Chronic Effect of Transrectal Split-Focus Ultrasonic Ablation on Canine Prostatic Tissue

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ABSTRACT. The treatment time needed for high-intensity focused ultrasound (HIFU) ablation might be decreased substantially by using the split-focus approach, so we made a prototype 4.2-MHz split-focus therapeutic transducer combined with a small 6.5-MHz imaging ultrasonic probe for transrectally treatment of canine prostatic cancer and used it to experimentally evaluate the feasibility of using split-focus transrectal HIFU to ablate canine prostatic tissue without injuring surrounding tissues. The prostates of 5 dogs were transrectally treated with split-focus ablation at a peak intensity in the water of 1.7 kW/cm² for 4 s (4 shots) under the guidance of ultrasonic B-mode imaging. After ultrasonic exposure, the prostates became stiff because of thermal effect of HIFU. For the first 3–5 days after treatment, dogs were catheterized daily for urinary management and treated with oral antibiotics to prevent urinary tract infection. The dogs were able to urinate normally by a week after. Within two weeks a large centrally located cystic cavity had formed in the prostate by replacing the necrotic parenchyma around the prostatic urethra. Necropsy three months after treatment found the rectum and prostate capsule to be normal grossly and histologically. The 4 shots of split-focus HIFU destroyed the prostatic parenchyma and created a prostatic cavity 0.34–0.45 cm³ in volume without injuring surrounding tissues. These results suggest that split-focus HIFU ablation could be used for noninvasive treatment of prostatic cancer in dogs.

KEY WORDS: canine, HIFU, prostate, split-focus, transrectal ablation.

Prostatic diseases such as benign hyperplasia, cystic hyperplasia, and abscesses are common problems in older, sexually intact male dogs. Prostate cancer is uncommon in dogs but does occur, and the most frequent type of prostatic neoplasm observed in dogs is malignant adenocarcinoma [11].

Radiographically, the prostate gland is of soft-tissue opacity and its appearance is influenced by the opacity of surrounding tissues, which varies from one dog to another. Because the prostate is normally intrapelvic and may be difficult to see in a radiographical examination, prostate cancer is sometimes detected too late to treat effectively. Since the prostate is normally located in an intrapelvic space just caudal to the urinary bladder, sometimes it is difficult to recognize by radiographic examination due to decreased contrast created by the changes of its surrounding tissues including ascites, inflammation, and so on. Therefore prostate cancer is sometimes underestimated until it becomes too late to be treated clinically properly and effectively.

As in humans, prostate cancer in dogs can cause problems in older animals. It is prone to metastasis to surrounding tissues like the pelvic lymph nodes, bladder neck, and ureters and also to the vertebral bodies and the lungs [4]. Surgical removal of the prostate gland is the most common treatment for prostate cancer in dogs, but a dog’s quality of life (QOL) after radical prostatectomy is compromised by urinary incontinence. Localized prostate cancer would therefore be better treated by using a minimally invasive nonsurgical procedure.

Sonography is an alternative diagnostic imaging which is widely used for abdominal examination, and it shows the better detailed inner structure of the prostate than radiography.

Transrectal ultrasonography is often used in human urology for imaging the prostate through the rectum wall [12] and has also been used for diagnosing ovarian cysts in goats [10]. As a guide in obtaining biopsy samples, it is useful in the differential diagnosis of prostatic disorders such as prostate cancer and benign prostatic hypertrophy.

High-intensity focused ultrasound (HIFU) surgery was first used to create focal lesions deep in liver tissue [8] and was further developed by the group headed by William Fly in Illinois in the 1950s. In the point where the ultrasound are focused (focal point) the sudden and intense absorption of the ultrasound beam can create a rapidly elevation of the temperature which destroys the cells located in the targeted area without damaging tissue elsewhere in the path of the beams. HIFU has been used to treat glaucoma in human patients [18] and for the ablation of prostatic tissue in dogs [7]. Clinical studies with human patients have also explored the use of HIFU for the transrectal treatment of benign prostatic hyperplasia and prostate cancer [1, 9, 17].

HIFU works by focusing a short pulse (several seconds) of high-energy ultrasound waves on a volume about the size of a grain of rice. Its main disadvantage is that only a small volume of tissue is damaged in a single exposure. When larger volumes of tissue are to be ablated, as in tumor therapy, it is necessary to scan the focus through the targeted region. Mechanical scanning methods result in long treatment periods and thereby adversely affect the patient’s
QOL.

The split-focus approach was developed about a decade ago to create a broad heating pattern without forming unwanted secondary foci in front of or behind the focal plane [3, 14, 15]. This approach has recently been reported to also have the potential to substantially improve the throughput of HIFU thermal ablation (that is, to reduce treatment time) because it heats a volume of tissue larger than that heated in the conventional single-spot scanning approach [5, 6, 13].

We therefore made a prototype split-focus transducer combined with a small imaging ultrasonic probe and evaluated the feasibility of using split-focus transrectal HIFU to ablate canine prostatic tissue without injuring the surrounding tissues.

MATERIALS AND METHODS

Transrectal ultrasonic transducer: The power transducer in our prototype split-focus transducer was a dual-element PZT transducer (Fuji Ceramics, Shizuoka, Japan) that had a resonant frequency of 4.2 MHz, a concave curvature radius of 35 mm, and an aperture measuring 40 mm by 20 mm. The area of each element was 40 mm × 10 mm. As shown in Fig. 1, the elements were mounted in an aluminum housing that also contained a small imaging probe (EUP-F331, Hitachi Medical Co., Ltd., Tokyo, Japan) operating at 6.5 MHz and having a convex curvature radius of 10 mm. The position and angle of the imaging probe relative to the power transducer were adjusted in calibration experiments before the animal experiments. The whole assembly was contained in a polymer housing having a 30-mm outer diameter and when used in experiments was covered with a latex water bag (Echo probe cover B, Utsunomiya Seisakusho, Osaka, Japan). To prevent cavitation bubbles from forming in the bag, we filled it with degassed water just before each use. Each element of the transducer was driven with an RF amplifier (2100L, ENI, Rochester, NY, U.S.A.). The input signal to the amplifier, the phase of which needed to be controlled, was generated by an arbitrary-waveform generator (HP33120A, Hewlett Packard, Palo Alto, CA, U.S.A.).

When the two elements of the power transducer were driven at opposite phases, the focused beam was split into two. In the split-focus mode, the two focal beams were separated from each other by about a millimeter. The detailed beam profile of the acoustic field from this power transducer has already been reported [13].

The total acoustic power output from the transducer was calibrated against the drive voltage by measuring the radiation force on a hollow aluminum plate in degassed water [16]. The acoustic intensity distribution pattern on the focal plane in degassed water was measured at a low drive voltage with a 0.5-mm-diameter needle-type hydrophone (Imotec, Coesfeld, Germany). Assuming that the intensity distribution pattern does not change significantly as the drive voltage increases, we calculated the spatial peak acoustic intensity as a function of drive voltage.

Animal experiments: Five clinically normal male beagles (10–15 kg, 2–5 years old) were used in this study. The dogs were obtained from CSK Research Park Co., Ltd. (Nagano, Japan). All animals were given commercial food (Mori-nyu Sun World Co., Ltd., Tokyo, Japan) twice a day at every 12 hr (9:00 and 21:00) and allowed free access to water. They were kept individually in cages. The animals were fast for 24 hr prior to experiments, and each dog’s rectum was cleaned by giving the dog a warm saline enema immediately before the experiments. Each dog was premedicated with atropine (0.04 mg/kg, sc) and then anesthetized with xylazine (1.0 mg/kg, i.m.) and ketamine (5.0 mg/kg, i.m.). During experiments, anesthesia was maintained by infusing Ketamine (0.1 mg/kg/hr). Before experiments, the prostate of each dog was transrectally examined by using a small 6.5-MHz diagnostic imaging probe (EUP-F334, Hitachi Medical Co., Ltd., Tokyo, Japan) operated by an ultrasonic scanner (EUB-565, Hitachi Medical Co., Ltd., Tokyo, Japan).

After the diagnostic imaging probe was removed, the prototype split-focus transducer was inserted into the dog’s rectum. (Before it was inserted, ultrasound gel was generously applied to the surface of a latex water bag covering it.) As shown in Fig. 2, the prostate was transrectally observed by the imaging probe attached to the power transducer. After real-time pulse-echo images obtained with the probe were used to position the focus of the power transducer in the prostatic tissue around the urethra, the prostatic tissue was sonicated for 4 s at a peak intensity (in the water) of 1.7 kW/cm². A treatment cycle consisted of a 4-s of split-focus HIFU insonation followed by a 12-s period for heat dissipation. Each prostate was treated with four of these cycles.

Two of the 5 dogs were sacrificed just after the experiment so their prostates could be removed and sliced for examination of the lesions produced by ultrasound expo-
sure. For the first 3–5 days after the other three dogs were lesioned, they were catheterized daily for urinary management. An 8-French flexible balloon catheter (Terumo Corporation, Tokyo, Japan) was placed in the urethra of the other three dogs, and the balloon tip was advanced into the bladder. Each dog was daily treated with enrofloxacine (10 mg/kg p.o.) to prevent urinary tract infections, and their prostates were periodically transrectally examined with an ultrasonic imaging probe. When ultrasonography showed a cystic cavity around the urethra in the prostate, the cavity was confirmed radiographically by filling the urethra with an x-ray contrast medium. Three months later the dogs were sacrificed and their prostates were removed and fixed in 10% formalin. The prostates were then sliced for observation of chronic changes induced by ultrasound exposure.

The longitudinal (A) and lateral (B and C) dimensions of the cavity formed in the prostate were measured with a slide caliper, and the volume $V$ of the cavity was calculated with the following equation:

$$V = 0.5 \times A \times B \times C.$$  

The prostate slices were then stained with hematoxylin and eosin for histological examination.

Animal experiments were conducted in accordance with guidelines for the care and use of laboratory animals, Faculty of Agriculture, Tokyo University of Agriculture and Technology.

**RESULTS**

As shown in Fig. 2(a), the power transducer was transrectally focused in the middle of prostatic tissue by using real-time pulse-echo images obtained with the probe. As shown in Fig. 2(b), a hyperechoic region was seen around the focus of the power transducer immediately after exposure. P: prostate. B: urinary bladder. R: rectum wall.

Figure 2. (a) Sonographic image of canine prostate just before HIFU exposure. The power transducer was focused on the prostate through the rectum wall by using real-time pulse-echo images obtained with the probe. (b) Sonographic image of canine prostate immediately after it was insonated with split focus at a peak intensity of 1.5 W/cm² for 4 s. A hyper-echoic region (open circle) was seen around the focus of the power transducer immediately after exposure. P: prostate. B: urinary bladder. R: rectum wall.
A cavity was evident in the middle of the prostate three months after treatment. Figure 6 shows the x-ray urography results for this dog. A cavity was filled with contrast media and connected to urethra and urinary bladder. The prostatic urethra clearly seen in the lateral view (Fig. 6(b)) of the prostate is connected to the prostatic cavity (Fig. 7).
Each dog sacrificed three months after HIFU treatment had a cavity in the prostate around the urethra. The volumes of these cavities were of 0.34, 0.35, 0.45 cm³. Glandular tissue could be seen surrounding each urethra, and the prostatic parenchyma was found to have been replaced by a cystic cavity. The rectum was normal grossly and histologically.

The histological photograph in Fig. 8(a) shows a part of cystic cavity in the prostate that is connected to the urethra. The magnified area in the lumen (Fig. 8(b)) shows complete re-epithelialization of the prostatic urethra.

**DISCUSSION**

Split-focus HIFU ablation could be used to destroy focal areas of prostatic tissue in dogs without injuring surrounding tissues. An ultrasonic image of the lesion in a prostate immediately after split-focus HIFU showed a hyperechoic region (Fig. 2(b)). Bush and coworkers have shown that the attenuation coefficient of tissue at the center of a HIFU lesion is significantly greater than that of normal tissues [2]. This may be due in part to the generation of gas by heating. We have demonstrated that split-focus HIFU created a contiguous thermal coagulation in pig liver tissue within a few
As shown in Fig. 3(b), we found that HIFU exposure can cause acute thermal coagulation of prostatic tissues in dogs. These results indicate that the prostatic tissue exposed to split-focus HIFU was heated enough to create an area of coagulation.

A cyst-like cavity within the prostate was visible with transrectal ultrasonography by two weeks after the HIFU treatment, and this cavity was connected to urethra as shown in Fig. 6. The necrotic parenchyma of prostate was found to have been replaced by cystic cavity. These results show that only four shots of split-focus HIFU can destroy the prostatic parenchyma and create a cavity of 0.34–0.45 cm³ in volume with no clear evidence of injuring surrounding tissues.

No dogs after treatment showed clinical signs of rectal disorder. After HIFU ablation, per rectal finger palpation of the prostate and rectal wall immediately after HIFU ablation, we felt induration of the prostate. Figure 3(b) shows that HIFU ablation to the prostate caused acute thermal coagulation of prostatic tissues. This focal coagulation most likely has led to inflammation and swelling of the prostate, which in turn may have been the reason that all of the dogs showed urinary incontinence within 3 to 5 days after the experiments. Oral antibiotics were prescribed to prevent catheter-associated urinary tract infections in the first 2

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Fig. 7. Sagittal cross section of the prostate of the same dog diagnosed in Fig. 5 and Fig. 6 obtained three months after HIFU ablation. The prostatic urethra was clearly seen in the prostate and was connected to the prostatic cavity. The cavity in this dog measured 8 (Height) × 12 (Length) × 9 (Width) mm.

Fig 8. (a) Histological photograph (× 40) of the inner surface of a cystic cavity connected to the urethra. (b) Higher-magnification photograph (× 400) shows complete re-epithelialization of the prostatic urethra.
weeks after HIFU ablation. Although necrotic tissues and cavities formed in the prostate are potential sites for infection, there were no evidences of urinary tract infection in any of these three dogs after they were no longer being catheterized daily. Since all dogs were continent by a week after treatment, it seems that transrectal split-focus HIFU does not adversely affect the lower urethral sphincter. The inner surface of a cystic cavity connected to urethra was completely covered by the re-epithelialization of the prostatic urethra, as shown in Fig. 8. The dogs were able to urinate normally. These clinical and histological findings suggest that split-focus HIFU ablation can be applied to localized prostate cancer in dogs noninvasively.

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