行政院國家科學委員會專題研究計畫　成果報告

高能聚焦超音波於組織內產生焦班之閥值、形變與偏移狀況研究

計畫類別：個別型計畫
計畫編號：NSC93-2320-B-002-097-
執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
執行單位：國立臺灣大學醫學院復健科

計畫主持人：陳文翔
共同主持人：林文澧
計畫參與人員：童耀生，吳志清，劉浩禮，朱&#22531；誠，陳文翔，林文澧

報告類型：精簡報告
報告附件：出席國際會議研究心得報告及發表論文
處理方式：本計畫可公開查詢

中　華　民　國 94 年 8 月 29 日

The Investigation of Contrast-Agent Enhanced Ultrasound Thermal Effect

Y.S. Tung, C.C. Wu, H.L. Liu, K.C. Ju, W.S. Chen* and W.L. Lin

National Taiwan University, Taipei, Taiwan

ABSTRACT

In recent years, high intensity focused ultrasound (HIFU) was shown to have promising effect on ablating both malignant and benign tumors. Despite its unique advantages such as minimal invasiveness and radiation free, the size of the ablation lesion is small and thus the duration for complete tumor ablation is usually too long. In this study, the effect of using ultrasound contrast agent (UCA) to enhance the ultrasound thermal effect, and thus enlarge the lesion size, was studied. Different concentration of UCA ranging from 0% (control), 0.001% to 0.1% (v/v) was mixed evenly with polyacrylamide gel phantoms containing egg white as a temperature indicator. A 1.85-MHz HIFU transducer was used to form thermal lesions inside the 2 cm*2 cm*4 cm phantoms. For the electric power of 50W and 70W, 'cigar' and 'tadpole' shaped lesions were formed inside the control phantoms, respectively. The volume enlargement ratio (VER), defined as the ratio of volume formed in experimental groups (adding UCA or increasing power) to the volume of controlled the sample, was used to evaluate the effect of UCA on thermal ablation. When the concentrations of UCA were 0.001%, 0.005%, 0.01% and 0.015%, the VER were 10.58, 39.11, 55.08, 64.65 at 50W, and 2.27, 5.29, 12.09, 10.61 at 70W, respectively. The administration of UCA significantly increased the lesion size up to 65 times!

UCA also reduced the necessary power to form a lesion of a certain size. For example, 0.001% of UCA at 50W produced a lesion close to controls at 70W in size. Same concentration of UCA at 70W formed lesions equivalent in size for phantoms without UCA at 100W. 30% reduction of the power level was achieved. However, the shift of the most heating position also increased with the concentration of UCA. investigated. For example, at UCA concentration of 0.015%, the shift could be 2.16 cm from the geometric focus. For concentration higher than 0.1%, the lesion was basically formed at the surface of the phantom.

The mechanism of lesion formation and transformation was also investigated. For samples without UCA insonified by high intensity ultrasound, the tadpole-shaped lesion was formed due to boiling effect. The larger lesion formed in samples with UCA was because of the generation of inertial cavitation and bubbles which scattered sound waves and evenly distributed energy absorption in a larger volume.

In conclusion, UCA could increase the size of lesion by enhancing scattering. However, the most heating center also moved toward the transducer when UCA concentration increased. A lower concentration (0.001%) of UCA and lower power (50 W) were enough to produce a lesion 39 times larger, and produced a minimal lesion movement (0.65 cm). *Corresponding author: wenshiang@ha.mc.ntu.edu.tw

INTRODUCTION

One of the major disadvantages of HIFU ablation is the small lesion size and thus the long treatment duration. An efficient method to increase the size of a lesion and reduce the time of ablation is thus attractive. Recent research shows that the presence of bubbles near the HIFU focus not only could result in higher temperature but also make the scope of the high temperature area larger (Fujishiro et al. 1998). It was found that the admission of contrast microbubbles could effectively reduce the treatment time and also the driving intensity (Binh et al 2003).

The objective of this study is to investigate the effects of microbubbles, such as UCA, on the formation and transformation of thermal lesions inside tissue phantoms, and the dominating mechanisms.

MATERIALS AND METHODS

HIFU system. A schematic representation of the experimental setup was shown in Fig. 1. A single element, focused, piezoelectric transducer (Imasonic, Besançon, France) was used as the source of high-intensity ultrasound waves. The diameter of the element was 10 cm, the curvature was 12.5 cm, the driving frequency was 1.85 MHz, and the efficiency was 75.5%. Using extrapolation, the focal pressure in the water was estimated to be 8.71 MPa and 10.28 MPa for the electrical power of 50 W and 70 W. Experiments were performed in a internal diameter 24 × 21 × 15 cm acrylic tank containing degas water at 37℃. RF signal was supplied by a function generator (Agilent 33120A, Palo Alto, CA USA) and the output was amplified by the RF power amplifier (Amplifier Research 150A250, Souderton PA, USA). Incident and reflected power were measured using a power meter (Bird 4421).

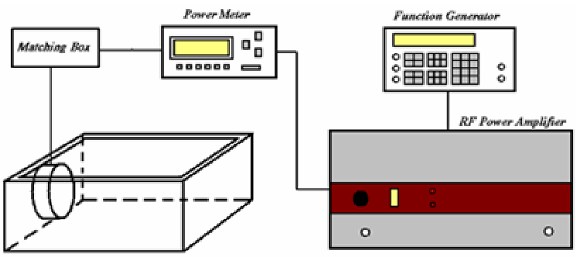


Fig. 1. HIFU device and the experimental setup.

Phantom components. The transparent tissue phantoms used in the current study was made of acrylamide/bis gel according to the report of Takegami et al. (2004). The components of the phantom are listed in Table 1.

Ultrasound contrast agent, The contrast agent used in the research was Definity®. In order to make the contrast agent in the phantom evenly, the contrast agent was added and shaken before the phantom was set.

Table 1. The composition of Acrylamide phantom

Component	Volume (ml)
Egg White	30
Degas-Water	40
Acrylamide/Bis, 19:1, 40% Solution	24.8
10% v/v APS (Ammonium Persulfate)	0.5
TEMED (N,N,N',N'-Tetramethylethylenediamine)	0.2
Glycerol, Anhydrous	4.5
Total	100

Concentration of UCA. The concentration of UCA in the phantom was volume percentage (v/v). To make a phantom with 0.1% of UCA, 0.1 mL of UCA was drawn from the vial and added directly to the 100 mL of the mixture in Table 1. The 0.1% concentration was equivalent to 1.2 × 10^4 bubbles/mm^3.

Experimental series. The distance between the focal point and the phantom surface was 2.5 cm. The total heating time was 30 s in every experiment.

Series 1, Energy dependence. The sizes and shapes of the thermal lesions formed at different electrical powers, 50, 60, 70, 80, 90, and 100 W, were recorded continuously.

Series 2, UCA concentration. Different concentration of UCA ranging from 0% (control), 0.001% , 0.005%, 0.01%, 0.015%, 0.025%, 0.05%, 0.075%, and 0.1% (v/v) was mixed evenly inside the polyacrylamide gel phantoms. The relationship between the UCA concentrations and lesion shapes, volumes and the VER were compared at both 50 and 70 W of electrical powers. The effect of power reduction after the addition of UCA was also estimated. Moreover, the forward shift of a lesion was also investigated.

Series 3, Mechanisms of lesion formation. To understand the mechanisms of lesion formation and transformation, the growing process with and without UCA at 70W was monitored continuously. The internal temperature change was also monitored using two inserted thermocouples at 2.5 cm (focus) and 1.25 cm (half way between the focus and surface) from the surface of the phantom. The concentration of UCA was 0.005% for all the series 3 experiments.

RESULTS

Series 1, Energy dependence.

The results of the series 1 experiments are shown in Fig. 2. The lesion was cigar-shaped when the power was 50 and 60 W. Once the electrical power was larger than 70 W, tadpole-shaped lesions were formed. The VER values at 50 and 70 W are shown in table 2. The mean volumes increased linearly with the ultrasound powers.

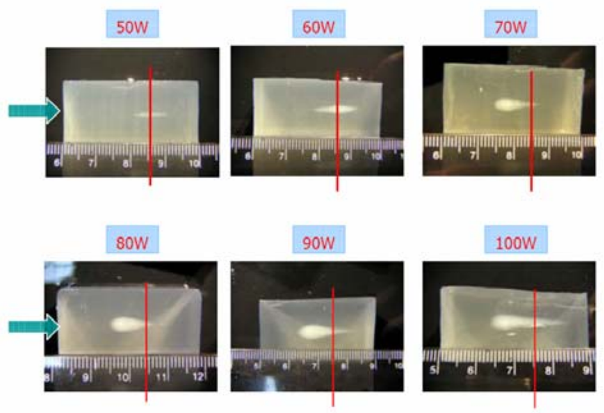


Fig. 2. Lesions formed at different electrical powers. The total heating time was 30s. The vertical red lines represent the focal plane. The arrow was the incident sonication direction.

Table 2. The VER of different electrical powers. The controls were the lesion formed at (a) 50 and (b) 70 W. No UCA was added.

(a) 50 W control					
Power (W)	60	70	8 0	90	100
VER mean	4.692	11.830	15.732	22.003	26.112
(b) 70 W control					

Power (W)	50	60	80	90	100
VER mean	0.085	0.397	1.335	1.859	2.207

Series 2, UCA concentration.

The relation between the UCA concentration and lesion shape at 50 and 70 W are shown in Fig.3. The lesion size and the forward shift of lesions increased with the UCA concentration. Once the concentration was greater than 0.1%, the lesion was formed near the surface of the phantom. The VER values of different concentration of UCA compared to controls at (a) 50 and (b) 70 W are shown in Table 3. The administration of UCA increased the lesion size up to 65 times!

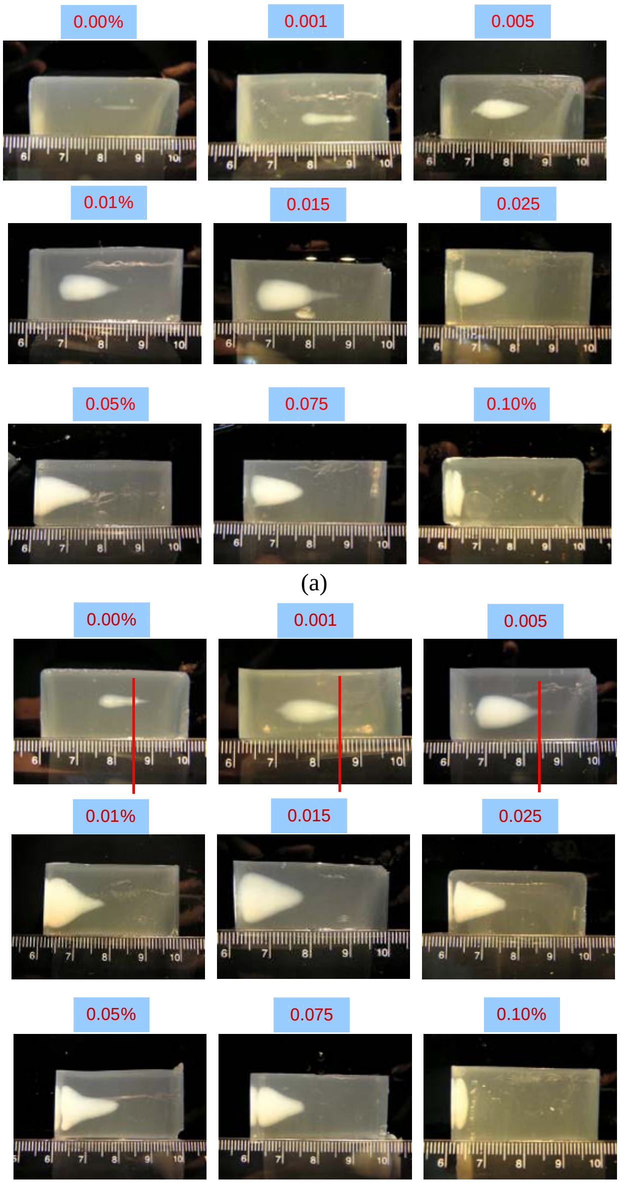


Fig. 3. The lesions formed after introducing UCA of differentt concentrations at (a) 50 and (b) 70 W. The total heating time was 30 s, and the transducer was placed in the left side.

UCA also reduce the necessary power to form a lesion of a certain size. The effect of reducing driving power of using UCA can be estimated from Table 2 and Table 3. For example, 0.001% of UCA at 50W produce a lesion close to controls at 70 W in size. Same concentration of UCA at 70 W formed lesions equivalent in size for phantoms without UCA at 100 W, 30% reduction of the power level was achieved.

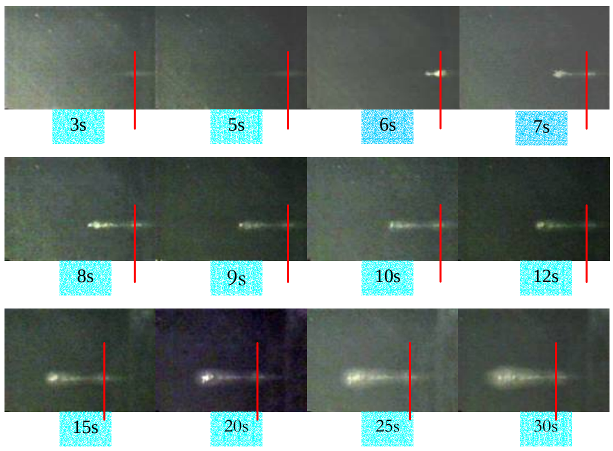
Table 3. The VER values of different concentrations of UCA relative to control lesions formed at (a) 50 and (b) 70 W without the addition of UCA.

(a) 50 W control					
Concentration	0.000%	0.001%	0.005%	0.010%	0.015%
VER mean	0.007	11.879	40.647	55.489	65.137
(b) 70 W control					
Concentration	0.000%	0.001%	0.005%	0.010%	0.015%
VER mean	0.112	2.342	5.687	11.504	10.470

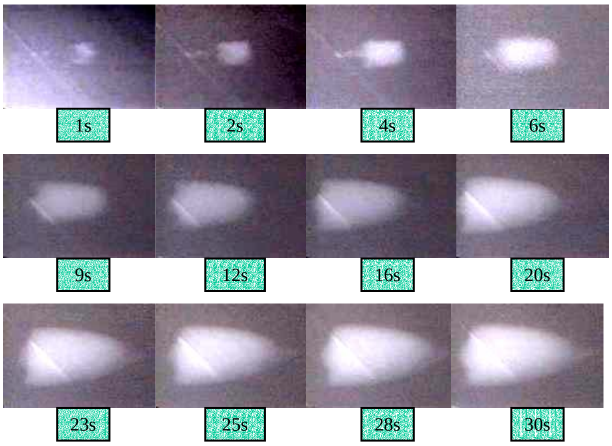
The relation between the concentrations of UCA and the forward shift of a lesion at (a) 50 and (b) 70 W are shown in Table 4. The forward shift of a lesion increased with the concentrations of UCA. At the same concentration of UCA, the forward shift of a lesion at 70 W is larger than that at 50 W.

Table 4. The forward shift of a lesion after adding different concentrations of UCA at (a) 50 and (b) 70 W

(a) 50 W control					
Concentration	0.000%	0.001%	0.005%	0.010%	0.015%
Mean (cm)	0.104	0.649	0.999	1.322	1.505
(b) 70 W control					
Concentration	0.000%	0.001%	0.005%	0.010%	0.015%
Mean (cm)	0.645	0.804	1.379	2.006	2.159



(a)



(b)

Fig. 4. The lesion growing process at 70 W ablation, the red line is the focal plane. (a) control group. (b) experimental group with 0.005% of UCA. The transducer is in the left side.

Series 3, Mechanisms of lesion formation.

The lesion growing process of controls and experimental groups (0.005% UCA) at 70 W is shown in Fig. 4a and 4b, respectively. In Fig. 4a, a sudden flash similar to a "explosion" at the focus is seen at the 6 s. From this moment, the lesion grew toward the transducer in a rapid pace initially, but the speed slowed until the 12 s, when the lesion began to grow laterally. A tadpole-shaped lesion was formed at the end of a 30 s sonication. Figure 4b shows the ablation process for a phantom mixing with 0.005% UCA. The lesion is larger than the control (Fig. 4a) and no explosion was seen.

The temperature changes during the lesion formation process of the control are shown in Fig. 5. At the HIFU focus (70 W), the temperature rose rapidly to 101 ℃, but dropped to 90℃ after the 'explosion'. Thereafter, the temperature decayed exponentially. No sudden temperature change was seen for the thermocouple in between the phantom surface and the focus, and in phantoms mixed with UCA.

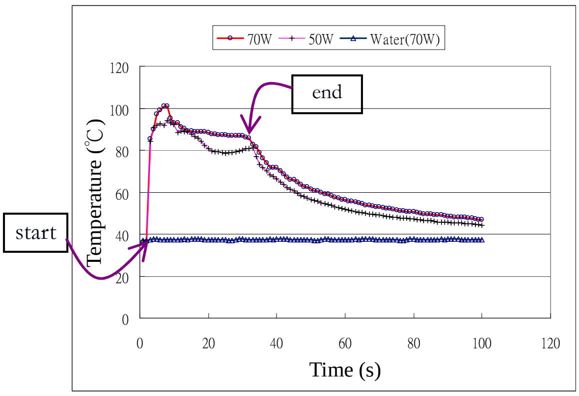


Fig. 5. The temperature change in phantoms with UCA insonified by ultrasound at electrical powers of 50 and 70 W.

DISCUSSIONS AND CONCLUSIONS

These results clearly demonstrated that UCA significantly increased the size of lesion under HIFU treatment. However, lesions also moved away from the expected focus when the concentration of UCA increased. The relation between concentrations and VER values or displacement were shown. Compared with controls (no UCA), the addition of UCA could decrease the driving power to create lesions of a certain size.

The lesion size and the forward shift of a lesion increased with the UCA concentration. The higher the UCA concentration, the larger the attenuation coefficient was, which made the size and the forward shift increase. Once the concentration of the UCA was greater than 0.1%, the lesion is basically formed at the surface of the phantom since most of the incident ultrasound waves were attenuated at the surface.

At 70 W, the shift of lesions was larger than that at 50 W for the same UCA concentration. It was probably because the increase of the incident pressure produced larger bubbles and elevated the attenuation coefficient (Quan, C. et al, 2002), which forced the sound energy to be attenuated faster.

Series 3 experiments explored the possible mechanisms of lesion formation at various conditions. Without the presence of UCA, the cigar-shaped lesions were formed by thermal effect, while the tadpole-shaped lesions were related to boiling. The coincidence of the "flash" (Fig. 4) event and the boiling temperature (Fig. 5) suggested heat accumulation and boiling effect. Large vapor bubbles reflected sound waves and forced lesions to shift forward. However, with UCA, inertial cavitation might be the dominant effect to create large lesions.

REFERENCES

Binh C. Tran, et al. (2003), "Microbubble-Enhanced Cavitation for Noninvasive Ultrasound Surgery". IEEE Ultrason., Ferroelect., Freq. Contr., 50(10): 1296-1304.

Fujishiro, S., M. Mitsumori, et al. (1998), "Increased heating efficiency of hyperthermia using an ultrasound contrast agent: a phantom study." Int J Hyperthermia 14(5): 495-502.Crum LA, Hansen GM (1982), "Growth of air bubbles in tissue by rectified diffusion." Phys. Med. Biol., 27(3):413-7.

Quan, C. et al. (2002), "Pressure-dependent attenuation in ultrasound contrast agents." Ultrasound Med Biol 28(8):1041-1051

Takegami, K., K. Y., Kaneko Y., Watanabe T, Maruyama T, Matsumoto Y (2004)," Polyacrylamide gel containing egg white as new model for irradiation experiments using focused ultrasound" Ultrasound Med Biol 30(10): 1419-1422.