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Assessment of in vivo Laser Ablation Using MR Elastography with an Inertial Driver

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Abstract

As a nonsurgical treatment for malignant hepatic tumors, percutaneous tumor thermal ablation requires accurate monitor and evaluation of cell death during and after the treatment, because if sufficient ablation is not achieved on tumors, then they can progress after treatment. Currently there is not a single effective way available to accurately monitor cell death during and after in vivo thermal ablation. For the first time, we used MR elastography with a new inertial driver to repeatedly measure tissue stiffness during and after in vivo laser ablation on porcine livers. During 2-minute ablations using 4.5-, 7.5- and 15-W laser power, the stiffness of the lesion underwent very complicated changes indicative of the dynamic protein folding and unfolding that occurred under the different levels of heating. After laser ablations of a lethal dose (2 min, 15 W), lesion stiffnesses were significantly greater than the baseline values ($p < 0.007$) and became stiffer over time; also, the mean [95% CI] stiffness increments from baseline were significantly greater than those after lower dose (2 min, 7.5-W) laser ablations (64.4% [32.8%, 96.0%] vs 22.5% [16.3%, 28.6%], $p = 0.009$), which reflected the irreversible cell denaturation during the laser ablation with the lethal dose.

Keywords

MR elastography; thermal ablation; in vivo; tissue denaturation

Percutaneous tumor thermal ablation has become an important nonsurgical treatment for primary and secondary malignant hepatic tumors (1,2). A critical part of the tumor ablation procedure is intratreatment monitoring to determine whether tumor cell death with an adequate ablation zone has been achieved. Without delivering the appropriate thermal dose, the tumor can continue to progress after the treatment due to incomplete ablation (3). A recent study looking at the long-term efficacy of radiofrequency ablation for the treatment of liver tumors over a 6-year period demonstrated that there was a high concordance rate (87%) between the exact sites of local tumor progression and insufficient ablative margins (4). Thermal ablation can be guided by medical imaging modalities such as computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI). However, MRI has unique capabilities for planning, guiding and monitoring ablation treatments due to its

inherent soft tissue contrast and many specialized imaging sequences. Using temperature-sensitive properties, such as proton resonance frequency (PRF) shift, MRI thermometry can measure temperature changes with a high degree of sensitivity (5). Using MR thermometry while monitoring the duration of treatment, the Arrhenius equation can be used to estimate the thermal ablation zone and the area of cell death (2,6). For example, Goldberg et al. found that heating tissue at 50–55°C for 4–6 minutes results in irreversible protein denaturation; between 60 and 100°C, tissue will be immediately coagulated with immediate cell death; and greater than 100°C, tissue will be vaporized and carbonized (7). However, the Arrhenius equation does not account for local tissue conductivity differences, local blood flow, or different tumor cellular sensitivity and it cannot be used to evaluate the tissue denaturation state after the thermal ablation. Furthermore, MR thermometry is limited in its evaluation of the ablation zone by its motion sensitivity and it is not meaningful after the thermal ablation because the temperature is dominated by the cooling process and blood flow.

On the other hand, data from ultrasound studies have revealed that tissue stiffness changes occur during thermal ablation and tissue stiffness increases with tissue denaturation correlating with complete ablation (8,9). A MR elastography (MRE) study using an ex vivo porcine muscle specimen showed increasing stiffness in tissue ablated using focused ultrasound ablation (10). Based on these studies, we have developed an in vivo MRE protocol using a new acoustic inertial driver to study the stiffness change of lesions during and after focal laser ablation. Our hypothesis is that MRE can be used to measure the stiffness change in the region of ablation, not only during, but also after the in vivo laser ablation and that a significant increase in stiffness from baseline will be observed in tissue experiencing a lethal thermal dose. The goal of this study is to demonstrate the feasibility of the new acoustic inertial driver for producing mechanical waves in the ablation region, and the capability of MRE for measuring the tissue stiffness changes due to the in vivo laser ablation.

Materials and Methods

Animal preparation and MRI scanner

With Mayo Clinic Institutional Animal Care and Use Committee approval, 5 juvenile female pigs (45-50kg) were used in this study. For each procedure, anesthesia was supplied as a mixture of telazol 4.4 mg/kg, ketamine 2.2mg/kg, and xylazine 2.2mg/kg. Intraprocedural monitoring was performed with a MRI-compatible anesthesia machine (Ohmeda, Excel 210 MRI Compatible, Madison, WI, USA), using 1-2% isoflurane to control the depth of sedation. The animal was put in a custom cradle with a foot-first, left decubitus position and then placed in a 1.5T whole-body scanner (Signa HDx, GE Healthcare, Wisconsin, USA). An 8-channel torso coil was used for all MRI scans. MRE and MRI scans were done with breath holds at the end of inspiration. The animal core temperature was not monitored, but continuous pulse oxygenation was monitored via a MRI-compatible sensor on the tongue.

Laser ablation system

The laser applicator used to deliver the 980-nm laser energy consisted of a diffusing fiber placed inside an optically clear cooling catheter (Visualase Inc., Houston, Texas). The laser

fiber consisted of a standard silica fiberoptic cable with a 400- μ m core diameter. The 15-W (100% power level) laser generator used a 400- μ m core fiber with a 10-mm cylindrical diffuser at the tip. The diffusing tip emits energy in a radially symmetric cylindrical light distribution pattern. The cooling catheter was constructed from two coaxial, flexible polycarbonate tubes and had a sharpened conical tip to facilitate penetration into tissue. Laser light is delivered from the fiber tip diffuser through the walls of the cooling catheter and into the tissue. The cooling catheter is used to prevent carbonization during heating, which could limit light penetration. The cooling catheter had an outside diameter of 1.65 mm (17Ga, 5F) for the 15-W laser with a usable length of 28 cm. The cooling catheter was connected to a peristaltic pump to provide a sterile, room-temperature saline flow from a regular IV bag. The laser fiber and cooling catheter IV tubing enter the MR suite through a standard wave guide in the MR suite wall approximately 6-7 meters away from the scanner.

Inertial MRE driver and setup

The pneumatic driver system for MRE consists of three important acoustic components: an active driver, a passive driver and a flexible tube that connects the two drivers. The active driver (consisting of a signal generator, amplifier, and audio speaker located outside of the MR suite), generates an oscillating acoustic pressure at a prescribed frequency. The flexible tube, running through a waveguide in the wall of the MR suite, connects the active driver to a passive driver placed on or near the subject in the scanner and works as an acoustic waveguide to convey the acoustic pressure variations from the active driver (source) to the passive driver. The passive driver converts the received oscillating acoustic pressure into mechanical vibrations of the tissue based on the acoustic-mechanical coupling between the passive driver and the subject. Passive drivers can be made in different shapes with different acoustic-mechanical coupling components to meet important design requirements, such as providing a high- or low-frequency response, producing waves in tissue with a preferential wave polarization, or accommodating the restrictive geometry of the human body and specific imaging coils. Various driver designs have been created to improve the performance of MRE in different organs, such as liver, spleen, brain, kidney, and muscle (11-14). Different passive drivers utilize the same flexible tube and active driver. This is the main advantage of the MRE pneumatic driver system: the passive drivers can be designed independently of the active driver and optimized for different applications.

In this study, a novel passive acoustic inertial driver (Fig. 1) was developed for MRE performed in conjunction with percutaneous ablation. The driver had a cylindrical shape with a diameter of 4 cm and height of 2.5 cm (Fig. 1.3 and Fig. 2.4). A piston (Fig. 1.11) inside the driver separated the acoustic cylinder chamber into 2 subchambers: an active subchamber which was closed and only connected to the active MRE pneumatic driver through the flexible tube, and an acoustic pressure-balanced subchamber which was open to atmospheric pressure through holes in its cover (Fig. 1.12) to balance the acoustic pressure caused by the vibration of the piston. IV connectors (Fig. 1.6 and 1.7) extended through both subchambers along the long axis of the driver. There was a small circular air gap (0.25 mm) between the IV connector and the cover of the active subchamber (Fig. 1.13) so as not to restrict the motion of the piston while keeping air losses to a minimum. Both subchambers were filled with elastic fiber springs (Fig. 1.10), which allowed free air flow in both of the

subchambers and stabilized the piston vibration around its equilibrium position. The inertial acoustic driver does not have to be attached to any belt or frame for support like the traditional external MRE drivers do. The acoustic chamber cylinder serves as an inertial mass that supports the vibration of the piston inside it. This piston configuration allows vibration and conveyance of mechanical energy to any device, such as the laser ablation applicator, connected to its central axis, even when suspended in air. Fig. 2 shows the experiment setup of the inertial driver in conjunction with the in vivo laser ablation catheter system. The percutaneous laser ablation applicator was inserted orthogonally into the porcine liver. The other end of the applicator was bent 90 degrees parallel to the pig body due to the narrow space in the scanner bore. The inertial driver (Fig. 2.4) was connected to the end of the applicator via Luer locks, and taped to the RF coil (Fig. 2.1) to secure the inertial driver and to avoid pulling on the laser applicator. The applicator is not seen in the picture because it is behind the inertial driver (Fig. 2.4). The laser fiber tip can pass through the driver and be positioned appropriately within the laser applicator. This in-line connection allows saline circulation through the laser applicator for cooling the tip of the laser applicator. The setup and use of the standard laser ablation components are not affected or disturbed by the inertial driver.

MRE imaging

MR elastography is a technology for characterizing the biomechanical properties (e.g., stiffness) of tissues in vivo. It uses MR phase-contrast techniques to acquire images of wave propagation in tissue which are produced by a source of mechanical vibration. The images of wave propagation are interpreted and processed by inversion algorithms to generate a tissue stiffness map called an elastogram from which the tissue stiffness is measured (15). It has been well documented that MRE can differentiate tissue stiffness due to pathological changes in tissue, such as due to progressive fibrosis development in the liver (11,16-23).

In the current study, MRE was performed before, during and after laser ablation to monitor the stiffness changes in the ablation region. A phase-contrast, single-shot, spin-echo EPI sequence was used to image the waves in the liver excited by the inertial driver (Fig. 3). MRE was performed in two oblique imaging planes, perpendicular and parallel to the laser applicator, using a driver vibration frequency of 60 Hz. The imaged slices covered the whole potential ablation region. The imaging parameters used included FOV = 26-32 cm, TR/TE = 1250/55 ms, matrix = 72×72 , NEX = 1, bandwidth = 250 kHz, number of slices = 15, slice thickness/spacing = 5/0 mm, vibration frequency = 60 Hz, displacement encoding sensitivity = $7.7 \mu\text{m/radian}$, 3 orthogonal motion-sensitizing directions, phase offsets = 3, parallel imaging acceleration factor = 2, scan time = 30 s. Bipolar motion-encoding gradients (6.45-ms duration) were placed on either side of the refocusing pulse and separated by 1.5 periods of the mechanical vibration (25 ms). A 3D phase-gradient inversion using 20 3D directional filters (cutoff frequencies of 0.1 and 80 cycles/FOV) was used to invert the MRE wave images and generate the elastograms (24). The cutoff frequencies of the directional filter corresponded to a tissue stiffness range of 32.4 MPa to 50 Pa at 60 Hz. The broad bandwidth was selected so that any possible wavelength change caused by ablation could be included for calculation, while other wave energy, such as background motion and noise that did not fall into the bandwidth, would be excluded from the calculation. In the elastogram of the last

posttreatment MRE scan (the 6-minute scan indicated below), 4-5 same-sized regions of interest (ROIs) were drawn in the ablation region while avoiding the location of the laser applicator (the wave source). The same ROIs were copied and pasted onto the elastograms from the other time points. The ROIs contained 14-48 pixels for different pigs. The average stiffness in each ROI was recorded at the different time points before, during and after the laser treatment for statistical analysis.

Protocol for in vivo Laser Ablation and MRI/MRE scans

It was known from a previous study that 2-min, 15-W, 980-nm laser ablation (1,500 J) causes tissue death in porcine liver (2), so that was used as the lethal dose in this study. Other lower laser doses (2 min at 4.5 W and 2 min at 7.5 W) were used to investigate the stiffness changes that occur during nonlethal laser ablations. The laser applicator placement in the porcine liver, the laser ablation procedure and the MRI/MRE scans were performed in the following manner.

1. At first, a small skin nick (~3mm) was made close to the porcine liver, followed by introduction of a 14-gauge, 14-cm long, Teflon catheter (Abbocath-T, Hospira, Sligo, Ireland) with a rigid titanium trochar (Visualase Inc., Houston, Texas) to a desired region of the liver under the guidance of MRI. The imaging parameters for MRI guidance were the following: fast spin echo sequence, FOV = 27-38 cm, matrix = 320×224 , TR = 3000-5000 ms, TE = 103.2 ms, slice thickness = 3.5 mm, slice number = 13-70, flip angle = 90 degrees, NEX = 1, bandwidth = 15.63 kHz.
2. After placement of the catheter, the trochar was removed and replaced with the laser applicator. The Teflon catheter was then pulled back over the shaft of the laser applicator to unsheath the laser applicator in the porcine liver. At this point, with the laser applicator in the liver, the animals were prepared for the laser ablation and MRE scans.
3. Pigs #1, #2 and #5 had one 2-minute laser ablation at 15 W at one location in the liver. One pretreatment MRE scan was performed to get a baseline elastogram before the laser ablation, while three posttreatment MRE scans were performed 2, 4 and 6 minutes after the laser ablation.
4. Pig #3 had a 2-minute laser ablation at 4.5 W, and then 8 minutes later had another 2-minute ablation at 15 W all at one location in the liver. At a different location in the liver, Pig #3 also had a set of 2-minute ablations at 7.5 W and 15 W separated by 8 minutes. Pig #4 had 2-minute laser ablations at 7.5 W and 15 W at one location in the liver, separated by 8 minutes.
5. Before each laser delivery, one pretreatment MRE scan was performed as a baseline measurement. Three intratreatment MRE scans (30 seconds each) were performed 0, 40 and 80 seconds into each 2-minute laser ablation while the ablation was still going on. After the laser delivery was finished, three MRE scans were performed within 2, 4 and 6 minutes after treatment.
6. After all the MRE scans were done, contrast-enhanced (CE) MRI scans were performed before, immediately after, and 3 minutes after the injection of

gadolinium contrast (gadodiamide, 0.1 mmol/kg, Omniscan, GE Healthcare, Oslo, Norway) to visualize the ablated region. The imaging parameters were the following: fast gradient echo sequence, FOV = 27-38 cm, matrix = 256×224 , TR = 130 ms, TE = 2.5-3 ms, slice thickness = 5 mm, slice number = 30, flip angle = 70 degrees, NEX = 1, bandwidth = 31.25 kHz.

Statistical Analysis

Stiffness values measured with MRE are continuous values. Stiffness incremental changes (%) from baseline are continuous values. The stiffness increments are calculated as:

$$(E_t - E_0) / E_0 \times 100 \quad [2]$$

Where E_t is the stiffness measurement at a time point before, during or after the laser ablation, E_0 is the baseline measurement before the laser ablation. Time points are categorical values. Multiple comparisons were performed using the least significant difference (LSD) procedure and paired t-tests. A p-value less than 0.05 was considered statistically significant. JMP 9.0 (SAS, Cary, NC, USA) was used to perform the statistical analysis.

First, the three posttreatment stiffness increments from baseline using the lethal dose (2 min at 15 W on pigs # 1, 2 and 5) and a lower dose (2 min at 7.5 W on pigs # 3 and 4) laser ablation were analyzed to determine any significant changes from baseline. Second, all three posttreatment stiffness increments were pooled and analyzed for differences between the lethal dose and the lower dose ablation. Finally, for pigs #3 and #4, absolute stiffness values were compared to investigate the stiffness response before, during and after the laser ablation at different doses (2 min at 4.5 W, 2 min at 7.5 W and 2 min at 15 W).

Results

MRE images

MR elastography was successfully performed using the new acoustic inertial driver. Fig. 4 shows MRE images of the liver perpendicular to the axis of the laser applicator. Changes can be seen in the MRE wave images (Fig. 4a and Fig. 4b) and elastograms (Fig. 4d and Fig. 4e) before and after a 2-min, 15-W laser delivery. Profiles across the ablation region in the wave images and elastograms are shown in Fig. 4c and Fig. 4f, respectively. After the ablation, the vibration amplitude and the wavelength increased in the wave images. The primary direction of the displacement in the wave images was along the direction of the laser applicator due to the piston-like operation of the driver. In the slices perpendicular to the laser applicator, the laser applicator worked as a point source for generating a circular wave pattern that propagated from the point source through the surrounding tissue.

MRE images were also collected in slices parallel to the laser applicator (Fig. 5). Changes in the MRE wave images (Fig. 5a and Fig. 5b) and elastograms (Fig. 5d and Fig. 5e) before and after a 15-W laser ablation were observed. Profiles across the ablation region in the wave images and elastograms are shown in Fig. 5c and Fig. 5f, respectively. After the ablation, the vibration amplitude and the wavelength increased. The primary direction of the

displacement in the wave images was along the direction of the laser applicator. In the slices parallel to the laser applicator, the laser applicator worked as a line source for generating waves that are parallel to the applicator as they propagate through the surrounding tissue.

Posttreatment stiffness change after laser ablation using lethal and sublethal doses

Because the absolute baseline stiffness values were different for different pigs, incremental stiffness changes calculated as percent change from baseline were used to study the stiffness response after the laser ablations using the lethal dose (2 min at 15 W on pigs # 1, 2 and 5) and a lower dose (2 min at 7.5 W on pigs # 3 and 4). Multiple comparisons with LSD showed that none of the three posttreatment stiffnesses were statistically greater than the baseline after the laser ablations with the sublethal dose. However, after the laser ablations using the lethal dose, all of the posttreatment stiffnesses were significantly greater than the baseline stiffnesses ($p < 0.007$) and tended to be stiffer over time (Fig. 6a). The pooled posttreatment stiffness increments obtained within 6 minutes after the laser ablation using the lethal dose was statistically significantly greater than that after the lower dose ($p = 0.009$): mean [95% confident intervals] = 64.4% [32.8%, 96.0%] vs. 22.5% [16.3%, 28.6%] (Fig. 6b).

Stiffness changes during and after in vivo laser ablation

Stiffness changes were observed during and after the 2-min laser ablations at 7.5 W (50% power) and 8 minutes later using 15 W (100% power) in the liver of pig #4 (Fig. 7). When the 7.5-W laser delivery began, the stiffness increased continuously from the baseline, but was not statistically significantly different from baseline until the end of the laser delivery (time point d, 80 second, $p = 0.040$). After the 7.5-W laser delivery stopped, the stiffness remained elevated, but was not statistically significantly different from the baseline during this time. When the 15-W laser delivery began, the stiffness immediately increased and then decreased a little, but all three intratreatment stiffnesses were statistically significantly greater ($p < 0.013$) than the baseline value. After the 15-W laser delivery stopped, the stiffness continued to increase, and all 3 posttreatment stiffnesses were statistically significantly greater ($p < 0.003$) than the baseline value.

In another case where 2-min laser ablations were performed at 4.5 W (30% power) and 8 minutes later at 15 W (100% power) in a different subject (pig #3), stiffness changes were also observed during and after the laser delivery (Fig. 8). When the 4.5-W laser delivery began, the stiffness decreased from the baseline, but was not statistically significantly different. After the 4.5-W ablation stopped, the stiffness remained below the baseline value, but was not statistically significantly different from the baseline during the time of monitoring. When the 15-W laser delivery began, the stiffness immediately increased and then decreased a little, but none of the 3 intratreatment stiffnesses were statistically significantly greater than the baseline value. After the 15-W ablation stopped, the stiffness continued to increase, and all 3 posttreatment stiffness values were statistically significantly greater than the baseline value ($p < 0.0004$).

Contrast-enhanced MRI

Fig. 9 shows examples of the contrast-enhanced MR images (at the same window and level) of the ablated region created with the lethal dose laser ablation (2 min at 15 W) in the liver of pig #1. The lesion was hyperintense before the contrast injection and hypointense immediately after the contrast injection, which indicated the lack of blood circulation in the lethally ablated tissue. This phenomenon was consistent with a previous study where ablated lesions were created in porcine livers using the same lethal dose (2), and consistent with tumor necrosis observed in other studies (25-27).

Discussion

Inertial MRE driver and wave pattern

This preliminary study showed that this novel inertial driver design is capable of delivering shear wave motion into the liver via a laser ablation applicator, thus allowing for a targeted MRE analysis of the laser ablation region. While inserted in the liver, the laser applicator is easier to vibrate longitudinally (along the length of the applicator) than it is in the direction perpendicular to the applicator because the applicator is constrained by the liver parenchyma. This results in the displacement field created in the liver by the applicator being polarized primarily in the longitudinal direction. We observed a circular wave pattern emanating from the driver in the slices imaged perpendicular to the laser applicator and a linear wave pattern parallel to the applicator in the slices parallel to the laser applicator (Fig. 4 and 5), which indicated a 3D cylindrical wave was being created by the axially vibrating laser applicator. Because of this wave pattern and the partial wavelengths observed in the data, we used broadband 3D directional filters and a phase gradient inversion algorithm for the MRE stiffness calculations.

The setup of the inertial driver coupled with the laser applicator is flexible and efficient for operating in the narrow scanner bore. Ideally, the portion of the laser applicator outside of the abdominal cavity should be kept as straight as possible in order to transmit the vibrations from the inertial driver efficiently. However, the scanner bore is too small to accommodate this straight-applicator configuration in practice. In our experiment, the outside part of the applicator was bent about 90 degrees without kinking to fit in the scanner, yet the results showed that the driver was efficient enough to still transmit vibrations deep into the liver due to the waveguide effect. The flexible laser applicator worked as a waveguide to transmit the axial vibrations from the driver all the way down to the tip of the applicator; any vibration perpendicular to the catheter was constrained by the surrounding tissue. The benefit of the inertial driver is that the driver can be positioned around the original laser catheter system without impeding its performance. The system also avoids some of the disadvantages that a traditional external MRE driver could have, such as interference with the catheter and significant wave attenuation since the motion normally has to propagate from the external driver through the body and deep into the liver. However, it has been shown that when an external MRE driver was used to deliver minimally attenuating longitudinal waves at a significantly high frequency (500-1000 Hz) into tissue, only stiff lesions, and not the surrounding soft tissue, could be detected through mode conversion

(28). Therefore, high-frequency mode conversion MRE with an external driver could potentially be utilized for the detection and characterization of ablated lesions.

Stiffness response to in vivo laser ablation

As far as we know, these results represent the first results of MRE showing the stiffness response of the liver to in vivo laser ablation. In vivo, it is not well understood how tissue physiology and blood flow affect thermal ablation. During a thermal ablation, the heat is deposited and accumulated in the tissue while the blood flow and tissue heat conductivity cool the tissue. The two processes will eventually result in a thermodynamic equilibrium. When the thermal ablation stops, the tissue will be cooled by the surrounding tissue and blood flow. Our preliminary data indicated tissue stiffness changes in a very complicated way during laser ablations at different power levels, as seen in Fig. 6, 7 and 8. After laser ablation, the posttreatment MRE measurements in all pigs showed that only the previously known lethal dose for laser ablation (2 min at 15 W) caused a statistically significant increase in tissue stiffness compared to the baseline value. The stiffness after ablation continued to increase even during the cooling phase (Fig. 6), which suggested that the tissue underwent an irreversible cell denaturation during the 2-minute 15-W laser ablation.

A previous temperature-controlled ex vivo tissue study observed 3 different phases of stiffness change during the heating and cooling of tissue (10). The first phase was low-temperature ($<60^{\circ}\text{C}$) reversible cell denaturation, where the tissue stiffness decreased with heating and reversibly increased with cooling. The second phase was high-temperature ($60^{\circ}\text{C} - 75^{\circ}\text{C}$) irreversible cell denaturation, where stiffness irreversibly increased with heating. During the second phase if the heating was stopped at some point, then the stiffness would continue to increase during the cooling process, which is the start of the third phase. In the third phase, the stiffness of the denatured tissue decreased with heating and reversibly increased with cooling again back to the new baseline stiffness. However, the ex vivo study did not have data about stiffness changes due to temperatures beyond 75°C and was not able to consider the effects of physiology and blood flow on the ablation process that would only exist in vivo. While we did not expect this preliminary study to provide a full understanding of the in vivo thermo-biomechanical interaction that exists during thermal ablation, we did find that the MRE-based tissue stiffness measurements could provide useful information for tracking biomechanical changes that occur during in vivo laser thermal ablation. This stiffness measurement may provide important information about the success of thermal ablation treatments beyond what current MR thermometry and contrast-enhanced MR techniques can offer. Also, this approach could be used to monitor other kinds of liver lesion ablation such as irreversible electroporation (29-31).

Study limitations

This feasibility study was limited by the small sample size, the lack of simultaneously acquired temperature measurements, the lack of any pathology results and the lack of tumor data to assess feasibility in tissue more heterogeneous than normal hepatic tissue. In fact, temperature information could be extracted from the phase images acquired by a GRE-based MRE sequence in addition to the MRE stiffness information as the phase accumulation caused by the PRF shift is linearly superimposed on the phase accumulation due to the wave

motion and can be isolated with appropriate processing (32). Unfortunately, we used a spin-echo MRE sequence in the current study, where the phase accumulation caused by the PRF shift before and after the 180-degree refocusing RF pulse cancel each other out. We are developing a 3D GRE MRE sequence which may prove useful for measuring tissue stiffness and temperature simultaneously. Future studies with larger sample sizes, hepatic tumors, and simultaneous temperature-stiffness mapping may improve our understanding and knowledge of the relationship between thermal dose, cell denaturation and tissue stiffness changes during the course of in vivo thermal ablation.

Conclusions

A novel inertial MRE driver has been shown which is capable of providing in vivo vibrations of thermally ablated tissue without requiring any modification of the original ablation system or RF coils. The setup of the driver was easy and delivered adequate mechanical waves directly into the liver to the spot of tissue ablation. For the first time, this study demonstrated the feasibility of using MRE to measure tissue stiffness changes due to in vivo laser ablation; the stiffness of the ablated liver tissue increased significantly from baseline after ablation using a lethal dose, which reflected irreversible tissue denaturation processes and cell death. If confirmed through additional studies, this technology may become clinically important and useful for the monitoring of thermal ablations for the treatment of tumors.

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FIG. 1.

Components of the inertial driver and its configuration with the laser ablation catheter system. The middle picture is an enlarged version of the top one. The bottom picture shows the components of the inertial driver. 1- Symbol for the active driver. 2- Connector for the tube connected to the active driver. 3- Inertial driver. 4- Laser ablation applicator. 5- Female IV connector from laser source. 6- Male IV connector on the driver. 7- Female IV connector on the driver. 8- Saline cooling circulation tubes. 9- Acoustic cylinder chamber. 10- Fiber springs. 11- Piston. 12- Pressure-balance subchamber cover. 13- Active subchamber cover.

FIG. 2.

The configuration of the inertial MRE driver and the laser ablation catheter system on a pig. 1- Eight-channel RF torso coil array wrapped in plastic sheets for sterilization. 2- Pig under anesthesia. 3- IV connector on the driver for the laser source catheter, the counterpart IV connector is secured to the laser applicator (on the back of the inertial driver). 4- Inertial MRE driver. 5- Air tube that connects the inertial driver and the active MRE driver. 6- Magnet bore. 7- Medical tape holding the driver to the coil.

FIG. 3.

The spin-echo EPI MR elastography sequence. The period of the driver (Dr) was 16.67 ms (i.e., 60-Hz vibration frequency). Two bipolar motion-encoding gradients (MEGs, duration = 6.45 ms) were positioned before and after the 180-degree refocusing RF pulse. The distance between the two MEGs was 1.5 times the period of vibration (25 ms). In successive acquisitions, the polarity and direction of the MEGs alternated to measure motion in the positive and negative X, Y, and Z directions to measure all 3 components of the vector motion in the tissue. The spatial-spectral excitation pulse was used to excite only the water signal.

FIG. 4.

MRE images before and after in vivo laser ablation in a porcine liver. The laser was turned on at 15 W for 2 minutes. The imaging slices were perpendicular to the laser applicator and covered the potential region of the lesion. (a) and (b): MRE phase/wave images before and 2 min after the ablation. The displacement direction was parallel to the laser applicator. Displacements in the other 2 directions were much smaller (not shown). (c): Profiles of the tissue displacement across the lesion before and after ablation. (d) and (e): The corresponding MR elastograms before and after the ablation. (f): Profiles of the stiffness across the lesion before and after ablation.

FIG. 5.

MRE images before and after in vivo laser ablation in a porcine liver. The laser was turned on at 15 W for 2 minutes. The imaging slices were parallel to the laser applicator and covered the region of the potential lesion. (a) and (b): MRE phase/wave images before and 2 min after the ablation with the motion-encoding direction vertical in these images. The dominant motion was parallel to the laser applicator and the other 2 directions were much smaller (not shown). (c): Profiles of wave displacement across the lesion before and after ablation. (d) and (e): The corresponding MR elastograms before and after the ablation. (f): Profiles of the stiffness across the lesion before and after ablation.

FIG. 6.

Posttreatment stiffness changes. (a) Stiffness increment (%) from baseline measured at different time points (2, 4 and 6 minutes) after laser ablation using the lethal dose (2 min at 15 W) and a lower dose (2 min at 7.5 W). Multiple comparisons showed that the three stiffness increments after the 7.5-W ablation were not different from baseline. However, the stiffness was significantly elevated at each of the time points after the 2-min 15-W laser delivery (2 min: $p = 0.007$, 4 min: $p = 0.0003$, 6 min: $p = 0.0002$). (b) The stiffness increase (64.4% [32.8%, 96.0%]) after the lethal dose was significantly greater than that after the lower dose ablation (22.5% [16.3%, 28.6%]; $p = 0.009$).

FIG. 7.

Plots of stiffness measured in the ablation region at different time points before, during and after in vivo laser ablation at 7.5 W (50% power) and 15 W (100% power). The laser was turned on for 2 minutes and then was turned off twice during the experiment. Time point (a) is baseline before ablation. Time points (b-d) are 0, 40, and 80 sec, respectively, from the beginning of the 7.5-W laser delivery. Time points (e-g) are 2, 4, and 6 min after the 7.5-W ablation stopped. Time points (h-j) are 0, 40, and 80 sec from the beginning of the 15-W laser delivery. Time points (k-m) are 2, 4, and 6 min after the 15-W ablation stopped. Multiple comparisons showed that the stiffnesses measured at time points d ($p = 0.040$), h ($p = 0.001$), i ($p = 0.013$), j ($p = 0.007$), k ($p = 0.003$), l ($p = 0.002$), and m ($p = 0.001$) were significantly larger than at baseline.

FIG. 8.

Plots of stiffness at different time points before, during and after laser delivery at 4.5 W (30% power) and 15 W (100% power). The laser was turned on for 2 minutes and then was turned off twice during the experiment. Time point (a) is baseline before ablation. Time points (b-d) are 0, 40, and 80 sec, respectively, from the beginning of the 4.5-W laser power ablation. Time points (e-g) are 2, 4, and 6 min after the 4.5-W ablation stopped. Time points (h-j) are 0, 40, and 80 sec from the beginning of the 15-W laser ablation. Time points (k-m) are 2, 4, and 6 min after the 15-W ablation stopped. Multiple comparisons showed that only the stiffnesses measured at time points k ($p = 0.0004$), l ($p < 0.0001$), and m ($p < 0.0001$) were significantly greater than the baseline value.

FIG.9.

Examples of contrast-enhanced T1-weighted images of the lesion created in a porcine liver using the lethal dose for laser ablation (2 min at 15 W). The lesion was hyperintense before the contrast injection (a) and hypointense immediately after the contrast injection (b), which indicated the lack of blood circulation in the lethally ablated tissue.