shown for one lesion. Panel C: MR imaging depiction of muscle tissue after delivery of HIFU exposures. The arrow points to the same lesion on histology and all imaging sequences. The arrow points to the same lesion on histology and all imaging sequences. Planned lesion diameter and acoustic power are shown for each lesion.

Figure 2.

Contrast-to-background ratios for contrast-enhanced T1, 2D T2 TSE, and 3D SHINKEI images of thermal lesions. Ratios for T2-weighted images were significantly weaker than the other sequences ($p < 0.001$, paired t-test). Representative images are of one thermal lesion obtained with each sequence. The dotted lines show the boundary of the regions selected to represent thermally damaged tissue, and the dashed lines indicate the regions selected as background signal in normal muscle. Scale bar = 1 cm.

Figure 3.

Lesion size comparison. Diameters (*top row*) and lengths (*bottom row*) measured using contrast-enhanced T1 (CET1), 2D T2-weighted turbo spin echo (T2), and 3D SHINKEI. The black line represents unity, the gray line is the linear fit with slope, intercept, and R^2 noted. The 95% confidence intervals are shaded. The mean difference and 95% limits of agreement are labeled. The strongest correlation was observed between T2 and SHINKEI images.

Figure 4. Bland-Altman plots comparing imaging lesion diameters with histological diameters of lesion core (zone C) and rim (zone R). The plots show the difference (imaging – histology) vs mean diameter for each lesion. The solid line represents the mean of all differences; dashed lines represent 95% limits of agreement. Agreement with histology was similar for SHINKEI, T2, and CET1.

Figure 5. Two lesions showing discrepancy in appearance between SHINKEI (top) and CET1 images (bottom). These lesions also fell outside of the 95% confidence intervals for Bland-Altman comparisons of SHINKEI and T2 versus histology.

Figure 6.

H&E staining of longitudinally sectioned muscle containing a region of thermal ablation.

Panel A depicts the entire lesion at 0.3 $\times$. At 10 $\times$ magnification, Panel B depicts the damaged skeletal muscle within the lesion, Panel C depicts the periphery of the lesion, and Panel D depicts the surrounding normal muscle tissue.

Figure 7.
H&E staining of transverse sectioned muscle containing a region of thermal ablation. Panel A depicts the entire lesion. Panels B, C, and D depict the lesion core, rim, and surrounding normal muscle tissue at 10× magnification.

Figure 8.
H&E staining of muscle containing a region of thermal ablation. Inset depicts a region of vascular congestion at 10 $\times$ magnification.

Table 1

Imaging parameters used for evaluation of thermal damage.

	2D T2 TSE	3D SHINKEI	3D CET1
Acquisition type	TSE	TSE	RF-spoiled FFE
Magnetization preparation	None	iMSDE duration 50 ms, venc 1 cm/s	Gadolinium
Fat suppression	mDixon 2 excitations, TE 1 ms	SPAIR	mDixon TE1 1.37 ms TE2 2.50 ms
Flip angle (°)	90	90	10
Repetition time (ms)	3298	2500	5.8
Actual echo time (ms)	80	161	1.37 / 2.5
TSE factor	20	100	-
Equivalent echo time (ms)	64	53	-
Field of view (mm)	280 × 280 × 240.5	380 × 400 × 240	350 × 350 × 240
Resolution (mm)	1.25 × 1.25 × 1.25	1.25 × 1.25 × 1.25	1.25 × 1.25 × 1.25
SENSE acceleration factor	2	1.5	2.6
Number of excitations	1	1	4
Acquisition time (MM:SS)	7:25	11:58	3:33

TSE = turbo spin-echo, FFE = fast field-echo, CET1 = contrast-enhanced T1, SPAIR = spectral adiabatic inversion recovery, mDixon = modified Dixon