Showa Univ J Med Sci **32**(1), 1～9, March 2020

Original

Development of a High-intensity Focused Ultrasound Exposure Device for Reducing Skin Burn Risk

Shogo NISHII[1)], Kohei SEO*[1)], Aleksander Tatsuya IZDEBSKI[1)], Miki KUSHIMA[2)], Ryo TAKAGI[3)], Shin YOSHIZAWA[4)], Shin-ichiro UMEMURA[4)], Kiyotake ICHIZUKA[1)] and Akihiko SEKIZAWA[1)]

Abstract: High-intensity focused ultrasound (HIFU) can non-invasively irradiate inside the body. However, when used to treat fetuses, it can cause thermal burns of the mother's abdominal wall at the skin interface. This study was carried out to determine whether a modified HIFU transducer enabling split-aperture irradiation can prevent thermal burns. Two HIFU transducers were compared: a conventional transducer using full-aperture irradiation and a modified transducer using split-aperture irradiation. The modified transducer was divided into six sectors for split-aperture irradiation and had a larger surface area and a smaller F number (focal length / aperture diameter) than the conventional transducer. HIFU was delivered to eight sites on the left and right leg of a three-month-old baby pig under general anesthesia, and the sites were assessed for thermal burning by two or more dermatologists. The same person performed all irradiations. Full-aperture irradiation with the conventional transducer caused deep dermal burns at all target sites, while split-aperture irradiation with the modified transducer caused only epidermal burns or superficial dermal burns. Split-aperture irradiation using a modified HIFU transducer with six sectors and a smaller F number reduces the severity of skin burns, and thus will improve the safety of HIFU therapy.

Key words: high-intensity focused ultrasound, exposure protocol, burn injuries

Introduction

Although improvements in prenatal diagnosis have increased the likelihood of identifying abnormalities in fetuses, there are a limited number of effective strategies for treating the abnormalities, particularly in a non-invasive manner. To improve this situation, various new medical devices have been and are being developed, along with advanced control methods. Before using these devices in the clinical setting, the possibility of damage to the patient should be considered and assessed. Because many fetal treatments involve the insertion of a device into the uterus from outside the body, treatment-related complications and infections can occur.

[1)] *Department of Obstetrics and Gynecology, Showa University School of Medicine,* 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
[2)] *Department of Pathology and Laboratory Medicine, Showa University Koto Toyosu Hospital*
[3)] *Theranostic Device Research Group, The National Institute of Advanced Industrial Science and Technology*
[4)] *Graduate School of Biomedical Engineering, Tohoku University*
* To whom corresponding should be addressed.

High-intensity focused ultrasound (HIFU) treatment uses a powerful ultrasonic wave from a transmission source (transducer). Ultrasonic energy is concentrated in the vicinity of a focal point in the target tissue, converted to heat, and thermally coagulates the tissue[1, 2]. HIFU has been used for several categories of treatment, including the treatment of solid cancers, such as liver and prostate cancers[3–6]. We used HIFU to treat twin reversed arterial perfusion sequence for the first time in 2013[7, 8]. The treatment had little influence on the intervening tissues outside the area of focus although the HIFU exposure duration had to be limited in order to avoid a possible skin burn of the mother. In fact, skin burn injuries have been observed in 0.29% of 27,053 patients who received HIFU treatment for benign uterine diseases[9].

HIFU can non-invasively irradiate the inside of the body, rendering it suitable for fetal treatment. The therapeutic actions of ultrasound are attributable to its thermal and non-thermal effects. The thermal effect of ultrasound occurs when ultrasonic energy is absorbed and converted into thermal energy. Depending on the absorption coefficient of the tissue, it is possible to thermally induce tissue coagulation necrosis by raising the focal temperature to 60°C or higher using HIFU irradiation for several seconds[2].

The non-thermal effect of ultrasound typically occurs due to the existence of microbubbles, whether they have been generated *in situ* via acoustic cavitation or transported from somewhere else; indeed, they can even enhance the thermal effect of ultrasound[10]. Ultrasonically-activated microbubbles cause tissue and cellular damage, including the destruction of cell membranes and breakdown of capillary blood vessels. In addition to thermal coagulation necrosis and degeneration, HIFU can cause tissue destruction via the above-mentioned mechanism, which can be an advantage of HIFU treatment as long as it is properly localized.

Acoustic cavitation can also be induced more easily in a standing wave than in a progressive wave field because microbubbles smaller than the resonant size migrate toward the antinode of the standing wave field where they grow to the resonant size through coalescence and rectified diffusion[11]. During HIFU exposure, HIFU waves can be reflected by the interfaces of the coupling water bag, as well as by the biological tissue boundaries intervening between the transducer and the focus, resulting in standing wave components in the HIFU field. We hypothesized that such standing wave components are one of the primary causes of skin burns due to HIFU exposure. The hypothetical scenario is that cavitation occurs in the vicinity of the intervening skin due to standing wave components of the HIFU field and then the cavitated microbubbles locally enhance the heating effect of HIFU, which will cause a skin burn[12].

Based on this hypothesis, two types of HIFU transducers were prototyped: a conventional HIFU transducer and a modified HIFU transducer enabling a split-aperture exposure. It takes time in the order of milliseconds for a microbubble to grow to the resonant size due to the effect of standing waves, whose duration can be controlled by the exposure duration. Therefore, the modified transducer was designed to enable intermittent exposure of the intervening tissues while maintaining continuous exposure at the HIFU focus. This paper reports an animal experiment comparing the biological effect of conventional continuous exposure using a conventional HIFU transducer with that of intermittent split-aperture exposure using a modified transducer.

Materials and Methods

HIFU transducer and system

Two HIFU transducers using piezoelectric transducers (C-213; Fuji Ceramic, Fujinomiya, Japan) were prototyped. Both air-backed transducers in aluminum housing had a central hole 34 mm in diameter reserved for an imaging probe. The conventional HIFU transducer (78 mm in diameter) had a spherical curvature radius of 75 mm (Fig. 1a). The modified HIFU transducer (100 mm in diameter) had a spherical curvature radius of 85 mm (Fig. 1b). Its aperture was divided into six sectors to allow split-aperture exposure as shown in Figure 2. In this exposure sequence, most of the tissues intervening between the transducer and the focus are exposed

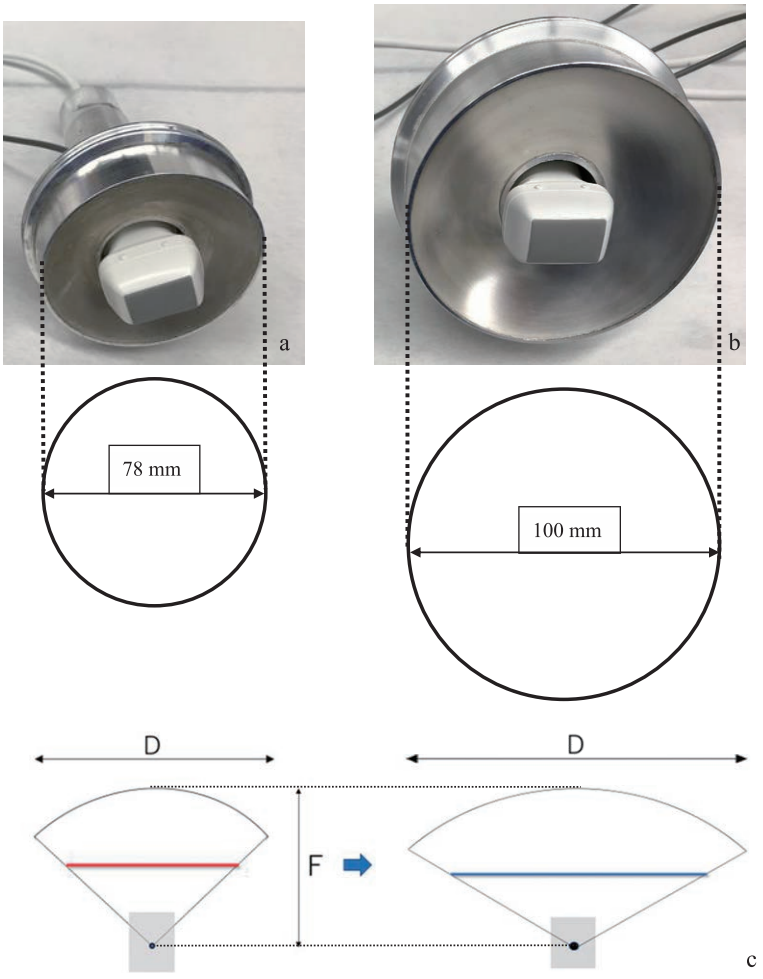

Fig. 1. (a) Unmodified and (b) modified second-generation high-intensity focused ultrasound (HIFU) transducers. In the unmodified unit, the imaging probe was located in the coaxial radiation area, and the diameter of the transducer was 78 mm. In the modified unit, the diameter of the transducer was 100 mm, and the F number was improved from 1.00 to 0.85. The modified HIFU transducer was divided into six sectors to split the ultrasonic exposure pulse. (c) Enlarging the surface area of the skin interface reduced the thermal burn in the skin without changing the focal distance. F, focal length; D, aperture diameter; F number, focal length / aperture diameter.

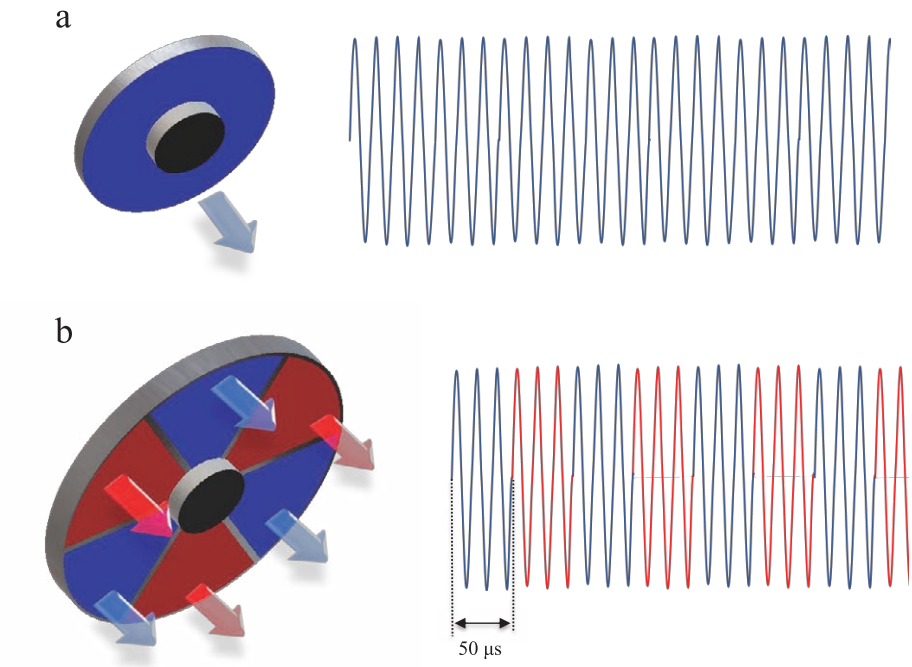

Fig. 2. Full and split irradiation. The total acoustic power of the high-intensity focused ultrasound (HIFU) was 200 W, the frequency was 1.1 MHz, and the irradiation time was 10 sec. These settings were the same for both irradiation protocols. (a) Full irradiation. (b) Split irradiation. The modified HIFU transducer was divided into six sectors to split the ultrasonic irradiation pulse. The path of the ultrasonic exposure was changed every 50 μsec to prevent the formation of a progressive wave.

intermittently while the tissue at the focus is exposed continuously.

The transducer with an imaging probe was sealed with a latex-free ultrasound probe cover (sterile, 17.8×147 cm, telescopically folded cover; Civ-Flex; Civco, Kalona, IA, USA) with circulating water inside, degassed and cooled below 20℃ by a Sonachill cooling system (Sonablate 500; SonaCare Medical, LLC, Charlotte, NC, USA). The conventional HIFU transducer was driven by a radiofrequency amplifier (RF Power Amplifier Model 1040L; E&I, Rochester, NY, USA) amplifying a sine wave from a function generator (WF1974; NF Corp., Yokohama, Japan). Both halves of the six sectors of the modified HIFU transducer were each driven by such an amplifier.

Laboratory animal experiment

The experiments were conducted using a 3-month-old baby pig (Landrace×Large White×Duroc three-way cross; weight, 35 kg). General anesthesia was administered with the animal in a supine position. The epidermis of the pig's thigh was regarded as a model of the epidermis of the mother's body, and the pig bristles were shaved. Blood pressure, pulse rate, respiration rate, and blood oxygen concentration were continuously measured before and after irradiation. The pig was killed by intravenous potassium chloride drip and necropsied after death; the muscle and skin were carefully examined for gross pathological lesions.

The study was approved by the Institutional Animal Care and Use Committee (Approval Number: IVT17-11), which operates in accordance with the Japanese Government for the care and use of laboratory animals. The experimental protocols were conducted in compliance with the Animal Management Act, under the approval of the Institutional Animal Care and Use Committee.

HIFU irradiation method

Each HIFU transducer was driven at an instantaneous acoustic power of 200 W and a frequency of 1.1 MHz for 10 sec. These parameters were chosen based on previous basic and clinical research studies[13], with ultrasonic energy at a level sufficient to denature tissue[7, 9, 14, 15]. Each half of the six sectors of the modified transducer (3 sectors each) was driven alternately, one after the other, with a switching period of 50 μsec. This irradiation sequence is referred to as split-aperture irradiation, while the other is full-aperture irradiation. In both irradiation sequences, a high-intensity short pulse at an instantaneous acoustic power of 760 W for 0.1 msec was irradiated every 100 msec to generate cavitation around the focal point. Even in the split-aperture sequence, the full aperture was used for this short pulse irradiation. The same operator performed all irradiations, which were separately delivered to the left and right legs (Fig. 3).

Evaluation method

Gross thigh skin evaluation. We irradiated eight randomly chosen sites on the femoral skin: four on the right and four on the left side of the animal. The irradiated femoral skin was excised, along with the muscle, and subsequently examined by two or more dermatologists.

Histological evaluation of the thigh. A total of eight sites in the skin and muscle were histologically evaluated. The tissue specimens were stained with hematoxylin and eosin.

Evaluation of complications. Blood pressure, pulse rate, respiratory rate, and blood oxygen concentration were analyzed for irradiation-related changes.

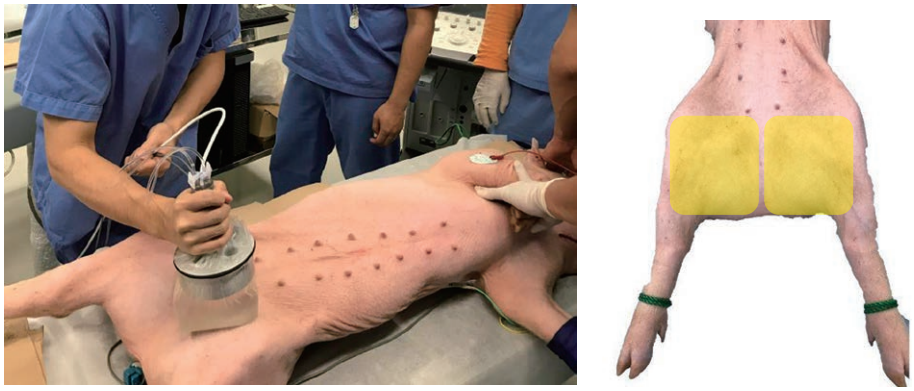

Fig. 3. High-intensity focused ultrasound (HIFU) irradiation. General anesthesia was administered with the pig in a supine position. Full irradiation and split irradiation were delivered to four sites on the left and four sites on the right internal region of the posterior limbs (within the yellow squares). All exposures were performed by the same person.

Results

Gross thigh skin evaluation

In the full-aperture protocol, white lesions near the hardened areas of all irradiation sites were observed, as was redness in the surrounding tissue. The white lesions were determined to be deep tissue burn injuries (Fig. 4). In the split-aperture protocol, scattered white lesions were observed in some areas, and all sites had epidermal burns or superficial dermal burns (Table 1).

Histological evaluation of the thigh skin

After full-aperture irradiation, heat denaturation was observed in almost all layers of the dermis, and the capillaries in the dermis exhibited vacuolar degeneration (Fig. 5). After split-aperture irradiation, heat denaturation was observed in the upper half of the dermis only, and there was no vacuolar degeneration of the blood vessels.

Evaluation of complications

Blood pressure, pulse rate, respiratory rate, and arterial oxygen saturation in the pig before and after HIFU exposure were similar for full- and split-aperture irradiation.

Discussion

The diagnosis of the burns by two or more dermatologists, along with the histopathological review of the tissue specimens, confirmed that full-aperture exposure using the conventional HIFU transducer caused deep dermal burns in all irradiated areas. In contrast, split-aperture exposure using the modified transducer did not cause deep dermal burns, despite basically the same ultrasonic power at the same frequency delivered to the same focal region, producing similar focal lesions. This result is consistent with the proposed hypothesis that microbubbles are generated in the vicinity of the intervening skin by the standing wave components of the

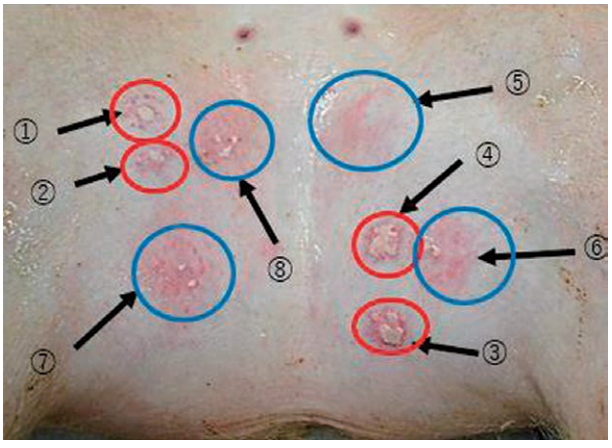

Fig. 4. Injuries at the irradiated sites. Red circles are sites that received full irradiation. Blue circles are sites that received split irradiation.

Table 1. Dermal findings according to irradiation protocol

Exposure site	Irradiation protocol	ED	SDB	DDB
1	Full			○
2	Full			○
3	Full			○
4	Full			○
5	Split	○		
6	Split		○	
7	Split		○	
8	Split		○	

ED, epidermal burn; SDB, superficial dermal burn; DDB, deep dermal burn.

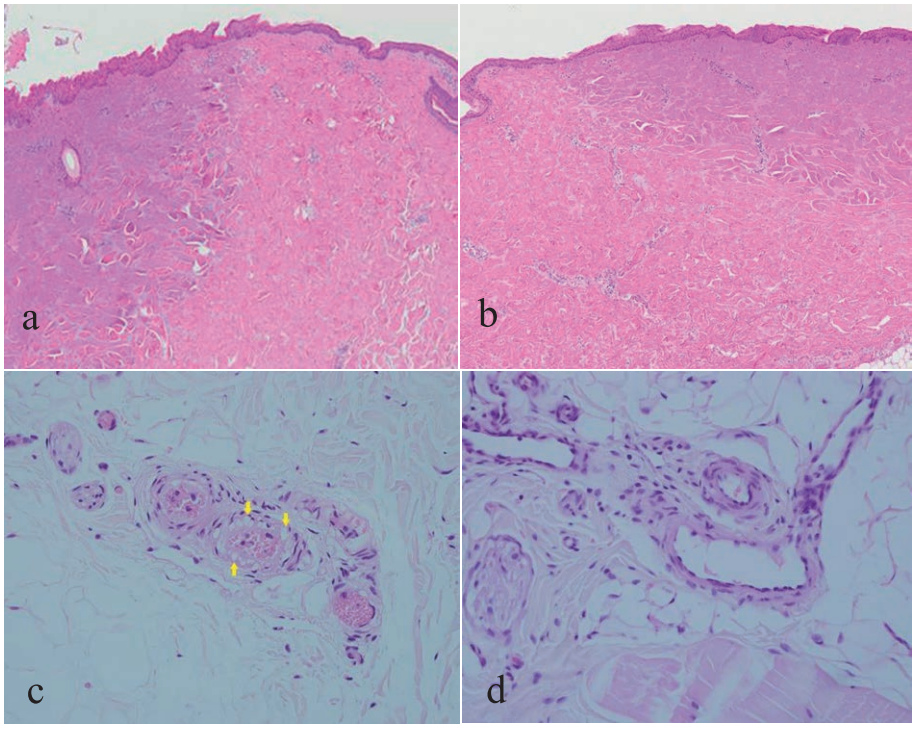

Fig. 5. Histopathologic evaluation. (a) Heat denaturation in all layers of the dermis after full irradiation. Hematoxylin and eosin (H&E), ×4. (b) Heat denaturation in the upper half of the dermis after split irradiation. H&E, ×4. (c) Vacuolar degeneration (yellow arrow) in the blood vessel capillaries of the dermis after full irradiation. H&E, ×40. (d) There was no vacuolar degeneration in the blood vessel capillaries of the dermis after split irradiation. H&E, ×40.

conventional HIFU field which locally enhances the heating effect, causing skin burns; therefore, the skin burn should be decreased by suppressing the standing wave formation.

In the split-aperture exposure, a period of 50 μsec was chosen for alternating irradiation using three of the six sectors of the modified transducer in turn. Assuming an ultrasonic reflector, such as the skin, is located halfway between the transducer and the focus, standing waves due to the overlap of more than two components will occur if the ultrasonic pulse train is longer than the round-trip distance between the reflector and the transducer. The switching period of 50 μsec, corresponding to a pulse train length of 75 mm, was chosen so that it would be shorter than the round-trip distance expected to be around the focal length, which was 85 mm for the modified transducer.

The F number of the modified transducer was 0.85, while it was 0.96 for the conventional transducer. The smallness of the F number of the modified transducer may have also contributed to suppressing standing waves. Assuming a semi-planar reflecting boundary such as skin, a standing wave field can be formed easily by plane waves. Moreover, a standing wave field can be formed less easily by a focused field with a smaller F number than with a larger F number.

When HIFU irradiation is applied to blood vessels, the cells of the vessel wall become vacuolated[12]. After the full-aperture irradiation, we observed vacuolar degeneration in the blood

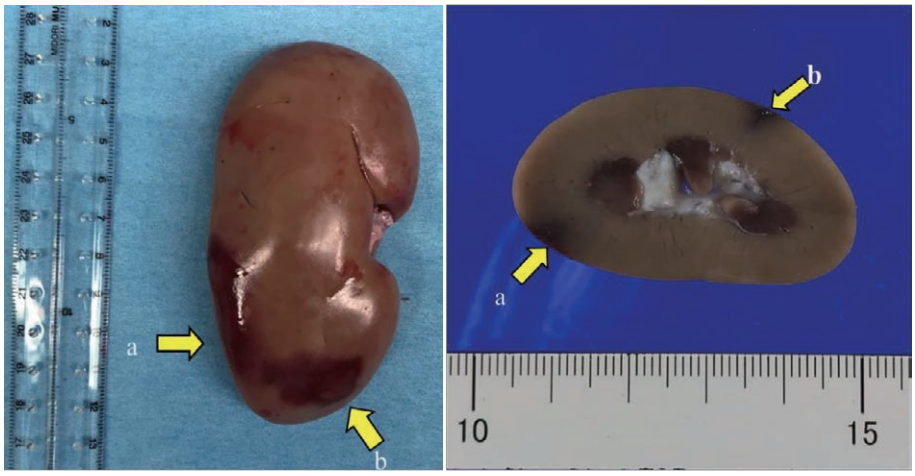

Fig. 6. Kidney evaluation. Reddish lesions were observed for both full-aperture irradiation (arrow 'a') and split-aperture irradiation (arrow 'b').

vessel capillaries of the true skin, which may have been caused by cavitation in vessel walls. In contrast, with the split-aperture irradiation, there was no vacuolar degeneration in the true skin blood vessel capillaries. Based on these findings, the extent of the burn injury was clearly reduced by the split-aperture irradiation. Under the same power and conditions, we irradiated the kidney of the pig percutaneously. After both full-aperture and split-aperture irradiation, similar reddish lesions corresponding to each HIFU focus were observed in the kidney, as shown in Figure 6. This proposed irradiation protocol using the modified HIFU transducer may have immense potential as a next-generation HIFU treatment.

The present study has some limitations. The radiation targets were pig skin, fat, and muscle, which differ from the human counterpart. In addition, human HIFU therapy is performed while the patient is conscious. Because our experiment was conducted under general anesthesia, the influence of muscle relaxants, body movements, and circulation must be considered. Another limitation is the lack of assessment of the efficacy of the transducer in detail; although burn injuries were reduced, the definitive goal is the complete prevention of burns. Thus, further improvements in the transducer and irradiation protocol may be needed.

In conclusion, the proposed split-aperture irradiation protocol reduced the severity of skin thermal burns in this animal experiment. Using the modified HIFU transducer and adjusting the HIFU irradiation protocol, the risk of skin burns should also be reduced in human patients. Thus, this combination is proposed as a next-generation HIFU treatment in the clinical setting.

Acknowledgment

We gratefully acknowledge the work of the past and present members of our laboratory.

Ethical statement

All institutional and national guidelines for the care and use of laboratory animals were followed.

Conflicts of interest disclosure

Shogo Nishii, Kohei Seo, Aleksander Tatsuya Izdebski, Miki Kushima, Ryo Takagi, Shin Yoshizawa, Shin-ichiro Umemura, Akihiko Sekizawa, and Kiyotake Ichizuka declare that they have no conflicts of interest.

References

1) Dubinsky TJ, Cuevas C, Dighe MK, *et al.* High-intensity focused ultrasound: current potential and oncologic applications. *Am J Roentgenol*. 2008;**190**:191–199.
2) Sofuni A, Moriyasu F, Sano T, *et al.* The current potential of high-intensity focused ultrasound for pancreatic carcinoma. *J Hepatobiliary Pancreatic Sci.* 2011;**18**:295–303.
3) Chaussy CG, Thuroff SF. Robotic high-intensity focused ultrasound for prostate cancer: what have we learned in 15 years of clinical use. *Curr Urol Rep*. 2011;**12**:180–187.
4) Rebillard X, Gelet A, Davin JL, *et al.* Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer. *J Endourol*. 2005;**19**:693–701.
5) Stewart EA, Rabinovici J, Tempany CM, *et al.* Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. *Fertil Steril.* 2006;**85**:22–29. Erratum in: *Fertil Steril*. 2006;**85**:1072.
6) Goldberg SH, Cohen MS, Young M, *et al.* Thermal tissue damage caused by ultrasonic cement removal from the humerus. *J Bone Joint Surg*. 2005;**87**:583–591.
7) Okai T, Ichizuka K, Hasegawa J, *et al.* First successful case of non-invasive in-utero treatment of twin reversed arterial perfusion sequence by high-intensity focused ultrasound. *Ultrasound Obstet Gynecol*. 2013;**42**:112–114.
8) Ichizuka K, Hasegawa J, Nakamura M, *et al.* High-intensity focused ultrasound treatment for twin reversed arterial perfusion sequence. *Ultrasound Obstet Gynecol*. 2012;**40**:476–478.
9) Liu Y, Zhang WW, He M, *et al.* Adverse effect analysis of high-intensity focused ultrasound in the treatment of benign uterine diseases. *Int J Hyperthermia*. 2018;**35**:56–61.
10) Gnanaskandan A, Hsiao CT, Chahine G. Modeling of microbubble-enhanced high-intensity focused ultrasound. *Ultrasound Med Biol*. 2019;**45**:1743–1761.
11) Umemura S, Kawabata K, Sasaki K. In vivo acceleration of ultrasonic tissue heating by microbubble agent. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2005;**52**:1690–1698.
12) Azuma T, Kawabata K, Umemura S, *et al.* Bubble generation by standing wave in water surrounded by cranium with transcranial ultrasonic beam. *Jpn J Appl Phys*. 2005;**44**:4625–4630.
13) Seo K, Ichizuka K, Okai T, *et al.* Evaluation of second-generation HIFU systems: less-invasive fetal therapy for TRAP sequence. *Showa Univ J Med Sci*. 2017;**29**:241–251.
14) Ichihara M, Sasaki K, Umemura S, *et al.* Blood flow occlusion via ultrasound image-guided high-intensity focused ultrasound and its effect on tissue perfusion. *Ultrasound Med Biol.* 2007;**33**:452–459.
15) Ishikawa T, Okai T, Sasaki K, *et al.* Functional and histological changes in rat femoral arteries by HIFU exposure. *Ultrasound Med Biol*. 2003;**29**:1471–1477.

［Received October 21, 2019 : Accepted November 28, 2019］