

## HIGH INTENSITY FOCUSED ULTRASOUND TREATMENT OF HUMAN BPH

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### INTRODUCTION

High intensity focused ultrasound is a means of focusing continuous ultrasonic energy at a point distant from the transducer, creating high energy at the focal point without damaging intervening tissue. The tissue at the focal point is heated to very high temperatures which results in coagulative necrosis. Alternatively, even higher energies can be deposited in the area of the focal zone creating cavitation with resultant immediate vaporization. The interest of the Department of Urology at Indiana University relative to focused ultrasound began in late 1986.

ICFAR, an affiliate arm of Indiana University had been involved in ultrasound related research for many years. First, Frank Fry and his brother Bill, followed by Narendra Sanghvi, had investigated the use of focused ultrasound in various animal tumor models. Subsequently, human studies attempting to employ focused ultrasound to destroy deep seated brain lesions was undertaken (Fry, et al., 1954).

In 1987 feasibility studies were begun at Indiana University under the auspices of the Department of Urology to determine whether or not focused ultrasound could be used to ablate prostate tissue. First, an extracorporeal transducer was used to successfully place lesions in canine prostates via a trans-abdominal suprapubic approach. After the successful completion of these experiments a decision point was

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reached whereby it was necessary to determine which sort of delivery system (transurethral, extracorporeal, transabdominal, or transrectal) would be most effective and applicable for human use. The transrectal route was ultimately selected because of favorable size considerations relative to the transducer, the lack of skin being in the beam path which would attenuate the beam, and the growing familiarity and acceptance of urologists around the world of diagnostic transrectal ultrasound.

After selecting the transrectal route for delivering the energy, the decision was made to explore treatment of human BPH rather than human prostatic carcinoma. This decision was made for several reasons. 1. It was felt that successful treatment of human BPH could be attained by creation of an ablated zone in the central aspect of the prostate without having to target distinct areas in the peripheral zone which would be necessary for the treatment of cancer. 2. It was elected to use the same transducer for imaging and therapy and it was determined that 4 mHz would be most ideal. Imaging for the detection of prostate cancer is done more capably with 7 1/2 mHz. 3. Regulatory constraints in the United States are such that it was felt approval for human use treating BPH would be more expeditious than attempting to obtain approval for the treatment of carcinoma of the prostate. These reasons then led to further canine experiments using a prototype transrectal probe and subsequently to the first human trials using this device (Foster, et al., 1993, Madersbacher, et al., 1993, Bihrlé, et al., 1993). These human trials were performed initially in Austria under the auspices of Michael Marberger because of bureaucratic constraints in the United States. Subsequently, in the autumn of 1992 studies were begun in the United States at Indiana University. These studies are the focus of this presentation.

## MATERIALS AND METHODS

### Technology

A transrectal probe employing a 4 mHz ultrasonic transducer capable of both imaging and high intensity therapy was developed. Initially in the canine studies the focal length of the transducer for therapy was 2.5 cm. Subsequently probes with focal lengths of 3 and 3.5 cm. were developed for the initial human trials.

A rectangular transducer with separate imaging and therapy elements was used to initially image the prostate using manual control. A catheter was inserted per urethra in order to adequately delineate the urethra. The imaging mode was then used to center the prostate in appropriate position relative to the transducer. The probe was next

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fixed to the table after which computer control was used throughout the remainder of the procedure.

After the probe is fixed in position the image is displayed on a computer screen. Software was developed in order to carry out the actual therapy. The operator uses a track ball in order to select a longitudinal zone of therapy along the urethra. Alternate imaging followed by therapy is then carried out along the entire linear aspect of the zone. After the initial zone is treated in the twelve o'clock position the transducer rotates laterally and creates another zone in the far lateral aspect of the transverse plane. Ultimately nine zones or sectors are subjected to therapy in the transverse plane. The length of the zone in the longitudinal plane is determined by the area selected by the operator on the computer screen. The depth of the focal zone is approximately 1 cm.

The attenuation of canine and human rectal wall in prostate are very similar, based on preliminary studies. This attenuation was assumed to be .7 db/mHz/cm. Based on prior canine experiments the power density at the focal point was set at 1680 watts per square centimeter.

**Technique**

Selection criteria for the patients entering into this phase I/phase II trial are shown in Table 1. The experimental protocol for monitoring the patients is displayed in Table 2. All research protocols were approved by the US FDA and were also approved by the Indiana University Institutional Review Board. Patients were given informed consent.

Patients were given a cleansing enema prior to the procedure. The U.S. FDA required that the first ten patients have thermal sensors placed in the perineum near the prostate. Because of this, the first ten patients were done under either a regional or general anesthesia. After

**Table 1. Patient Inclusion Criteria.**

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Patient is/has:	Between 50 and 80 years old
	Symptomatic BPH w/AUA score 12-35 (old AUA score)
	Maximum urinary flow rate $\leq$ 12/ml/sec
	Prostate weight $\leq$ 80 gms
	Prostatic AP dimension $\leq$ 25mm and Transverse dimension $\leq$ 27mm
	Post-void residual volume $\leq$ 300ml
	Voided urine volume $\leq$ 125 ml

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**Table 2. Experimental Protocol for Monitoring the Patients.**

Study Procedures	Study Visit		
	48 hr	30 day	90 day
Symptom Score	*	*	*
Flow Rate	*	*	*
PVR		*	*
TRUS	*	*	*
Renal U/S	*	*	*
U/A & Urine C&S	*	*	*
Cystoscopy			*

induction of anesthesia a standard 7.5 mHz imaging probe was used to place the needles via a transperineal route into the area near the prostate. Two needles (each with three thermistors per needle) were placed lateral to the prostate and one was placed anteriorly. Hence, nine thermistors were available to monitor temperature during the procedure. At the completion of the procedure proctoscopy was performed. Some of the early patients had suprapubic cystostomy tubes placed after induction of anesthesia because of the unsure outcome relative to edema and inflammation leading to urinary retention. Subsequently, it was clear that this practice could be abandoned since at least some patients do not need bladder drainage. Subsequent patients were given the option of having the procedure performed under intravenous sedation. Because of the unclear nature of anesthetic requirements, an anesthesiologist was present in order to provide analgesia and sedation and monitor the patient.

## RESULTS

Twenty patients have undergone focused ultrasound therapy at Indiana University. Long-term follow-up is available on fifteen, the other five have recently undergone therapy by virtue of an FDA release to do twenty more patients to determine anesthesia requirements.

### Thermometry

No temperature measurement in any patient registered a sustained rise of greater than 3° C. above pre-treatment baseline. However, transient elevations of relatively larger magnitude were observed in three patients. One had a 17° C. rise to a maximum of 52° C. In retrospect,

measuring the AP diameter of this patient during therapy revealed that the AP diameter was 22 mm. less than the 26 mm. distance necessary for disqualification from therapy. The fact that the AP diameter during treatment was only 22 mm. placed the therapy zone very close to the thermistor itself and explains a temperature rise of this magnitude. It also points out the necessity of measuring AP diameter during therapy as the pre-therapy measurement in this patient was greater than 26 mm. Each of the three transient temperature elevations were registered in the anterior needle. The rise in temperature correlated to individual pulses of therapy. The transient temperature rise decayed very quickly and no patients experienced any complication, either acutely or long-term, related to these temperature elevations. Nonetheless, this illustrates the necessity of proper patient selection.

**Uroflowmetry**

The mean peak flow in the first fifteen patients was 9.3 pre-therapy. This value increased to 10.2 one month post therapy and 14.0 three months post therapy. This increase was sustained at six months post therapy with a mean value of 13.5. Differences at three months and six months are significant with p values of less than .005 and .025 respectively. Stated another way, twelve of fifteen patients experienced a greater than twenty five percent increase in peak flow. The remaining three patients displayed no evidence of an increase in peak flow at ninety days post treatment.

**Symptom Scores**

Symptom score assessment is available for fifteen patients, all of whom have had ninety day follow-up. At thirty days the average score dropped from a pre-treatment value of 31.2 to 17.1. At ninety days average symptom score was 15.8. The range of changes and symptom score improvement are displayed in Table 3.

**Table 3. Number of Patients Showing Ranges of System Score Improvement.**

	N	<0	0-9.9	10.0-19.9	20.0-29.9
30 days	15	1	3	8	3
90 days	15	2	1	6	6

### **Cystoscopy, Ultrasonography, and MRI**

Ultrasonography was carried out on all patients at thirty days and ninety days post treatment. Findings varied from being very dramatic (Figure 1) on ultrasound to no discernible change. Cystoscopy was performed 6 weeks-3 months post treatment. Again, the findings were varied. Some patients had dramatic "channel TUR-P" cavities and other patients exhibited very little evidence of periurethral prostatic ablation.

MRI was performed on five patients pretherapy and approximately ten days to two weeks out from the initial therapy. These patients demonstrated evidence of a change on MRI indicating that some effect on tissue had occurred. Proctoscopy was performed immediately post treatment in all fifteen patients and demonstrated no mechanical or therapy effect on the rectum.

### **COMPLICATIONS**

There were no long-term complications of therapy. The most frequent complication was that of urinary retention which occurred in eleven of fifteen patients. In the first ten patients a suprapubic tube was placed prior to therapy because it was unclear as to whether or not urinary retention would ensue post therapy. Nine of ten patients instrumented with thermo-couples developed urinary retention which persisted from one to four days. In contrast, three of ten patients treated without placement of thermistors developed urinary retention requiring urethral catheterization for an average of two days.

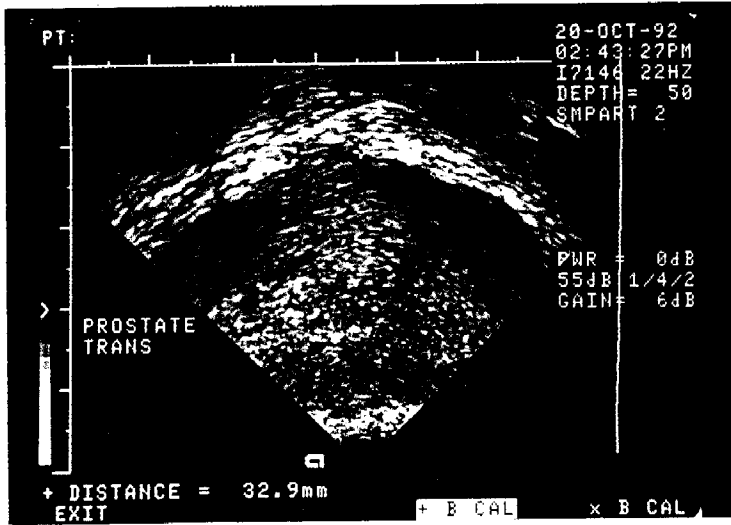
Hemospermia was reported in seven of fifteen patients between two and four weeks post treatment. Hemospermia subsequently cleared spontaneously. No patient experienced a change in erectile or sexual function.

At ninety days post treatment no patient had evidence of a complication. Also to be noted was the fact that none of these patients experienced irritative voiding symptoms related to therapy.

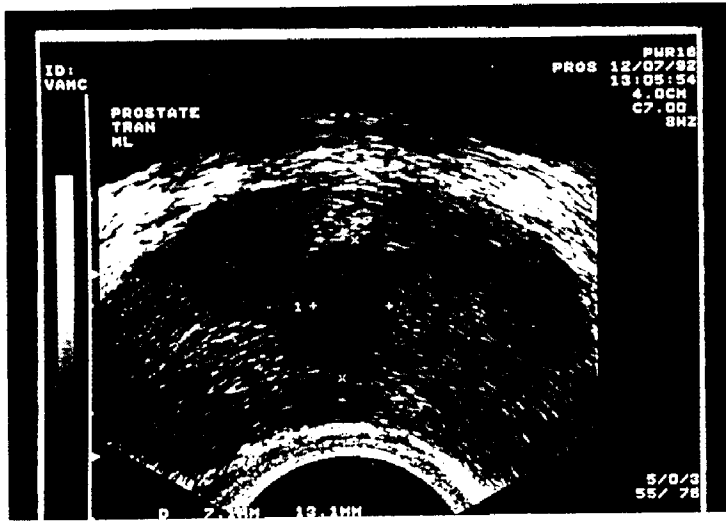
### **DISCUSSION**

This study represents a phase I/phase II study of focused ultrasound in the treatment of human BPH. Parameters used to treat patients, such as the amount of energy at the focal point, the time on/time off of the transducer in terms of therapy pulses, and the protocol for positioning the lesions in the prostate, had been set based on a canine protocol approved by the FDA (Foster, et al., 1993). Whether these set parameters are optimal in the individual patient is unclear. Certainly, an abil-

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Figure 1. (A) Pretherapy transrectal ultrasound; (B) Post therapy transrectal ultrasound showing periurethral cavity

ity to vary the energy density at the focal point and also to vary the treatment pattern is desirable. However, varying these parameters in humans at this point in time is prohibited by the US FDA.

Nonetheless, this initial experience has shown that it is indeed possible to ablate prostatic tissue using transrectally administered focused ultrasound. Seventy five percent of patients experienced a significant increase in peak flow and the degree of decrease in symptom scores was also encouraging. However, great care should be exercised in extrapolating these results to the clinical situation since it is now very clear that evaluating various treatments of human BPH requires appropriate blinding and control populations.

The first ten patients were done under either regional or general anesthesia because of the necessity of placing thermistors in the perineum. Subsequent to this ten further patients have been attempted using intravenous sedation alone (five patients under the original protocol and five patients under the subsequently approved FDA anesthesia requirement protocol). Of these ten patients attempted under IV sedation, nine have been successful. Small doses of Propofol, Fentanyl, and Midazolam are used and patients are treated as outpatients with no post anesthetic recovery room time. If most patients can be treated under intra-venous sedation alone, potential great cost savings may be achieved.

The Department of Urology at Indiana University views this initial experience as a "first try" attempt. Many parameters can be varied in focused ultrasound treatment. These include power density at the focal site, time on/time off of the transducer, pattern and site of treatment, and other perhaps less important parameters. This initial experience is encouraging since it has shown prostatic tissue can be ablated. However, significant work remains to be done in order to optimize the treatment in an individual patient and to obtain better results in the twenty five percent of patients who experience little change in flow parameters.

Whether or not treatment is best performed using energies resulting in heating alone versus higher energies resulting in cavitation is also unclear. Nonetheless, focused ultrasound represents an exciting new method of performing tissue ablation without affecting tissue in the beam path. As such, it undoubtedly will generate great interest in the field of minimally invasive surgery, administered by a variety of approaches (extracorporeal, transrectal, transvaginal, etc.) for a variety of types of tissue destruction.

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