Noninvasive Surgery of Prostate Tissue by High-Intensity Focused Ultrasound

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Abstract—**Modern ultrasound transducer material and matching layer technology has permitted us to combine the ultrasound visualization capability with production of high-intensity focused ultrasound (HIFU) on the same ceramic crystal. This development has lead to the design of a transrectal probe for noninvasive surgery of prostate tissue by HIFU. The combined capability using the same ceramic crystal simplifies treatment planning, targeting, and monitoring of tissue before and during the HIFU treatment. This mechanically scanning transrectal probe was introduced for clinical use in 1992 for noninvasive surgery of the prostate to treat benign prostatic hyperplasia (BPH) condition. This paper reviews major steps progressing from conception to the present clinical trial status of the HIFU device. During these clinical studies generation of microbubbles and cavitation were observed. Data from microbubble generation, temperature monitoring in tissue, and autopsy of HIFU-treated animal prostates are presented. Results of human clinical studies are briefly summarized to indicate performance of the device.**

I. Introduction

HIGH-INTENSITY focused ultrasound (HIFU) has been envisioned since the 1940's [1], [2] as a potential modality for the noninvasive treatment of focal disease in tissue and organs. Focal disease sites of essentially any size and shape were considered potential targets for ablation, provided an adequate acoustic window was available for introducing the focused beam from the entry area to the site to be ablated in the body. Despite some encouraging results of early HIFU clinical studies and research efforts by others [3], routine clinical use of HIFU for noninvasive surgery is yet to come to fruition. In the early days of HIFU development for the treatment of brain disorders [4], associated technology for beam guidance, treatment planning, monitoring, and controls were not entirely adequate or available. More recently, HIFU for the treatment of glaucoma was implemented with modern technologies and proven clinically effective [5], however, the HIFU technique did not become commercially viable because of competing technologies. Since these investigations, recent advances in the field of computers, imaging, and material science have permitted us to more readily implement HIFU for noninvasive therapeutic applications for the treatment of prostate diseases. In tandem with these technological advances, the recent success of lithotripsy for the noninvasive treatment of kidney stones has made urological professionals more aware and receptive to noninvasive treatment modalities.

In this paper, we are concerned with a transrectal noninvasive treatment of prostate disease known as benign prostatic hyperplasia (BPH) using an HIFU device. The material presented here is a small fraction of the data collected on temperature measurements, autopsy, and histology from canines, as well as echographic information both from canines and humans during the prostate treatment. This paper briefly reviews major steps progressing from conception to the present clinical status of the device. Reported here are new findings on microbubbles ("clouds") and cavitation ("popcorn") during treatment of the prostate by HIFU. These terms are defined based on their appearances in the ultrasound images. The "popcorn" term was used for a transient hyperechoic region, confined to the focal zone that occurred in a random fashion. The "clouds" term was used for large echogenic changes, initiated in the focal zone, which persisted and quickly grew, and transported toward the transducer during the treatment. Both phenomena were first observed in the human and later verified in the canine.

This specific project for ultrasound treatment of the prostate began at Indiana University, Indianapolis, in 1987 culminating in the Food and Drug Administration (FDA) approved Investigational Device Exemption (IDE) medical device in 1992. The device was called Sonablate™ (Focus Surgery Inc., Fremont, CA) for the treatment of BPH. More than 600 BPH patients have been treated with this device and clinical trials are being conducted at several sites in Europe, Japan, Canada, and the United States.

A. Experimental Studies

The essential role of experimental animal (canine) studies was revealed through the initial feasibility studies. These studies produced data on production of large-sized lesions within the prostate with temperature recordings at tissue sites in and around the ultrasound beampath. These results were used to demonstrate the safety of the device and to design the

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TABLE I
PARAMETERS AND RESULTS OF THE FEASIBILITY STUDY

No. of animals	No. of treatments / No. of Individual lesions	Ultrasound energy (kW / cm^2 * second) at focus	Focal peak intensity (Isp) in W / cm^2	Tissue volume irradiated in mm^3	Lesion
3	5 / (22 to 64)	1.49 - 2.98	370	11.25 - 32	No
10	15 / (54 to 1568)	4.1 - 9.1	400 - 710	27 - 784	Yes

protocol for human clinical trials to follow. During the clinical trials, several tissue responses to HIFU were observed which were not observed in the early animal studies. To elucidate those responses, additional animal studies were conducted. Later, as follow-up data from the clinics were available, it became clear that the efficacy of this device needed to be improved. For this purpose, additional experiments were carried out with modified treatment protocols. Clinical results with the modified protocol are summarized.

II. MATERIALS AND METHODS

The experimental studies were divided into four phases. Phase I—Feasibility study, Phase II—Development of a transrectal imaging and therapy device, Phase III—Good laboratory practice (GLP) study, and Phase IV—Animal studies parallel to clinical trials.

A. Phase I—Feasibility Study

Since transurethral resection of the prostate (TURP) is a widely used and accepted "gold standard" surgical procedure for the treatment of BPH it was essential to demonstrate in the canine that HIFU would produce tissue ablation that could mimic the TURP procedure. The goals of this study were to 1) determine the required ultrasound energy needed to produce a single focal lesion in the canine's prostate and 2) study short- and long-term effects of HIFU on the animals in general and on the prostate in particular. Production of overlapping multiple focal lesions to create a contiguous 1 cc lesion centered around the urethra was judged to be an appropriate first step. Thirteen (13) canine prostates were surgically exposed in the transpubic region and placed under a degassed saline solution for ultrasound irradiation. The experimental setup included a sector scanning ultrasound imaging probe (7.5 MHz) and a 5.5-cm-diameter 7.5-cm focal length 4-MHz HIFU transducer attached to an x–y–z coordinate system. The -6 dB beamwidths of the HIFU transducer were 7 mm and 0.65 mm in axial and transverse planes, respectively. A range of focal peak intensities (I_{sp} = 300 to 800 W/cm^2) and exposure from 4 to 12 s, with a long off-time between exposures (from 1 to 2 min), were used to produce thermally coagulative lesions [6]. To produce a contiguous large lesion, a three-dimensional (3-D) matrix of individual focal lesions

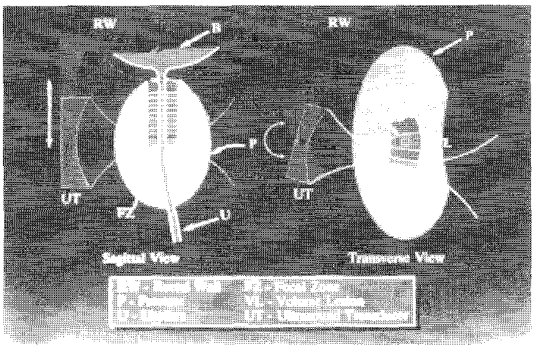


Fig. 1. Schematic diagram showing a lesion planning for the prostate treatment. The large lesion is created by placing a matrix of lesions. The transducer is mechanically moved in axial and transverse planes by a fixed distance to create a lesion matrix.

was created. The distance between individual lesions was at 1 mm and 3 mm in lateral and axial planes, respectively. The experimental study was divided into acute and chronic groups. The acute group (number of animals = 9) was used to establish the minimum ultrasound energy required to produce a thermal coagulative lesion in the prostate. These treatment parameters were used in the chronic group (number of animals = 4) study. Treatment details are given in Table I.

B. Phase II—Design and Development of a Transrectal Ultrasound Imaging/Therapy Device

Once it appeared that appropriate-sized lesions could be produced in the prostate, the Phase II study was initiated with the objectives of 1) defining rectal and prostate tissue attenuation of ultrasound *in vivo* in animals and *in vitro* for human tissue, 2) defining the operating frequency, size, and shape of the transducer for a transrectal device, 3) determining on/off cycle times with appropriate peak intensity levels to produce a 1-cc contiguous prostatic lesion through the rectal wall, and 4) determining temperatures at the rectal wall, inside and outside the prostate, and in the surrounding tissues. Details of the device have been published previously [7], [8] and briefly described here for the purpose of continuity. A first prototype transrectal probe was designed with both linear and sector motions as shown schematically in Fig. 1. The rectangular-shaped transducer was designed to provide maximum surface area while keeping the overall dimensions

clinically acceptable. The transducer incorporated both the ultrasound pulse–echo visualization and HIFU capabilities on the same ceramic crystal operating at 3.8 MHz. The transducer was fabricated from modified lead titanate material (Etalon Inc., Lebanon, IN) with appropriate matching layers to increase acoustic efficiency and image resolution [9]. The transducer frequency selection was based on 1) finding an optimum frequency to result in a maximum intensity gain at the focus for given transducer dimensions, 2) providing clinically acceptable resolution for imaging of the prostate, and 3) operating at the frequency high enough to avoid cavitation [10], [11].

Based on transducer aperture, focal length, and tissue absorption coefficient the approximate focal intensity (FI) can be calculated as follows for an unaltered diffraction-limited ultrasound beam [12]:

$$\mathrm{FI} \cong \frac{\text{Transducer surface area}}{\text{Focal beam area}} * e^{-2*\alpha(F)*\ell} \qquad (1)$$

where

$$\text{Focal beam area} \propto \left(\frac{\text{Focal length} * C}{F * \text{Transducer Aperture}}\right)^2.$$

F = frequency in MHz, α = pressure amplitude absorption coefficient in Np/m/MHz, C = speed of sound in tissue in m/s, and ℓ = tissue depth in meter. For a curved rectangular transducer, an aperture area was approximated by its width × length dimensions.

For the transducer of a 12 mm × 30 mm aperture with a focal length from 2.5 to 3.5 cm, and tissue absorption coefficient equal to 10 Np/m/MHz, higher focal intensity is produced in the frequency range from 2.5 to 4 MHz. Based on these specifications, a transrectal device operating at 3.8 MHz was constructed during 1989–1990.

Twenty canine prostates were treated using this device to optimize ultrasound focal peak intensity levels with combinations of on/off times to minimize treatment time while reliably producing thermal coagulative necrosis of the prostatic tissue through the rectal wall. However, the ultrasound intensity at the rectum was unacceptably high, producing rectal injury in some animals. Therefore, the next series of animals was treated with a 4-MHz 2.5-cm focal length 22 mm × 30-mm aperture transducer. The larger aperture and shorter focal length transducer produced higher focal intensity gain. Therefore, power density at the rectal wall was significantly reduced, preventing rectal injury.

C. Phase III—Good Laboratory Practice (GLP) Study Using the Sonablate-1 Device

The GLP experimental study is generally based on consultation with the FDA and the local institutional review committee to define the protocol so that a new medical device can be validated for human use in the USA. Generally, the main purpose is to establish a very high level of confidence in the safety of the device with some evidence of efficacy prior to clinical trials.

Upon completion of software and hardware design with incorporated safety features, the Sonablate™-1 device was manufactured. The device is shown in Fig. 2 with a transrectal probe and an articulated arm attached to an operating table. The Phase III study was initiated for the Sonablate-1 with objectives of 1) demonstrating safety of the device in animals and 2) following a GLP protocol. The study required treatment of 26 canines (beagles). The treatment parameters are listed in Table II.

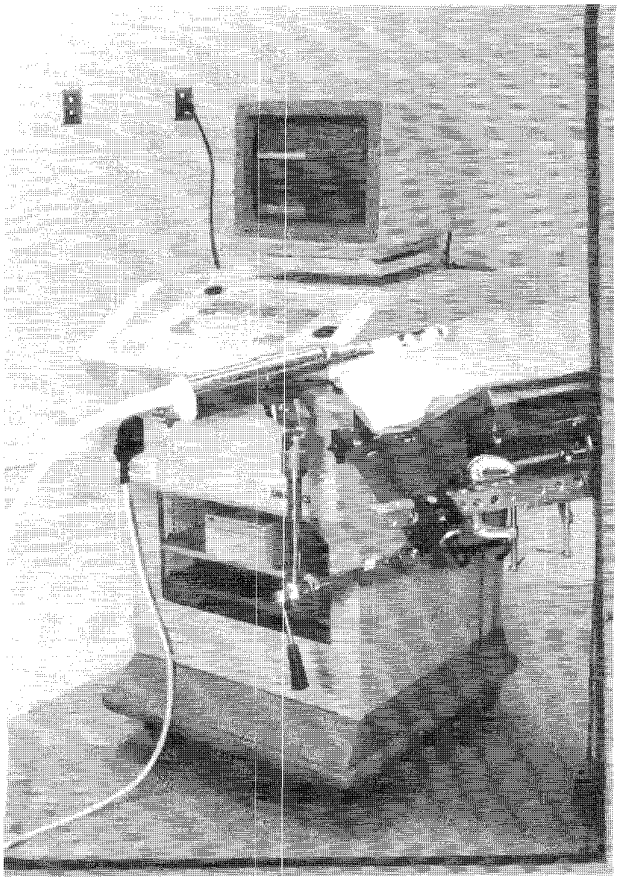


Fig. 2. The Sonablate™-1 system with a transrectal probe attached to an articulated arm and an operating table.

1) In Vivo Temperature Measurements: On-line temperature measurements were made using bare wire tip thermocouples (TC's) (type T, tip diameter of 60 to 100 μm) and implanted needle TC's. Bare wire tip TC's were used to minimize self-heating and other associated artifacts [13]. The needle TC's were fabricated using an 18-gauge needle, 12 cm long attached to a 3.5-cm-long 21-gauge needle tip. This dual needle size design was used to meet requirements of mechanical strength and TC housing. Three 100-μm-diameter TC's were placed in the 21-gauge needle tip, at a distance of 1 cm apart. The TC's were electrically isolated from the needle case. All TC's were designed in our laboratory and manufactured by Physitemp Instruments, Clifton, NJ. The TC's were made from 25- or 50-μm-diameter wires giving a fast thermal response, with a time constant as low as 0.005 s. The TC's were accurate within 0.1°C. Bare wire tip TC's were implanted in the prostate tissue to measure temperatures in the near-field and in the focal zone. The needle TC's were transperineally inserted outside the prostate capsule and

TABLE II
GLP STUDY TREATMENT PARAMETERS

Peak Focal Intensity (I_{sp})	1680 (W/cm^2)
Sound On / Off time	4/12 (sec)
Average treatment length (on axial position)	10 mm
Step size between lesions for Linear / Sector position	1.8 mm
No. of Sectors	5

at some distance from the ultrasound focal zone. The TC's were implanted under high-resolution linear-sector transrectal ultrasound (TRUS) guidance using a Hitachi EUB-410. To implant a bare wire TC, a 19-gauge 15-cm-long needle with a trocar was inserted transperineally in the tissue. The needle tip was precisely localized under TRUS. The trocar was carefully removed, the needle was filled with saline, and a bare wire thermocouple was slowly advanced inside the needle to a fixed distance. Afterward, the needle was slowly pulled back by about 2 cm, leaving the thermocouple tip in the tissue at the desired site. Similarly, two needle TC's were placed on the transverse sides (right and left) and one on the anterior side of the prostate. This provided a total of nine locations surrounding the prostate tissue for temperature sampling. Rectal mucosa temperatures were monitored during treatment with tiny bare wire tip TC's. Two bare wire TC's (25-μm-diameter wire) were tied to the HIFU probe with a silk suture (size OO). One TC was positioned at the probe tip and the second was positioned on the center of the acoustic window such that it transected the ultrasound beam most of the time. Extreme care was exercised to minimize beam interactions with sutures and thermocouple wires. The water temperature inside the probe was continuously sampled. An on-line 16-channel simultaneous temperature recording device, LT-100 (Labthermics, Champaign, IL), was used to record the thermocouple output. The LT-100 has a range from 20 to 100°C with an accuracy of ±0.1°C. Prior to a therapy session, all TC's were attached to the LT-100 for calibration of the complete system. To calibrate the system, the TC's were placed in hot and cold water baths where the temperatures were measured with a calibrated mercury thermometer and entered into the LT-100 for each channel. These two measured temperature points were used by the LT-100 computer to derive a slope for a line to fit the temperature range. During experiments, all the TC's were sampled simultaneously every 0.5 s. Data were digitized and stored in the LT-100 memory buffer and transferred to a PC when the buffer was full. Thermal data were recorded during the entire procedure including the on cycle and off cycle for each irradiation. Thus, the accumulated data presented tissue temperatures when the TC's were inside or outside the ultrasound field. The results produced temperature profiles as a function of time, relative location of TC to the beam, and spatial distribution of the ultrasound beam. Thermal data were then computer processed and analyzed to remove thermocouple artifacts. When the TC's were in the ultrasound field, the viscous effect due to thermocouple response during the first 0.5 s of sound on and off period was noted, and removed from the data [14], [15].

D. Phase IV—Animal Studies Parallel to Clinical Studies

The main objectives of the animal studies parallel to clinical studies were: 1) to better understand tissue responses to HIFU in human prostate tissue that were not observed in our earlier animal studies and 2) to improve efficacy of the device. During this phase the following experimental studies were conducted.

1) Cavitation Observation and Detection: During the early clinical studies, it was observed that some patients developed hypoechoic regions ("cavity") in the prostate following the HIFU treatment while others did not. The cavity location was correlated to the region of treatment. The ultrasound images during treatment showed hyperechoic ("popcorn") regions for these cases. The patients who had cavities seemed to respond better to the treatment than others. Also, some physicians suggested that more tissue volume should be removed (similar to a TURP procedure) to improve urine flow rates. To demonstrate the ability to produce larger lesions and "popcorn"-type tissue response, an animal experimental protocol was developed and a series of canines were treated both with higher intensity levels and additional sectors.

The hyperechogenicity was believed to be the result of local cavitation or formation of vapor generated gaseous bubbles at the focus [11], [16]. Therefore, using a 3.0-cm focal length probe, focal peak intensity (I_{sp}) was gradually increased from 1680 to 2200–3400 W/cm^2 until a consistent "popcorn" response at the focal site was observed after each irradiation. The hyperechogenicity was accompanied by an audible popping noise. To listen to this noise, a stethoscope was placed on the suprapubic region. Sometimes, the popping noise was heard without a stethoscope. To measure the frequency broadening of the transmitted signals and subharmonics associated with the event, a broad-band ceramic needle hydrophone (Mediscan, no. 72), diameter $<$ 1 mm, with a wide angular response and a dual memory storage frequency spectrum analyzer (HP 8557A) was used. The hydrophone was directed toward the prostate from the superapubic region and was in direct contact with the animal skin. The transmitted ultrasound signals were received by the hydrophone through the rectum, prostate, muscle, subcutaneous fat, and skin. The location and position of the hydrophone were optimized by first observing the signals received during the pulse–echo mode. The hydrophone output was amplified by a linear broad-band (30 MHz) 60-dB amplifier (Panametric 5050PR). The amplified signals were fed to the spectrum analyzer. The spectrum analyzer was in max-hold mode, setup with an autosweep (generally better then 10 ms/sweep) and 50 kHz/Div. resolution. At the very start of HIFU on cycle, spectra were captured and held in channel

A while channel B was used to capture spectra during the entire on period. During the off period, spectra from both the channels were plotted and channels were cleared for the next recording cycle. The ultrasound images were video recorded with a sound channel to correlate the "popcorn" events with the frequency spectra. In this series, all except three animals were killed at 72 h post-HIFU while three animals were followed for 55 days. Post-treatment animals were examined by TRUS at 72 h and subsequently on a weekly basis to observe changes in the prostate tissue and to measure the hypoechoic region dimensions. Gross pathology and histology of the prostate, rectum, and bladder were performed on all animals and the results were evaluated by a pathologist.

2) Microbubble Clouds: Later on during the human clinical trials, two cases of echographic events were observed and reported to us. These two events were quite different from those seen previously as "popcorn." A major difference between the "popcorn" and this event was the formation of echogenic "clouds." These echogenic "clouds" were generated after a few ultrasound irradiations. The hyperechoes once originated at the focal site were persistent. These echoes enlarged rapidly and migrated toward the transducer as the therapy continued. We termed the events as "clouds" because of their size. The "clouds" became so large that they completely shadowed the interior portion of the prostate during the imaging. These observations made it necessary for us to search for those parameters that would hopefully mimic the human echogenic "cloud" formation during the animal treatment. Our approach to this research was empirical in nature since we did not know exactly which parameter to exploit first. We hypothesized from our analysis of human echograms [16] that these events were due to initiation of cavitation and a subsequent migration of microbubbles in the vascular system. The microbubble migration was further accelerated (and/or facilitated) due to overall prostate temperature elevation. The temperature elevation could be due to many convoluting factors. Therefore, to rapidly elevate the prostate temperature, the total acoustic power delivery was raised to 45–50 W while keeping the focal peak intensity closer to 1800 W/cm^2. These experiments ($n = 6$) were carried out using a 4.0-cm focal length transducer. At this power level, the formation of echogenic clouds and their migration in the canine's prostate was enhanced and repeated. Temperatures at the rectal wall and inside the probe were monitored as described previously. Temperature inside the prostate was not monitored.

These experiments revealed the essential aspects of the echogenic cloud formation and its contribution to temperature increase in the posterior prostate and at the rectal wall. This resulted in the development of a simple method to cool the rectal wall. The simple cooling method involved an external supply of circulating degassed water in the probe at a constant rate maintained at room temperature.

All animals' prostate, rectal wall, and bladder were removed at 24 to 72 h post-HIFU treatment and histo-pathology examinations were conducted to clearly define the damage at the microscopic levels.

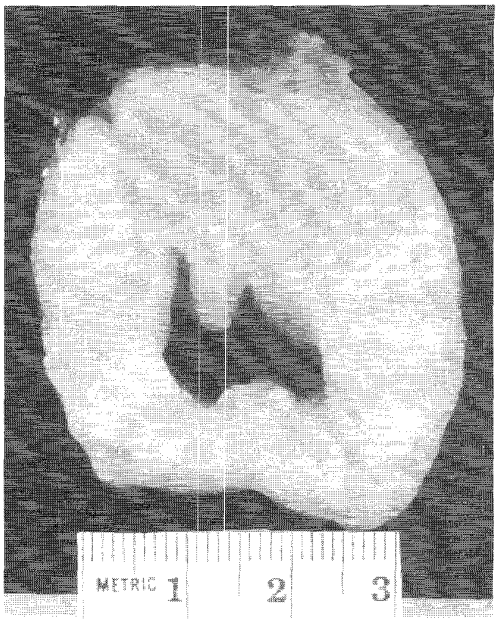


Fig. 3. Canine's prostate transverse cross section, 12 weeks post-HIFU surgery, showing an enlargement of the urethra in the center.

3) Treatment with an Indwelling Catheter: As more extensive clinical data were analyzed ($n > 150$), it was evident that the protocol had to be modified to produce the dramatic urine flow rate increase seen in many cases, but not in all the patients.

A modification of the protocol involved placing an 18 or 24 French catheter (Dow Corning Corporation, MI) in the urethra and leaving it in place during the HIFU treatment. In 12 canines, an 18 French catheter was inserted through the urethra guided by ultrasound imaging, and in three canines a 24 French catheter was placed by a well-established surgical method called urethrostomy. This technique was motivated in part by the relative resistance of the urethra and bladder neck tissue to ultrasound ablation compared to other tissue of the prostate gland. The new treatment protocol involved addition of a catheter and two treatment zones. One treatment zone was at the canine's bladder neck and the second was in the midprostate gland. The objectives of these changes in the protocol were to maximize the energy deposition at the bladder neck and along the urethra, and to increase the amount of tissue necrosed and removed post-HIFU.

III. Results

A summary of the lesion descriptions of the initial 13 canine series irradiated from the anterior prostate with the open abdomen is shown in Table I.

Based on this study, it was concluded that a large contiguous lesion, made of multiple small individual focal lesions, could be produced in the prostate. The ultrasound energy (UE), similar to that described by Frizzell for liver ablation threshold [17], (UE $\cong I_{sp} * T^{0.5}$, where I_{sp} is the spatial peak focal intensity and T is time in s), above 1150 W/cm^2 $*$ s$^{0.5}$ was necessary to produce an individual necrotic thermal lesion in

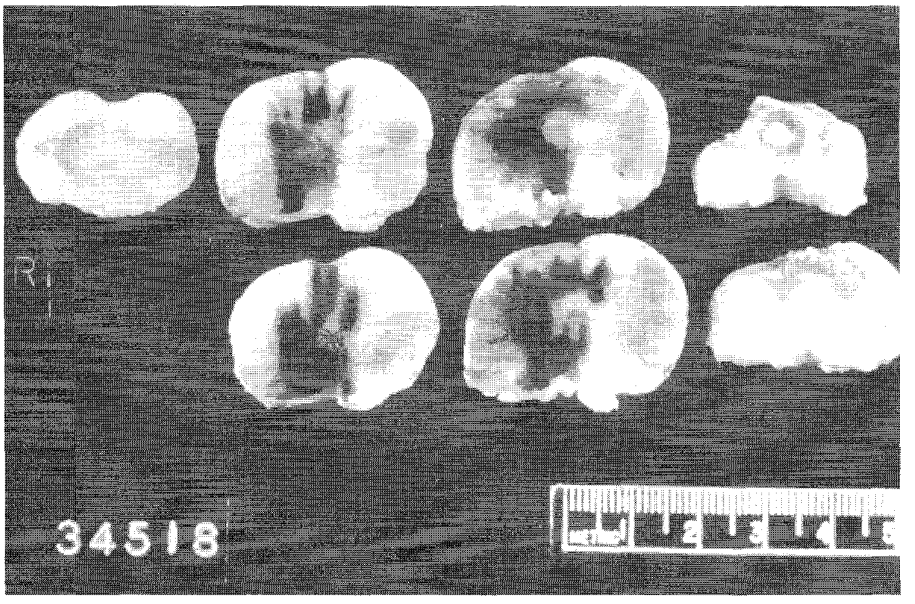


Fig. 4. Serial transverse sections of a canine prostate 72 h post-HIFU treatment from the GLP study. The dark area is due to US treatment.

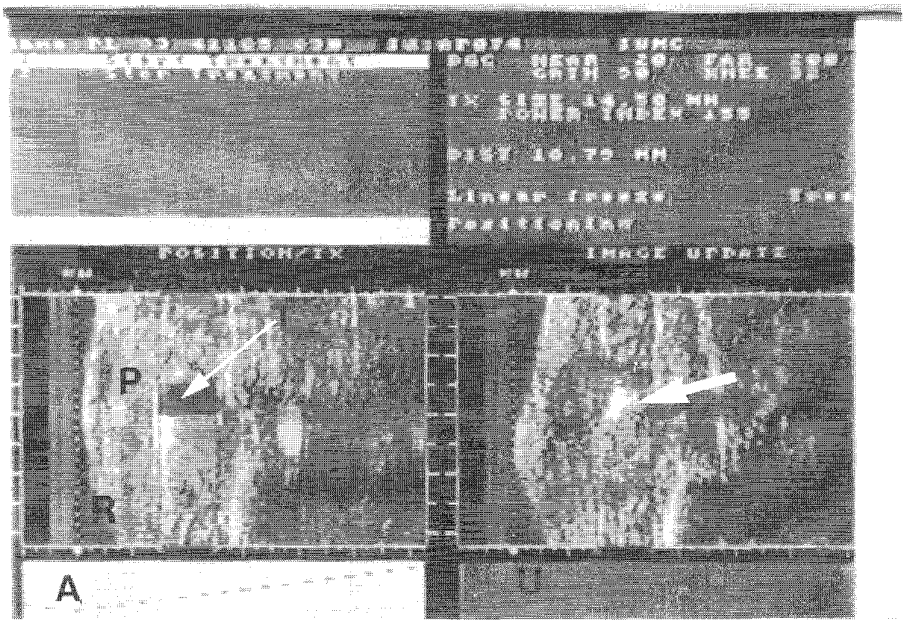


Fig. 5. An echogram of a canine prostate showing a "popcorn" confined in the focal zone. (P = prostate, R = rectal wall; small arrow is for treatment zone, large arrow points at "popcorn.")

the canine prostate. The lesions in the acute group of animals ($n = 9$, number of large lesions = 13) showed a reddish brown coagulative discoloration in the prostate. The size of contiguous lesions was consistent with the region irradiated with ultrasound. The chronic group of animals ($n = 4$) survived for 2, 4, 6, and 12 weeks post-HIFU and had cavities covered by an epithelial lining in the treated tissue. Long-term canines did not show any undesirable complications [6]. The transverse cross section of a 12-week survival canine prostate is shown in Fig. 3 which shows an expanded urethra cavity in the center. Based on the pathological description of these prostates, it was concluded that 1) HIFU was potentially capable of treating BPH and 2) a transrectal system should be designed to further test the capability of HIFU with a combined visualization and therapy unit that could be applied to the canine as well as the human.

The initial clinical specifications called for a treatment time of 30 min to ablate 1 cc of tissue. Therefore, it was decided to place a 5 × 5 lesion matrix. Each individual lesion as being at least 1 cm long by 2 mm wide with

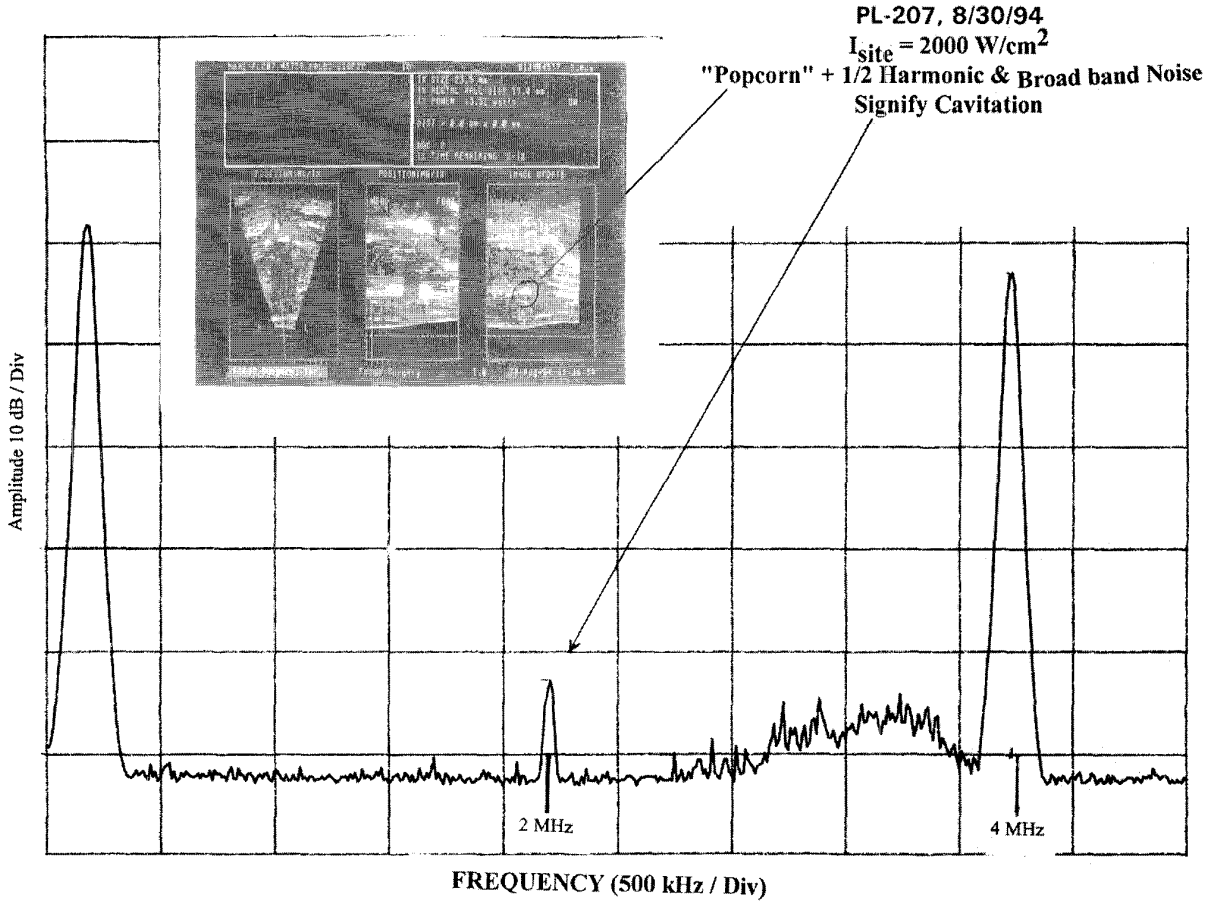


Fig. 6. Frequency spectra showing 1/2 harmonic signal and broad-band noise associated with "popcorn" as seen in the associated echogram.

a lesion spacing of 2 mm. The treatment time and desired tissue ablation volume required us to optimize the treatment parameters. Total acoustic power (TAP), focal peak intensity, and on/off times were experimentally adjusted to produce thermal coagulative lesions without injuring the rectal wall. It was anticipated that human prostates would be larger than most canine prostates requiring deeper tissue penetration and higher total acoustic power. The higher power density would impact on the rectal wall. Therefore, the larger aperture (22 mm × 30 mm) transducer was found to be essential. Rectal wall injury in the canine was prevented with this transducer, when used with treatment parameters as listed in Table II. Typical contiguous lesion in a canine is shown in Fig. 4 with transverse 3–4 mm thick cross sections of the prostate.

Results of the GLP study have been published by Foster *et al.* [7] and are described here briefly. The total acoustic power required to produce focal peak intensity (I_{sp}) of 1680 W/cm^2 was calculated based on tissue depth, focal intensity gain of the transducer, and 0.7 dB/cm attenuation coefficient for the tissue. The attenuation coefficient for canine prostate through rectal wall tissue was experimentally derived in our laboratory. A total of 26 animals was treated in this study with survival times from 24 h to 12 weeks post-treatment. Prostate lesions were observed in all animals. There was no rectal injury or any abnormality found in kidney and bladder functions based on extensive serum and urine tests. The conditions of all canines were normal during their survival. The temperature results showed a transient rise in the focal zone close to 70–90°C, ($n = 12$) and 3 to 4°C ($n = 20$) near the rectal interface. The surrounding prostate tissue temperatures were normal during the entire procedure.

With the IDE and local institutional approvals, a total of 15 patients were treated at the Indiana University School of Medicine in 1992–1993. The details of the protocol and clinical results are described by Bihrle *et al.* [18].

The first 10 patients out of this group underwent on-line temperature monitoring at nine sites surrounding the prostate capsule [18], [19]. Also, in two patients, temperatures at the rectal wall mucosa were monitored. There were no significant temperature rises recorded in these patients. Similarly, the same protocol for temperature monitoring in human was implemented at the University of Vienna, Austria. In this study, temperatures in the focal zone, prefocal zone, and in the urethra were measured [20], and temperatures in the focal zone were recorded at 80–100°C.

For the initial study, the treatment zone was concentrated along the urethra and did not encompass the bladder neck. Other clinical sites outside the USA began patient treatment

[21], and the collective data on echographic visualization analysis revealed two phenomena that were not encountered in the initial canine studies. 1) Calcium deposits in the human prostate can appear as continuous echogenic structures or as more diffuse scattering elements. An exact criterion for excluding patients with calcification was established. 2) Two different types of echogenic changes were recorded during the clinical studies. One was a transient hyperechoic region mainly confined in the focal zone and appearing randomly. These events were termed as "popcorn." The second observation, although limited to only two clinical cases, was of a large echogenic change initiated in the focal zone. These echogenic changes persisted and grew rapidly in size toward the transducer as therapy continued. This was considered due to a migration of bubbles in the vasculature system and therefore it was called microbubbles [16]. The two phenomena are described below.

With the requirement to produce individual large lesions and consistent "popcorn," a series of canines was treated with peak intensities of 2200–3400 W/cm^2. Fig. 5 shows the hyperechoic region ("popcorn") in the focal zone due to higher intensity level. The hyperechogenicity was due to formation of vaporized gaseous bubbles at the focus. The hyperechogenicity was accompanied by an audible sound. A broad-band hydrophone and frequency spectrum analyzer measurements showed subharmonics associated with the event. There was a definite correlation between broad-band frequency spectra below the fundamental frequency (4 MHz) with a distinct signal at the half harmonic (2 MHz) and the hyperechogenicity as shown in Fig. 6. The long-term canines treated with these intensity levels resulted in a tissue cavity at the site of treatment. The canines killed at 72 h post-treatment showed a large lesion at the site of treatment. The central zone of the lesion was hemorrhagic and filled with destroyed blood vessels, glandular and stroma tissue, with a total mechanical disintegration of the tissue matrix. Surrounding the central zone was a brown coagulative lesion as shown in Fig. 7. The overall lesion was confined within the width and the length of the treatment boundaries, however, the anterior–posterior dimension was longer than 1 cm. In the long-term canines, a hypoechoic region was observed at the site of treatment at 72 h post-treatment with TRUS. This hypoechoic region grew in size and shape for several days and finally became a smooth spherical or ellipsoidal-shaped cavity. These animals were killed 55 days post-treatment. The prostate contained a large smooth cavity in place of the original urethra. The cavity was completely re-epithelialized. The size of the cavity was slightly smaller than the treatment dimensions, but was confined within the treatment boundaries. The pathology report indicated that the cavity was similar to a cavity produced by the TURP procedure in man. The rectal wall and other surrounding tissue were found normal. The gross transverse section of a canine prostate with the cavity is shown in Fig. 8.

The echogenic "clouds" in two clinical cases moved toward the posterior capsule and completely obscured visualization of the prostate as shown in Fig. 9. As a consequence of this finding, an effort was initiated to determine if similar events could be demonstrated in the animal experiments. A similar

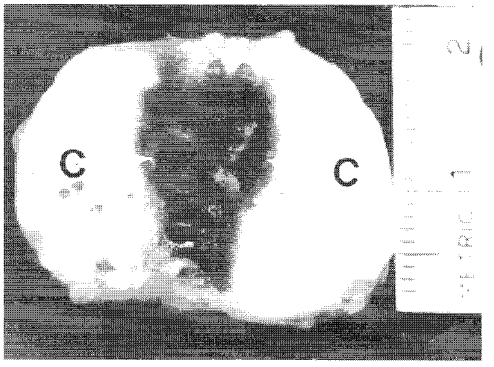


Fig. 7. A transverse section of a canine prostate after 72 h HIFU showing a cavity due to "popcorn" in the focal zone with a surrounding coagulative lesion.

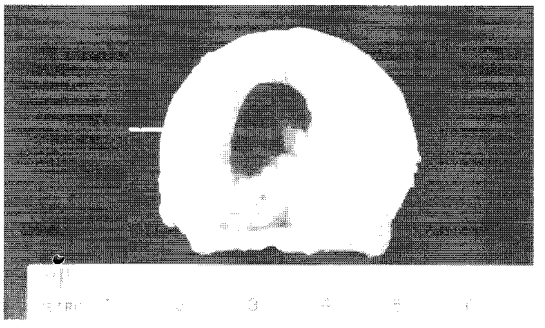
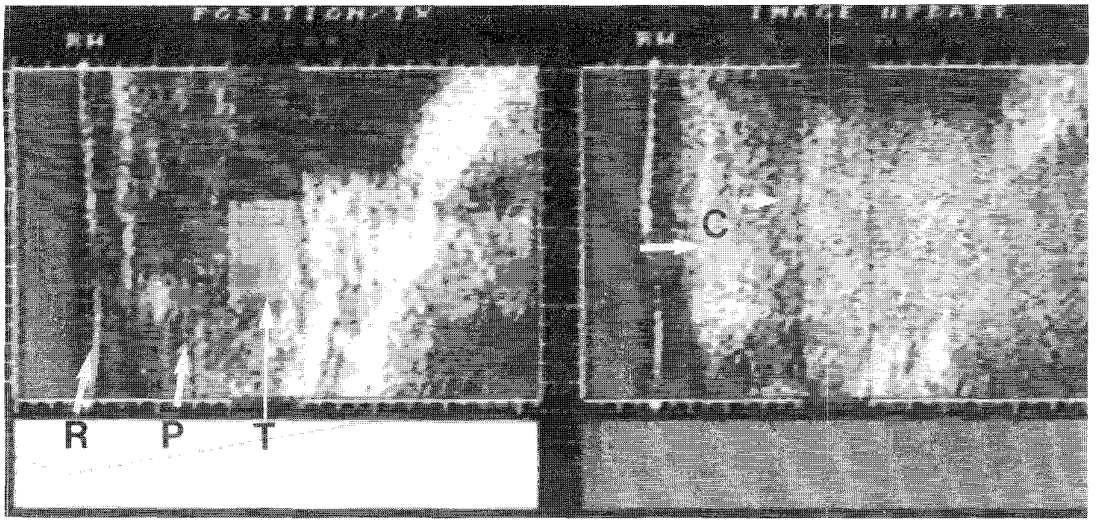


Fig. 8. A large "cavity" in the animal's prostate that correlates with the site of "popcorn" (55 days post-HIFU).

effect was clearly seen using a 4.0-cm focal length probe when driven to deliver 45–50 W of TAP with a peak focal intensity of 1800–2000 W/cm^2. The images showed diffuse echogenicity in the prostate which progressed toward the transducer and eventually completely shadowed visualization of the prostate. The temperature measured at the mucosa layer of the rectum increased steadily and at the onset of the "clouds," the temperature increased to more then 45°C. The temperature continued to rise as therapy continued and the "clouds" grew in size. Also, the probe water temperature continued to rise.

The gross pathology of these animals revealed a large serosal and mucosal injury. The prostate had a gross hemorrhagic and necrotic lesion extending from the anterior to posterior capsule with a pale central zone. The microscopic examination revealed extensive hemorrhage into the prostatic glands and stroma. In major areas, the glandular epithelium had lost its nuclei and cystoplasmic membranes were disrupted. In the center of the prostate, the tissue had undergone coagulative necrosis without significant hemorrhage.

To prevent rectal injury, a simple cooling method was employed with an external supply of circulating degassed water at a constant rate maintained at room temperature. With this system, the rectal wall temperature was kept at or below 37°C. This method demonstrated safe treatment in animals ($n = 20$) with no rectal injury with a large number of treatment sectors ($n = 17$) when the focal intensity was kept below 1700



(a) (b)

Fig. 9. (a) Human prostate echogram with an outline of a therapy zone. (b) An echogenic "cloud" that shadows the visualization of the prostate. R = rectal wall, P = prostate, T = treatment zone, and C = microbubble cloud.

TABLE III
RESULTS (PEAK FLOW RATE (QMAX) CHANGE) BASED ON THE TREATMENT PROTOCOLS

Treatment Protocol	Pre Qmax (ml/sec)	90 days post HIFU Qmax (ml/sec)
Prostate only (n=15)	9.2 (SD=3.6)	13.9 (SD=5.3)
Prostate+ Bladder neck (n=7)	9.8 (SD=2.1)	17.3 (SD=5.8)

W/cm^2 and TAP less than 40 W. With these findings, all the clinical sites were informed to pause the HIFU treatment if the echogenic "cloud" extended closer to 1 cm to the posterior capsule.

Data from a recent series of human patients in which the bladder neck and prostate gland were treated are shown in Table III and compared to previous data from patients without the bladder neck treatment.

A further evolution of the HIFU process was to look at the results of prostate lesions with an indwelling catheter left in the urethra during the treatment. With the catheter inside the urethra, there is always evidence of echogenicity at the catheter urethra interface, presumably caused by cavitation and gas bubble formation and trapping on the catheter surface, as shown in Fig. 10. Histology of this contact area in canines found complete ablation of tissue and in most cases mechanical shredding of urethra. Temperature measurement at the interface of tissue and catheter recorded by a TC is shown in Fig. 11. As the beam moves along the axial and sector positions, the temperature peaks rise and fall based on the relative position of the beam to the thermocouple. The step size of each axial and sector position is 1.8 mm and the focal beam size (−3 dB) is 0.5 mm. Therefore, the highest temperature (above 100°C) was recorded during the on time when the TC was intersecting the beam. During the off time, the temperature was above 80°C. This persisting elevated high

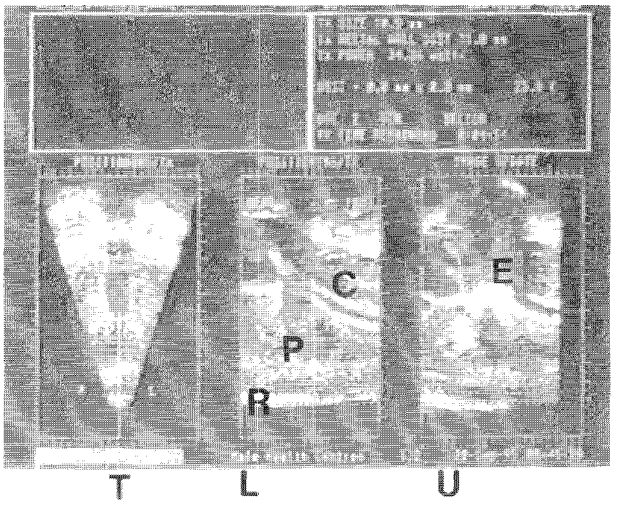


Fig. 10. Human prostate treatment with a catheter. The left two images are sector–linear modes before treatment. The vertical line indicates treatment position. The right image shows "echogenic" activities near the catheter–urethra interface. T = transverse, L = longitudinal, U = update image, R = rectal wall, P = prostate, C = catheter, and E = echogenicity during the treatment.

temperature during the treatment cycle is consistent with the desire to guarantee ablation of the urethra.

IV. DISCUSSION

The canine prostate is an adequate model for the experimental studies since the full-sized probe and protocol were implementable as a prelude to clinical application. Few canines have sufficiently large prostates to present the conditions met in the entire spectrum of clinical studies, but this has not been a serious limitation.

The initial feasibility study used a focal peak intensity of 700 W/cm^2, which at 4 MHz did not produce ultrasonically observable cavitation in the canine prostate. In the production

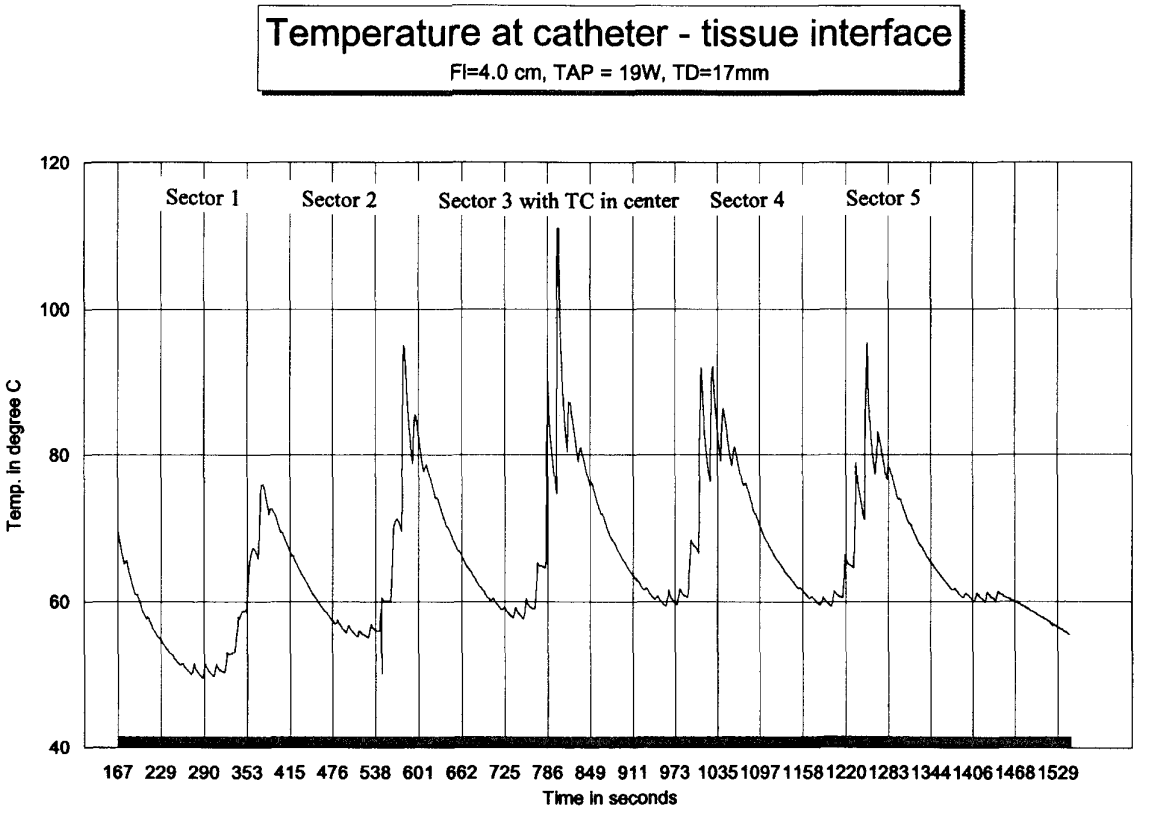


Fig. 11. Temperature profile generated during the canine prostate treatment with an indwelling catheter. The profile is for the entire treatment. A bare wire tip thermocouple was placed at the catheter–tissue interface located in the focal zone. The temperature profile shows peaks and valleys as a function of sound on/off cycle and the location of the ultrasound beam relative to the TC position. The relative step size between sectors and axial positions was 1.8 mm. The highest temperature was recorded above 100°C when the TC intersected the beam (sector 3, axial position 2). The high temperature remains throughout the treatment, ensuring the tissue destruction.

of large contiguous lesions, we used an off period of one to two minutes between individual lesion sites. Hence these lesions were of the thermocoagulative type, with tissue returning to normal temperature after each HIFU exposure. The threshold ultrasound energy dosage required to produce lesions in the canine prostate was found higher compared to liver ablation threshold reported by Frizzell [17]. The total treatment time required for prostate tissue debulking under these conditions was considered prohibitive from a clinical requirement. Therefore, the focal peak intensity was raised to 1680 W/cm^2 and the on/off period between individual site exposure was set at 4 and 12 s.

The temperature study data both from animals and humans resulted in a very high level of safety when operating the device below a peak intensity level of 1700 W/cm^2 and TAP less than 40 W. Additionally, safety was established for the tissue surrounding the prostate. Although these parameters produced vaporized bubbles in some patients at the focal sites as evidenced by the "popcorn" in the images, the canine studies indicated that to produce "popcorn" on a consistent basis required peak intensity in the range of 2200–3400 W/cm^2.

In a short clinical study (Royal Jubilee Hospital, Victoria, B.C.), 12 patients were followed to correlate cavity versus change in peak urine flow rate. The patients were examined by endoscopic and TRUS procedures to confirm prostatic cavities in four patients. The patients with cavities reported a urine flow rate increase of more than 100% with a final rate of 15 mL/s or higher.

A significant finding in the clinic which was not present in the initial animal studies was the migration of echogenic "clouds" from the beam focal zone cavitation seeding site. Although cavitation ("popcorn") could be present in the canine as discussed above, it did not result in subsequent proliferation of echogenic "clouds" which moved from the focus toward the transducer at the lower total acoustic power levels. Discovery of this event lead to studies to evaluate its significance. It was apparent that such echogenic areas would reduce sound transmission to regions beyond which could serve as an energy trap and could be a source of cavitation leading to mechanical damage of blood vessels and tissues. This phenomenon required users to be informed to watch ultrasound images carefully during the HIFU treatment. The request was to pause the HIFU treatment if the echogenic "cloud" extended closer than 1 cm to the posterior capsule.

Clinical trials using an indwelling catheter in the prostate are on going in Canada and Japan. Preliminary patient results indicate faster relief of BPH symptoms in all patients and an acceptable improvement of urine peak flow rate in 90% of the patients. Thus with this treatment protocol, the outcome rate has become more reliable for majority of the patients.

V. CONCLUSION

The significant aspect of noninvasive surgery using HIFU has been implemented from conceptual perceptions to animal studies and finally in the clinical trials. As of now, over 600 BPH patients have been treated using this device. The project demonstrated the importance of close working relationships among engineers, scientists, and physicians as it involved new therapeutic aspects for noninvasive surgery of the prostate.

The first 15 patients were treated with a protocol that did not include bladder neck ablation and only 59% of these patients were judged to be treated effectively. With the revised protocol and methodology, the clinical efficacy has improved considerably which appears to meet certain standards set by the TURP procedure.

It was presumed that ablating the urethra and periuretheral tissue would alleviate the urethra constriction and result in relief of BPH. However, it was found essential to treat bladder neck tissue to help improve clinical efficacy. In addition to BPH relief, HIFU was supposed to provide other clinical benefits, such as minimal use of anesthesia, reduced bleeding, reduced morbidity, and reduced hospital stay. The early clinical trials have shown to achieve some of these benefits [18], [21].

Furthermore, the invaluable role of animal studies in proving safety and presumptive efficacy has been clearly demonstrated. The extensive animal studies have also provided a through evaluation of device performance, which has helped prevent clinical down time.

Note: The animal protocols were approved by the Indiana University School of Medicine Institutional animal care and use committee.

ACKNOWLEDGMENT

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REFERENCES

[1] J. G. Lynn, R. L. Zwemer, A. J. Chick, and A. F. Miller, "A new method for the generation and use of focused ultrasound in experimental biology," *J. General Physiology*, vol. 26, pp. 179–193, 1942.

[2] P. D. Wall, W. J. Fry, R. Stephens, D. Tucker, and J. Y. Lettvin, "Changes produced in the central nervous system by ultrasound," *Sci.*, vol. 114, pp. 686–687, 1951.

[3] G. ter Haar, "Ultrasound focal beam surgery," *Ultrasound Med. Biol.*, vol. 21, pp. 1089–1100, Sept. 1995.

[4] W. J. Fry, J. W. Barnard, F. J. Fry, and J. F. Bernnan, "Ultrasonically produced localized selective lesions in the central nervous system," *Amer. J. Phys. Med.*, vol. 34, pp. 413–423, 1955.

[5] D. J. Coleman, F. L. Lizzi, J. Driller, A. L. Rosado, S. E. P. Burgess, J. H. Torpey, M. E. Smith, R. H. Silverman, M. E. Yoblonski, S. Chang, and M. J. Rondeau, "Therapeutic ultrasound in the treatment of glaucoma II. Clinical applications," *Ophthalmology*, vol. 92, pp. 347–353, Mar. 1985.

[6] N. T. Sanghvi, R. S. Foster, F. J. Fry, R. Bihrle, A. M. Snoddy, S. L. Griffith, and T. D. Franklin, "Preliminary findings of treatment of canine prostatic tissue using high-intensity focused ultrasound," *J. Ultrasound Med.*, vol. 10, p. s45, Mar. 1991.

[7] R. S. Foster *et al.*, "Production of prostatic lesions in canines using transrectally administered high-intensity focused ultrasound," *Eur. Urology*, vol. 23, pp. 330–336, Feb. 1993.

[8] N. T. Sanghvi, R. S. Foster, F. J. Fry, R. Bihrle, C. Hennige, and L. V. Hennige, "Ultrasound intracavity system for imaging, therapy planning and treatment of focal disease," in *Proc. IEEE 1992 Ultrason. Symp.*, pp. 1249–1253.

[9] N. T. Sanghvi and J. N. Zink, "Curved rectangular/elliptical transducer," U.S. Patent 5 117 832, June 1992.

[10] F. J. Fry, G. Kosoff, R. C. Eggelton, and F. Dunn, "Threshold ultrasonic dosages for structural changes in the mammalian brain," *J. Acoust. Soc. Amer.*, vol. 48, pt. 2, pp. 1413–1417, June 1970.

[11] K. Hynynen, "The threshold for thermally significant cavitation in dog's thigh muscle *in vivo*," *Ultrasound Med. Biol.*, vol. 17, pp. 157–169, Feb. 1991.

[12] K. Hynynen and D. K. Edwards, "Temperature measurements during ultrasound hyperthermia," *Med. Phys.*, vol. 16, pp. 618–626, July-Aug. 1989.

[13] W. J. Fry and F. Dunn, "Ultrasound: Analysis and experimental methods in biological research," *Phys. Tech. Biol. Res.*, vol. 4, pp. 261–394, 1962.

[14] W. J. Fry and R. B. Fry, "Determination of absolute sound levels and acoustic absorption coefficient by thermocouple probes—Experiments," *J. Acoust. Soc. Amer.*, vol. 26, pp. 311–317, 1954.

[15] K. J. Parker, "The thermal pulse decay technique for measuring ultrasonic absorption coefficients," *J. Acoust. Soc. Amer.*, vol. 74, pp. 1356–1361, Nov. 1983.

[16] F. J. Fry, N. T. Sanghvi, R. S. Foster, R. Bihrle, and C. Hennige, "Ultrasound and microbubbles: Their generation, detection and potential utilization in tissue and organ therapy—Experimental," *Ultrasound Med. Biol.*, vol. 21, pp. 1227–1237, Dec. 1995.

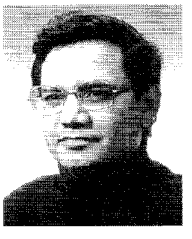
[17] L. A. Frizzell, "Threshold dosages for damage to mammalian liver by high intensity focused ultrasound," *IEEE Trans. Ultrason., Ferroelect., Freq. Contr.*, vol. 35, pp. 578–581, Sept. 1988.

[18] R. Bihrle, R. S. Foster, N. T. Sanghvi, J. P. Donohue, and P. J. Hood, "High intensity focused ultrasound for the treatment of BPH: Early U.S. clinical experience," *J. Urology*, vol. 151, pp. 1271–1275, May 1994.

[19] N. T. Sanghvi, R. S. Foster, R. Bihrle, R. F. J. Fry, M. Phillips, and C. Hennige, "Transrectal ablation of prostate tissue using focused ultrasound," in *Proc. IEEE 1993 Ultrason. Symp.*, vol. 2, pp. 1207–1210.

[20] S. Madersbacher, M. Pedevilla, L. Vingers, M. Susani, and M. Marberger, "Effect of high intensity focused ultrasound on human prostate cancer *in vivo*," *Cancer Res.*, vol. 55, pp. 3346–3351, Aug. 1995.

[21] S. Madersbacher, C. Kratzik, M. Susani, and M. Marberger, "Tissue ablation in benign prostatic hyperplasia with high intensity focused ultrasound," *J. Urology*, vol. 152, pp. 1956–1961, Dec. 1994.



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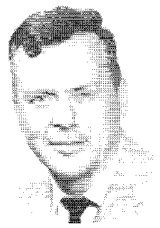

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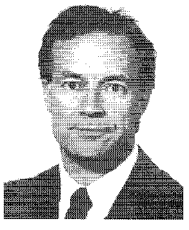
Dr. Bihrle belongs to eight professional societies and serves on various committees.



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Jayne Syrus has a background in the development, testing, and marketing of medical instruments. She was involved with two start-up companies who manufactured and distributed ultrasound equipment. As an Application Specialist, she participated in the clinical trials and research projects of the Sonablate, a noninvasive surgical instrument used to treat prostate disease, which is currently used outside of the United States. She assisted in research projects at Indiana University Medical Center, Indianapolis, during the preliminary phase of research using animals. Her nursing background introduced her to the wide applications and benefits of ultrasound as a valid diagnostic tool for physicians.

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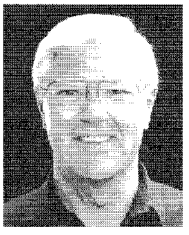

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