

# HIGH-INTENSITY FOCUSED ULTRASOUND IN THE TREATMENT OF PROSTATIC TISSUE\*

RICHARD BIHRLE, M.D.  
RICHARD S. FOSTER, M.D.  
NARENDRA T. SANGHVI, M.S.E.E.  
FRANK J. FRY, M.S.  
JOHN P. DONOHUE, M.D.

From the Indiana University Medical Center,  
Indianapolis, Indiana

**ABSTRACT—Objective.** Beginning in 1987, high-intensity focused ultrasound was investigated in the canine model to determine the feasibility of destroying prostate tissue. After demonstrating the ability to ablate prostate tissue reliably in a canine model, a 15-patient pilot clinical study was undertaken at Indiana University in the fall of 1992. This pilot study was undertaken to assess the safety in the human clinical situation, as well as to give some early efficacy results.

**Methods.** The early canine feasibility studies were conducted via a suprapubic extracorporeal approach using two separate transducers, one for imaging and the other for therapy. Subsequent to this, a transrectal probe, which had the dual capability of both imaging and therapy, was developed and used to treat canine prostates in a formal, "good laboratory practice" study to determine the safety of this technology prior to beginning treatment of human benign prostatic hypertrophy.

**Results.** The formal canine studies demonstrated that prostatic tissue could be reliably ablated in the therapy zone. The dosimetry and duty cycle required to ablate canine prostatic tissue effectively was also determined in this study. The study also demonstrated that the prostatic tissue could be ablated without injury to the intervening rectal tissue or periprostatic tissue. The human pilot study has also demonstrated safety of high-intensity focused ultrasound, as well as early efficacy.

**Conclusions.** These early clinical results are encouraging, but assessment of efficacy will require a randomized study comparing high-intensity focused ultrasound to sham and to transurethral prostatectomy. This multicenter trial is currently planned.

For the past several decades, transurethral prostatectomy (TURP) has been the accepted, preferred treatment for men with symptomatic benign prostatic hyperplasia (BPH). Despite the relative success and safety of transurethral resection of the prostate, the morbidity and mortality associated with TURP has spawned a host of alternative treatments to TURP.<sup>1-5</sup> Less invasive technologic alternatives have ranged from thermal cell destruction to placement of expandable stents and coils. The majority of new technologies have centered around the delivery of thermal energy to the

prostate, via a side-firing right-angle laser, transrectal microwave hyperthermia, and transurethral microwave thermotherapy. Among the alternative thermal treatments is that of high-intensity focused ultrasound (HIFU), which is delivered via a transrectal approach.

HIFU is a method of delivering ultrasonic energy with resultant heat and tissue destruction to a discrete, distant point, without causing significant temperature increase or cellular injury to tissue lying in the path of the ultrasound beam. Different from other forms of thermal energy being used to treat BPH, ultrasound has the unique ability of being tightly focused at a distant point. This focusing can create temperatures in the focal zone

\*Supported by a grant from Focal Surgery Inc., Milpitas, California.

of 80–90°C. Heating of tissue to this extent will lead to a small area of coagulative necrosis. By using computer control to place small focal volumes of coagulative necrosis in a predetermined three-dimensional contiguous matrix, many small lesions of coagulative necrosis are created, resulting in a volumetric ablation of prostatic tissue.

The ability to focus ultrasound is not new. By the 1950s, work with focused ultrasound had progressed to the point that lesions in the feline central nervous system could be created without injuring surrounding brain tissue.<sup>6</sup> In the 1960s and 1970s a small number of human patients with deep-seated brain tumors were treated with focused ultrasound after removal of the cranial bone flap.<sup>7</sup> In 1984 Goss and Fry<sup>8</sup> reported the use of HIFU in the treatment of subdermally implanted sarcomas in the rat model. Further studies were designed to determine the feasibility of ablating neuroblastomas using HIFU.<sup>9</sup> Although ultrasound energy has long been able to be focused, clinical applicability was hampered by the inability to target the ultrasound beam adequately. Since improved resolution has led to the widespread use of ultrasound as a diagnostic tool, combining imaging with focal tissue ablation has long been a desired goal. In addition, the development of newer piezoceramics has made possible the development of a transducer that has the combined ability of both visualization and high-powered ablation using a common element. This technologic advance led to a device with a transducer size that was small enough to be introduced into body cavities, such as the rectum, thus allowing treatment of the prostate via a transrectal approach.<sup>10</sup>

In 1987, feasibility studies were performed at Indiana University and the Indiana Center for Advanced Research (ICFAR) to determine whether focused ultrasound was capable of ablating prostatic tissue. These initial studies, which were performed using an extracorporeal suprapubic approach, determined that focused ultrasound was indeed capable of destroying prostatic tissue with good control and without injury to intervening tissues. Between 1987 and 1989, a specially developed transrectal probe that had the ability of both imaging and therapy was developed and used in canine studies. These studies were important in defining dosimetry, attenuation of the canine rectal wall and prostate proper, and the proper on and off time of ultrasonic pulses. Following these preliminary studies, a more formal study using 26 canines was commenced. This study, which was conducted under regulations set out by “good lab-

oratory practice” standards, used a set protocol and included monitoring of periprostatic temperatures. These studies resulted in the development of a human protocol.

Initial human studies were planned at Indiana University to commence in the spring of 1992. However, due to United States regulatory issues, it was determined that a second site was necessary. For this reason the University of Vienna was chosen to perform the procedure on the first patients in the early summer of 1992. Both the University of Vienna and Indiana University now have initial experience using HIFU to treat human BPH.

This article will discuss the formal canine study of 26 dogs, which was submitted to the Food and Drug Administration (FDA) to gain approval for initial human studies. The results of this study have been previously published by Foster *et al.*<sup>11</sup> In addition, some brief comments regarding the early results of the initial human clinical experience at Indiana University will be presented.

## MATERIAL AND METHODS

### DEVICE

The transrectal probe used was a 4-MHz ultrasonic transducer that was capable of both imaging and therapy. This transducer was a modified lead titanate ceramic that is configured into a curved element measuring 30 mm in length by 22 mm in width. This material is capable of withstanding the high electrical power density needed during therapy while remaining a satisfactory material for operating in the pulse echo mode that is required for imaging. To image at the necessary depth of field in the pulse echo mode, only the central circular 12-mm diameter portion of the transducer is excited. During therapy, the entire transducer surface is excited in a continuous wave burst mode. Based on earlier canine studies, the attenuation of the canine rectal wall and prostate was assumed to be 0.7 dB/MHz/cm. Also based on previous preliminary studies, the power density at the focal point was set at 1,680 W/cm<sup>2</sup>. In order to produce lesions of adequate size and shape, the transducer is driven up to 25 W of total radiofrequency power for 4 seconds. To allow dissipation of heat, therapy is turned off for 12 seconds between continuous wave bursts. Between therapy cycles, the central portion of the element is operated in the pulse echo mode to update the image and monitor the position of the chosen therapy zone. The focal length of the transducer was 2.5 cm.

Beagle dogs between 10 and 15 kg were used as the animal model. All dogs were fasted 48 hours prior to therapy. Therapy was conducted under

anesthesia, which consisted of a ketamine "cocktail," intubation, and maintenance with oxygen and nitrous oxide. Cleansing enemas were performed prior to insertion of the therapy probe. Prior to insertion of the therapy probe, a standard 7.5 MHz imaging probe was used to image and assess the perimeters of the canine prostate adequately. Renal ultrasonography was also performed to ascertain normalcy of the upper urinary tract. Venipuncture was done to determine pretreatment serum values. Multisensory needles with thermocouples placed 1 cm apart were placed percutaneously into the periprostatic area using both ultrasound and digital guidance. Thermometry was conducted both posterolaterally and anterior to the prostate.

The therapy probe was prepared for insertion by covering it with a latex condom and filling the condom with degassed water. The condom was liberally covered with ultrasound gel prior to insertion into the canine rectum. With the combined imaging-therapy probe in place, the imaging mode was used to localize the canine urethra, which was delineated with the use of either a wire or small Meditech balloon catheter. Once the desired periurethral tissue was within the therapy zone, the probe was fixed to the table. Using a track ball, a desired zone of ablation was chosen and stored in the computer. Therapy was then begun and carried out under computer control. The therapy was therefore carried out without the need of hands-on control, using a four-second continuous wave ultrasonic pulse, followed by a twelve-second imaging period.

Ablation was carried out by sequencing individual lesions 1.8 mm apart in a longitudinal midline plane. The transducer is capable of rotating laterally up to 10°. This rotation allows for multiple sectors to be treated. In this study seven consecutive sectors were treated, first the midline and then three sectors on each side of the midline. The length of the longitudinal zone was determined by the zone selected on the computer screen.

A total of 26 dogs were used in this study. Twenty-four of these dogs underwent therapy with HIFU and two were used as shams. The two sham animals were sacrificed at 2 and 12 weeks. In order to determine evolution of the ablation area over time, the remaining 24 dogs were sacrificed at six different intervals. Four each were sacrificed acutely, at seventy-two hours, fourteen days, twenty-eight days, six weeks, and twelve weeks after therapy. Euthanasia was performed using thiopental sodium, after which tissues were

perfused with formalin. The rectum, as well as all periprostatic tissue, bladder, and prostate were excised and blocked. Tissues were fixed for gross and histologic analysis.

## RESULTS

The thermometry data are somewhat difficult to interpret due to technical difficulties with the thermocouples themselves or with the software. Because of these difficulties thermometry data could not be obtained in six of the treated dogs. Consequently, data were available in 18 of the 24 treated dogs and the two sham dogs. In addition, the desired goal of placing the thermistors just outside the prostatic capsule was not always achieved. At sacrifice, it was noted that several dogs had thermistors placed within the prostate itself. Despite these limitations some observations can be made.

Of 20 dogs available for analysis, eight treated dogs and the two sham dogs did not exhibit any increase in temperature above 42°C during any point in the therapy. The other 10 treated dogs experienced a transient increase above 42°C lasting for 1–2 seconds and then rapidly returning to normal. Even in situations in which the thermistor was placed within the prostate, and therefore was either within or very near the beam, the temperature rose to 55°–60°C and lasted only seconds.

A comprehensive report of results of the canine study has been published previously.<sup>11</sup> Consequently, this will serve as a summary of the canine results.

No clinically significant alteration in serum levels was noted following therapy. Although statistically significant alterations were seen, the values remained within the normal range for canines. Relative to changes in the urinalysis, an increase in urine protein was seen immediately after therapy. However, this mild increase returned to normal levels between two and six weeks post-therapy. All dogs urinated normally post-therapy and in no instance was gross hematuria seen.

Renal function, as measured by serum creatinine and renal ultrasonography, was not altered regardless of the interval to sacrifice. Specifically, serum creatinine remained within the normal range and hydronephrosis was not seen on any follow-up study.

Both gross and microscopic pathologic lesions were seen in all 24 treated dogs. Although there was variability in the size of the lesion produced from that which would be predicted by the size of the delineated zone chosen on the computer screen, some general comments regarding lesions

can be surmised. Dogs sacrificed at greater intervals after treatment tended to have smaller lesions than dogs sacrificed acutely or at shorter intervals. Gross pathologic lesions evolved from a reddish brown discoloration in the acute dogs to dark brown/black discoloration in the seventy-two-hour sacrificed dogs to black discoloration with early cystic cavities seen at the fourteen-day sacrificed dogs. By twenty-eight days, complete cystic cavities surrounded by normal prostate were seen, and this gross pathologic picture was consistent at six and twelve weeks. Histopathologically, the lesions evolved from coagulative necrosis at acute and seventy-two hours to cavities lined with regenerative squamoid-type epithelium and surrounded by zones of fibrosis containing inflammatory cells at two weeks. At twenty-eight days and beyond from the time of treatment, the cavities were lined with urothelium that was in communication with prostatic ducts. Both the gross pathologic and histopathologic findings in the sham dogs showed no evidence of tissue abnormality. No evidence of rectal injury was noted grossly or histopathologically in any of the 26 canines.

No complications were noted during therapy. Post-therapy, two dogs developed epididymo-orchitis, demonstrated by fever and scrotal induration. Both dogs went on to scrotal abscess formation, which drained spontaneously without requiring surgical intervention.

#### HUMAN STUDIES PRELIMINARY RESULTS

Fifteen patients were treated at Indiana University under an FDA approved protocol. This study was set up as a Phase I/II pilot study to assess safety of HIFU prior to commencing a multicenter randomized study. Because safety was a priority, the FDA required the first 10 patients to undergo periprostatic thermometry. Due to the fact that at the time of this symposium results were not final, only general comments regarding the human pilot study can be made.

The first 10 patients underwent periprostatic thermometry via three thermistors that contained three thermocouples each. Thermistors were placed posterolaterally at 4 and 8 o'clock and anteriorly at 12 o'clock. None of the thermocouples registered a sustained elevation more than 3°C. Transient elevations of 3°C were seen in three patients, the greatest rise being 17°C in one thermocouple. In all cases the temperature returned to baseline within seconds. None of the patients experiencing a temperature increase developed a complication related to periprostatic heating.

#### ANESTHESIA

Because the first 10 patients required placement of transperineal thermistors, it was thought appropriate to offer these patients either general or regional anesthesia. The five patients not requiring thermometry were offered therapy under local anesthesia with intravenous sedation. Of these five patients, four were successfully treated with intravenous sedation, but the fifth patient required general anesthesia.

#### EFFECTIVENESS

A detailed report of the results of the pilot study will be the subject of a forthcoming article dedicated to the early human studies only. However, a few general comments at thirty- and ninety-day follow-up can be given.

Symptom score assessment at thirty days showed a marked improvement of approximately 50 percent, which was sustained at the ninety-day interval.

Peak flow rate assessment at 30 days showed variability in improvement. Although some patients demonstrated a mild-to-moderate improvement, others had virtually no improvement. However, at the ninety-day follow-up, all but two of the patients showed a marked improvement in peak flow rate.

Postvoid residual, on the other hand, showed significant improvement at thirty days, while being somewhat inconsistent at ninety days.

There was a significant variability seen in the degree of tissue destruction as demonstrated by prostate ultrasonography. Some patients exhibited dramatic evidence of tissue destruction (Fig. 1), whereas others demonstrated lesser degrees of hypoechoic lesions, and some had no evidence of tissue destruction.

No significant complications were noted during therapy. Proctoscopy performed immediately post-treatment showed no evidence of excoriation or injury to the rectum. The first 10 patients who underwent thermometry had suprapubic tubes placed at the time of treatment. Generally, these tubes were removed in two-three days. The five patients not undergoing thermometry were treated without suprapubic tubes. Three of these patients voided spontaneously and two required catheterization for one-two days.

The only significant complication noted post-therapy was that of hematospermia, which occurred in about half of the patients. However, all cases of hematospermia had resolved by the ninety-day follow-up.

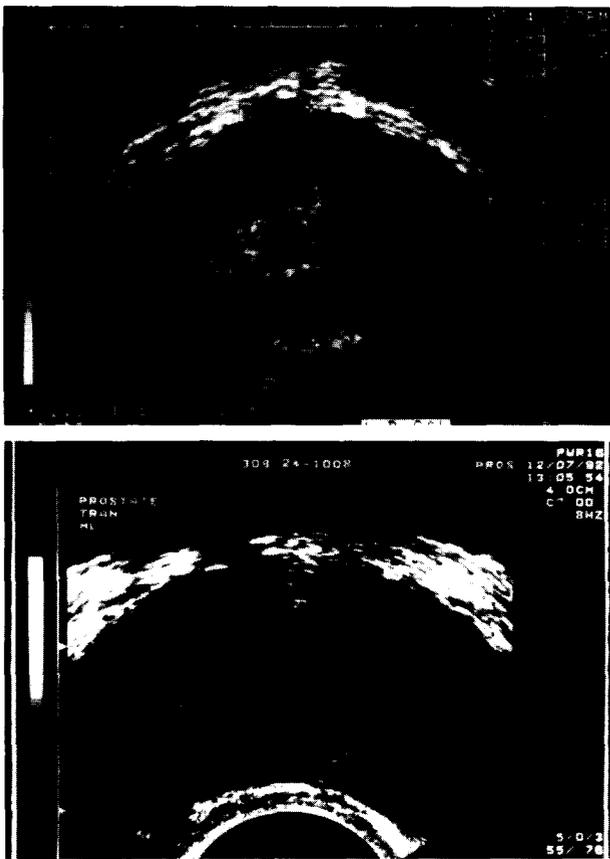


FIGURE 1. (A) Transverse ultrasound image of the prostate prior to treatment. (B) Transverse ultrasound image of the prostate at 30 days post-treatment.

#### COMMENT

These formal canine studies and initial human studies demonstrated that prostatic tissue can be destroyed using HIFU via a transrectal approach. Based on these studies, the therapy appears to be safe and associated with only minimal morbidity. The only complications seen in the canine study were two episodes of epididymo-orchitis. In humans, the only significant side effect was that of hematospermia, which was self-limiting in all cases.

Review of the canine pathologic findings showed the thermal injury created by focused ultrasound to be that of coagulative necrosis. Over time, this lesion appears to evolve to a cystic cavity resulting in a net loss of tissue. Based on these canine pathologic studies, there is some concern over the fact that cystic lesions were not produced consistently in each dog. Although pathologic results are not available in the human study, cystic cavity formation and net tissue loss measured by ultrasound imaging also appears to be quite variable and somewhat inconsistent from patient to patient. There are a number of treatment variables that can be altered to implement a change in the

degree of tissue destruction. The optimal power intensity at the focal zone, on-off times, sequence and spacing of lesions, and volume of prostate treated have not been completely defined. As this technology advances, optimal treatment parameters will emerge and consistency from patient to patient will improve. The ability to characterize tissue changes radiographically during treatment, and to correlate these changes with a successful ablation outcome, is a desirable goal that undoubtedly will be developed in the future.

Although the human data are not mature, the early results are encouraging. Objective urodynamic evaluation and subjective symptoms score improvements are similar to those seen with early results of laser prostatectomy. In clinical practice the therapy has the potential to be performed under intravenous sedation, local anesthesia, or prostate block. In addition, as demonstrated in our initial clinical trials, the potential to perform this on an outpatient basis is quite likely. A United States multigroup randomized study comparing HIFU to sham and TURP has been designed and will commence shortly.

Many of the alternative treatments for alleviating prostatic obstructive symptoms use thermal change in the prostate tissue. The patient advantages of ultrasound over the other thermally mediated treatments are that ultrasound is focusable. This allows for high-energy density (heat) to be delivered to a distant site without alteration of intervening tissue. Therefore, it has some theoretic advantages over energy forms that must be delivered transurethraly in order to attain meaningful periurethral tissue temperature elevation. It may reduce the risk of complications that are related to urethral instrumentation (i.e., urinary tract infection, urethral stricture, or bladder neck contracture). It is hoped that this energy modality will add to the armamentarium that is evolving for the treatment of BPH. The degree of success that HIFU has in the treatment of BPH will impact on future potential applications of this non-invasive therapy. Potential areas of study, some of which have already begun, include intraoperative tumor ablation, other intracavitary approaches to benign and malignant tumors, and transcutaneous ablation of tissue.

Richard Bihrlle, M.D.  
Indiana University Medical Center  
Indianapolis, Indiana 46202

#### REFERENCES

1. Lepor H, Sypherd D, Machi G, and Derus J: Randomized double-blind study comparing the effectiveness of bal-

loon dilation of the prostate and cystoscopy for the treatment of symptomatic benign hyperplasia. *J Urol* **147**: 639–644, 1992.

2. Ogden CW, Reddy P, Johnson H, Ramsay JW, and Carter SS: Sham versus transurethral microwave thermotherapy in patients with symptoms of benign prostatic bladder outflow obstruction. *Lancet* **341**: 14–17, 1993.

3. Lepor H: Non-operative management of benign prostatic hyperplasia. *J Urol* **141**: 1283–1289, 1989.

4. Montorsi F, Galli L, Guazzoni G, Colombo R, Bulfamante G, Barbieri L, Matorzo V, Grazioli V, and Rigatti P: Transrectal microwave hyperthermia for benign prostatic hyperplasia: long term clinical pathological and ultrastructural patterns. *J Urol* **148**: 321–325, 1992.

5. Roth RA, and Aretz HT: Transurethral ultrasound-guided laser-induced prostatectomy (TULIP procedure): a canine prostate feasibility study. *J Urol* **146**: 1128–1135, 1991.

6. Fry WJ, Mosberg WH Jr, Barnard JW, and Fry FJ: Production of focal destructive lesions in the central nervous system with ultrasound. *J Neurosurg* **11**: 471–478, 1954.

7. Heimburger RF: Ultrasound augmentation of central nervous system tumor therapy. *Indiana Med* **78**: 469–476, 1985.

8. Goss SA, and Fry FJ: The effect of high intensity ultrasound irradiation of tumor growth. *IEEE Son Ul* **31**: 491–496, 1984.

9. Rescorla FJ, Yang R, Reilly CR, Sanghvi NT, Fry FJ, Franklin TD, Lumeng L, and Grosfeld JL: Evaluation of high intensity focused ultrasound in the treatment of murine neuroblastoma. *Surg Forum* **41**: 581–583, 1990.

10. Sanghvi NT, Foster RS, Fry FJ, Bihrlle R, Hennige C, and Hennige LV: Ultrasound intracavity system for imaging, therapy planning and treatment of focal disease. *IEEE 1992 Ultrasonics Symposium Proceedings 2*: 1249–1253, 155N1051-0117, 1992.

11. Foster RS, Bihrlle R, Sanghvi N, Fry F, Kopecky K, Regan J, Eble J, Hennige C, Hennige LV, and Donohue JP: Production of prostatic lesions in canines using transrectally administered high-intensity focused ultrasound. *Eur Urol* **23**: 330–336, 1993.