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Enhanced-heating effect during photoacoustic imaging-guided high-intensity focused ultrasound

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Photoacoustic imaging (PAI) technique has been used to monitor thermal lesion formation during high-intensity focused ultrasound (HIFU) treatment. While previous studies focused on photoacoustic detection of changes in temperature during HIFU treatment, we report an enhanced-heating effect when PAI is used to monitor HIFU treatment. We found that the temperature induced by HIFU could be significantly enhanced when the diagnostic laser system for photoacoustic detection was operating during HIFU treatment. This finding demonstrates an advantage of using PAI to guide HIFU therapy. © *2011 American Institute of Physics*. [doi:10.1063/1.3669441]

High-intensity focused ultrasound (HIFU) is a truly non-invasive thermal-ablation technique that avoids insertion of probes into targeted tissue. HIFU works through rapidly depositing high-intensity ultrasound energy into a small region to induce cell death, primarily by hyperthermia, after high-intensity ultrasound is absorbed by soft tissue.[1–4] HIFU has been demonstrated in animal models of cancer and in limited clinical studies in the United States.[5]

To perform HIFU treatment non-invasively, an imaging technique is required. Photoacoustic imaging (PAI) is one of the imaging modalities[6,7] currently being studied to monitor HIFU therapy. PAI is a promising non-ionizing and non-invasive biomedical imaging technique based on the photoacoustic effect[6] with simultaneous sensitive optical contrast and high ultrasonic resolution. This imaging technique has been applied for detecting early cancers[6,8,9] and monitoring thermal lesions generated by HIFU or other means.[10,11]

In this study, we report an enhanced-heating effect during PAI-guided HIFU therapy. Further study shows that this enhancement is due to the nucleation of cavitation during the PAI-guided HIFU process. This finding demonstrates another advantage of PAI-guided HIFU. The technique will be able to facilitate the HIFU treatment process by enhancing heating at a relatively low HIFU intensity, and without the injection of micro- or nano-size particles into the blood stream.

Figure 1 shows the schematic of the PAI-guided HIFU system. A tunable optical parameter oscillator (OPO) laser (Surelite OPO PLUS, Continuum, CA), pumped by a Q-switched Nd:YAG laser with a pulse repetition rate of 10 Hz, was employed as the irradiation source. The generated laser pulses were directed by a couple of prisms and then formed into a ring-shaped illumination by a conical lens. A condenser lens was used to make the laser light confocal with a 5-MHz HIFU transducer (SU-108-013, Sonic Concepts, WA) (35 mm focal length), which was mounted in the middle of the condenser lens. A 10-MHz focused ultrasonic transducer (V315, Olympus NDT, MA) (37.5 mm focal length; 70% −6-dB fractional bandwidth), which acted as a photoacoustic (PA) signal detector, was aligned to be confocal with the HIFU transducer and laser light prior to the measurements. The 10-MHz PA detector can also be used as a passive cavitation detector (PCD) to detect cavitation events by sensing the broadband acoustic emissions generated by the collapse of bubbles during HIFU ablation. Both 10-MHz and 5-MHz transducers were immersed in a water tank, which had a window on the bottom. The window was sealed with a polyethylene membrane. Samples coated with ultrasound gels were laid on the other side of the membrane. A 50-μm diameter, T-type thermocouple was inserted into the tissue sample through a needle and placed 0.5 mm away from the focal point of the HIFU transducer to measure the temperature rise during the HIFU ablation. In all experiments, beef kidney samples were used. The laser intensity on the tissue surface was measured to be 18 mJ/cm^2.

During the experiment, a function generator (HP33250A, Agilent Technologies, CA) was used to provide the source signals to drive the HIFU transducer. The source signals were first amplified by a 50-dB radio frequency amplifier (350L, ENI Technology, Inc., NY) and then sent to the HIFU transducer in order to induce thermal lesions in the sample. During PAI-guided HIFU, burst HIFU waves with 95% duty cycle were transmitted by the HIFU transducer with a repetition rate of 5 Hz in order to avoid signal interference from HIFU on PAI. Therefore, a clear PA signal could be collected by the 10-MHz transducer at 5 Hz when the HIFU waves were off. Because the laser system was running at 10 Hz, 50% of the laser shots illuminated the tissue sample when HIFU was running. During the PAI-guided HIFU model, signals from these 50% of the laser shots were discarded due to the strong interference between the HIFU waves and the PA signals.

During temperature measurement, we found that there was a temperature enhancement when the laser system was operating (PAI was on) during HIFU ablation. Figure 2 shows an example of the measured average temperature with standard deviation (STD) from five HIFU sonications through the T-type thermocouple. In these measurements, HIFU focal intensity level was 1000 W/cm^2, and the

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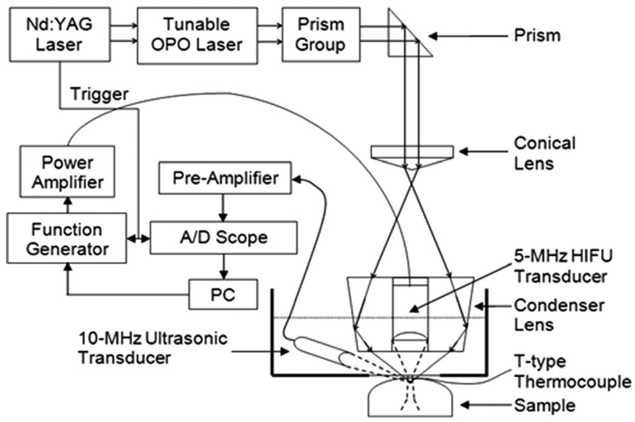

FIG. 1. System schematic.

sonication duration was 20 s. Although no temperature rise could be observed when the PAI system was operating alone, (i.e., HIFU exposure was stopped), there was clearly a temperature enhancement of ∼15 °C when the PAI system was operating during HIFU exposure. This result indicates that the HIFU heating is significantly enhanced by the assistance of laser light.

After HIFU exposure, the tissue sample was cut open, and a photograph of the lesions was taken. Figure 3 shows a photograph of HIFU lesions inside the tissue sample. Each HIFU lesion was induced by a single HIFU sonication. We can clearly observe that the sizes of the HIFU lesions are bigger when the PAI system is on in comparison with that of when the PAI system is off. In addition, from one example, the measured lesion volumes were 3.52 mm^3 (with the laser on) and 1.43 mm^3 (with the laser off), respectively. This result shows great enhancement in HIFU ablation due to the presence of laser light. The histological results further confirm that HIFU heating is enhanced when PAI and HIFU systems are operating concurrently. Additionally, empty cavities were observed in the central region of the HIFU lesions and suggested that cavitation might have occurred during the heating process when the laser system concurrently illuminated the sample.

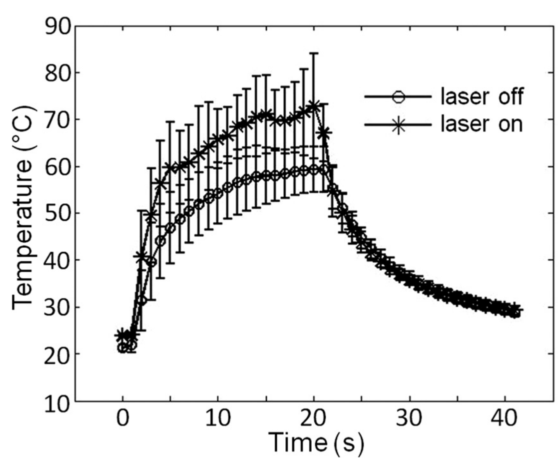

FIG. 2. Temperature enhancement during PAI-guided HIFU. Lines with stars and circles represent the temperature measured by a T-type thermocouple during HIFU exposure when PAI system was on and off, respectively.

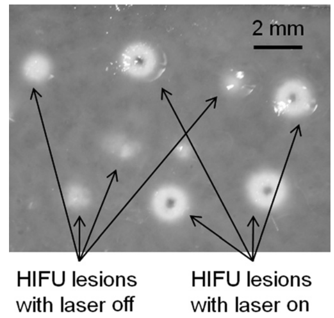

FIG. 3. Photograph of HIFU lesions inside a tissue sample after HIFU exposure.

To further confirm the occurrence of cavitation and explain the enhanced heating during PAI-guided HIFU, the 10-MHz photoacoustic detector was used as a PCD (Ref. 12) to detect broadband acoustic emission from the HIFU focal zone. During this test, HIFU was running continuously with different focal intensities and sonication duration of 20 s, and PCD signals were collected with the laser system on and off. The PCD received two types of signals. The first type of signals was sound scattered by the tissue sample, which consisted of primary 5-MHz waves from HIFU. The second type of signals was sound emission from cavitation, which consisted of higher harmonics of the 5-MHz waves. In order to separate the emissions of cavitation from the 5 MHz HIFU waves, a 10-MHz high-pass filter was used. With this system, an abrupt increase in higher harmonics of the 5-MHz waves could appear in the signal spectra when cavitation occurred. For data collection, detected PCD time-domain signals were amplified by a pre-amplifier (5072PR, Olympus-NDT, MA), captured by the GageScope (CS21G8-256MSn Gage, IL), and then downloaded to a personal computer. At each HIFU intensity level, five HIFU lesions were induced on the sample by five HIFU sonications. The number of HIFU lesions with acoustic cavitation at different HIFU intensity levels was counted, and the results are shown in Table I. It is shown that acoustic cavitation occurred at a lower HIFU intensity (800 W/cm^2) with the laser illumination. However, without the laser illumination, cavitation would not occur until the HIFU intensity reached 1700 W/cm^2. Cavitation has been demonstrated to enhance HIFU heating by increasing the effective ultrasound absorption.[12,13] Therefore, the HIFU heating enhancement at a relatively low HIFU intensity when the PAI system was operating in this study was due to the induced acoustic cavitation in soft tissue.

TABLE I. Number of HIFU lesions with cavitation from five HIFU sonications at each HIFU intensity level with laser on and off.

Laser on		Laser off	
HIFU intensity (W/cm^2)	Number of lesions with cavitation	HIFU intensity (W/cm^2)	Number of lesions with cavitation
600	0	1500	0
700	0	1600	0
800	3	1700	4
900	5	1800	5
1000	5	1900	5

While the application of HIFU therapy is expanding, the concerns related to HIFU treatment include prolonged treatment time for large tumors and skin burns. To reduce the prolonged treatment, it is necessary to enhance the heating induced by HIFU exposure. In general, to enhance HIFU heating, we can simply employ ultrasound waves with higher intensity levels. However, high-power output will induce severe skin burns and also present great challenges for the design of the HIFU system, including the design of transducers and the electronic circuits. An alternative to very high ultrasound intensity is to increase the local ultrasound absorption so that more ultrasound energy can be deposited in the local region at a relatively low HIFU intensity level. The introduction of cavitation has been investigated as a mechanism to increase the local ultrasound absorption and enhance heating in HIFU.[12,13] Cavitation has been shown to yield elevated heating rates above those produced by classical absorption in tissue[14,15] and can provide a means for improving the efficacy of HIFU treatment. However, preexisting nucleation sites for cavitation are not omnipresent in most tissues *in vivo*. Either ultrasound contrast agents (UCA)[16–18] or nanoparticles have been studied as methods of delivering nuclei into the target region.[13] The use of UCA and nanoparticles, however, requires the systematic injection of foreign particles into the blood stream and would cause much concern regarding the toxicity, efficiency, etc.

This letter reports a particle-free, photo-enhanced HIFU heating method with the utilization of a diagnostic laser system. HIFU heating was enhanced through inducing cavitation in soft tissue by the combination of laser light and ultrasound. In comparison with the other means to enhance HIFU heating, the current technique does not involve the use of any nanoparticles or UCA. The other advantage of the current technique is that a diagnostic laser system for PAI can be used. Therefore, the heating enhancement can be easily achieved while the treatment process is monitored by PAI.

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