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Urethral Sparing Histotripsy of the Prostate in a Canine Model

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Abstract

Objective—To evaluate the feasibility and healing response to urethral sparing prostate histotripsy a canine model of benign prostatic hypertrophy.

Methods—Histotripsy was performed on 10 canines using a 750 kHz piezoelectric ultrasound transducer targeting the prostatic parenchyma while avoiding the urethra. Periprocedure prostatic urethral integrity was evaluated with serial cystourethroscopy. Evolution of histotripsy treatment effect and subjects' response to urethral sparing was evaluated with serial ultrasound and laboratory evaluation, respectively. Subjects were euthanized acutely or chronically and findings were confirmed histologically.

Results—Bilateral treatment was possible in 8/10 subjects while unilateral treatment was performed in 2/10. Failure to spare the urethra was observed in 2/18 treatments; one acutely and one chronically despite normal cystourethroscopy for the first week. Modest prostatic volume reduction was seen in subjects survived to 8 weeks post-histotripsy. Laboratory studies revealed transient perioperative increases in mean white-blood cell count, C-reactive protein, and lactate dehydrogenase. On histology, 80% of successful urethral sparing treatment cavities were completely epithelialized, containing simple fluid with minimal cellular debris at 8 weeks despite no communication with the urethra.

Conclusions—Urethral sparing histotripsy of the prostate is feasible and well tolerated in a canine model, resulting in modest volume reduction and prompt resorption of homogenized tissue debris. Human studies to evaluate the clinical utility and symptomatic response of urethral sparing are needed.

Keywords

Histotripsy; Benign Prostatic Hypertrophy; Prostate; Ultrasound; TURP

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GRS: None

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Introduction

For decades, the gold standard surgical therapy for benign prostatic hyperplasia (BPH) has been transurethral resection of the prostate (TURP). TURP aims to debulk BPH adenoma, creating a widely patent channel to alleviate prostatic obstruction. With many men now presenting later in life with greater comorbidities and greater risk of preoperative complications and morbidity¹ there is a need for the development of less invasive treatment modalities that replicate the functional outcomes of the TURP with less operative morbidity. Towards this end, laser based therapies including photovaporization of the prostate (PVP) and holmium laser enucleation of the prostate (HoLEP) have emerged as promising alternative debulking therapies with decreased morbidity compared to transurethral resection of the prostate (TURP).^{2, 3} However, these therapies remain invasive with associated surgical risks. In the quest for less invasive approaches, microwave (TUMT) and transurethral needle ablation (TUNA), which thermally coagulate BPH tissue while sparing the urethra from damage have been explored.⁴ While these approaches achieve therapeutic benefit, they have failed to replicate the efficacy and durability of TURP.^{5–7}

Histotripsy, an experimental noninvasive extracorporeal focused ultrasound technology, has been explored as a less invasive approach to surgical management of BPH, demonstrating the ability to homogenize prostate tissue in an *in vivo* canine model with resultant tissue debulking.⁸ Histotripsy involves delivery of high amplitude, short (<50 μ s) pulses of ultrasound energy at a low duty cycle (<1 %) to a cigar shaped geometric focal volume. The resulting compression and rarefaction causes the development of microbubbles that oscillate, coalesce, and collapse producing mechanical fractionation of targeted tissues at the cellular level, reducing tissue architecture and cellular structures to a fine slurry of acellular debris. Volumetric ablation is accomplished by passing the transducer focal volume through the targeted region. As targeted tissue is homogenized, the US appearance becomes progressively hypoechoic.^{9–12} Transabdominal histotripsy of the prostate is safe and effective in an *in vivo* canine benign prostatic hypertrophy (BPH) model¹³ producing dose dependent tissue debulking of the adenomatous BPH tissue¹⁴ with minimal hematuria, even in an anticoagulated model.¹⁵

The prostatic urethra is more resistant to the cavitation effects of histotripsy than prostate parenchyma, requiring a greater number of acoustic pulses to achieve tissue disintegration and hence a longer treatment time. As a result, we set out to explore the feasibility of urethral sparing histotripsy of the prostate in a canine BPH model, hypothesizing that urethral sparing is both feasible and well tolerated with minimal risk of complications.

Material and Methods

Subjects

After receiving approval from the university committee for animal use and care 10 intact male canine subjects weighing 19.1 to 30.5 kg were obtained. Subjects were anesthetized with subcutaneous acepromazine (0.1 mg/kg) and intravenous propofol (2–8 mg/kg) and intubated. They were prepped with a warm tap water enema with digital rectal disimpaction after intubation. The lower abdomen and suprapubic region were shaved before positioning each subject supine on the procedural table. Inhalational anesthesia (isoflurane 1–2%) was maintained throughout treatment. Subjects were allocated to one of three groups, treatment with harvest acutely on post-procedure day (POD) 0 (4 subjects), POD7 (2 subjects), or POD56 (4 subjects). All chronic subjects received intramuscular Penicillin G benzathine (40,000 IU/kg) prior to the procedure and on post procedure days 3 and 7 for prophylaxis. Carprofen (2.2 mg/kg/day) was administered orally prior to the procedure and for 24 hours afterwards for analgesia.

Histotripsy Procedure

Transrectal ultrasound (TRUS) imaging was performed using a Logiq 6 ultrasound scanner (GE Healthcare, Waukesha, WI) with a model ERB probe positioned manually and fixed in a custom holder. The prostate volume was estimated using the stepper volume technique at 2.5 mm intervals tracing the prostate perimeter on transverse slices. The therapeutic histotripsy system consisted of a 16-element piezoceramic composite array (750 kHz, 11 × 14-cm diameter oval shape, focal length 10 cm, focal volume 3 × 3 × 8 mm; Imasonic, Voray sur l'Ognon, France) on a 3-axis computer-controlled positioning system (MATLAB, MathWorks, Natick, MA). Coupling was achieved by inserting the therapeutic transducer into a bath of degassed water contained in a plastic membrane directly in contact with the shaved abdomen. Histotripsy pulses consisted of 5 cycle bursts of acoustic energy at 750 kHz, with a duty cycle less than 1% and pulse repetition frequency 500 Hz. Histotripsy treatment was targeted at the lateral lobe of the prostate using both transverse and longitudinal TRUS imaging with care taken to avoid the urethra, which is well visualized on TRUS imaging in canines, even without a urethral catheter.

During histotripsy treatment we attempted to preserve at least 5 mm of prostatic parenchyma adjacent to the urethra. The cavitation bubble cloud was then moved throughout the lateral lobe of the prostate under sagittal TRUS imaging to create a rectangular treatment volume parallel to the urethra of approximately 1–2 cm³. Treatment was continued until hypoechoic changes were visualized in the targeted volume on TRUS indicating adequacy of treatment. After completing treatment on the ipsilateral lobe, the same procedure was attempted on the contralateral side. After completion of histotripsy treatment, flexible cystourethroscopy was performed with an 8.2 French flexible ureteroscope (Dur-8, Gyrus ACMI) to examine the urethra for signs of histotripsy treatment effect. A urinary catheter was not left in place following completion of treatment.

Post-procedure Evaluation

Subjects recovered from anesthesia were monitored for treatment-related adverse events and cystourethroscopy was repeated on PODs 3 and 7. Subjects survived to POD56, had further endoscopic assessment on PODs 14, 28 and 56. TRUS imaging and prostate stepper volume measurement was repeated on POD7 in subjects euthanized on POD7 and on PODs 28 and 56 in those survived to POD56.

To objectively assess post-urethral sparing histotripsy convalescence serum hemoglobin, white blood cell count (WBC), C-reactive protein (CRP), and lactate dehydrogenase (LDH) were measured with serial lab draws beginning pre-histotripsy and then just prior to each surveillance cystourethroscopy (PODs 3, 7, 14, 28, 56).

Euthanasia and Specimen Processing

At the predetermined time points, subjects were euthanized with intravenous pentobarbital sodium 140–160 mg/kg and TRUS imaging was repeated as outlined above. Next, a suprapubic incision was made and a cystotomy was created through which antegrade cystourethroscopy was performed using a 16 Fr flexible cystoscope (Cy2, Olympus) (superior optics compared to flexible ureteroscopy). The prostate, bladder and adjacent rectum were then surgically removed en-bloc. The prostate, bladder, and rectal tissues were inspected grossly for injury. Harvested prostates were fixed in formalin for 1 week, cut into 5-mm thick slabs, dehydrated in 25% ethanol, paraffin embedded, cut using a microtome in 5µm sections at 1 mm increments, mounted, and stained with hematoxylin and eosin for histologic assessment.

Statistical Analysis

Prostate volumes and serial laboratory results were reported as means $\pm$ standard deviation. Mean serial laboratory results were plotted graphically and reported with standard deviation using basic statistical software (Excel 2011, Microsoft, Redmond, WA)

Results

Eighteen histotripsy treatments were performed in total: bilateral treatments were feasible in 8 subjects accounting for 16 treatments, and in two subjects, only the left lateral lobe could be targeted accounting for 2 additional treatments. Contralateral treatment was not feasible in these subjects secondary to the retropubic position and rotation of the prostate prohibiting adequate urethral sparing while targeting the right lobe of the prostate. TRUS monitoring during histotripsy confirmed cavitation bubble activity in all cases, with progressive loss of internal echoes within targeted prostatic parenchyma without evidence of intraurethral cavitation (Figure 1). Mean histotripsy treatment time was 10.8 minutes (range 4.8–22.9 minutes) per treatment, related to prostate size (and resultant targeted volume size) and tissue susceptibility.

Slight mistargeting in two cases resulted in communication of the targeted prostate volume with the urethral lumen: the first subject had evidence of urethral treatment effect immediately after treatment on cystourethroscopy at the left apex consisting of hyperemia and small petechial areas of hemorrhage with a normal appearing contralateral side. The left hand side evolved to a small area of frank urethral disintegration at the apex that did not extend across the midline at POD14. The second subject developed punctate unilateral urethral fenestrations on the left at POD28 despite normal appearing cystourethroscopy until POD7 when a small area of pale urothelium was visualized at the left base. The contralateral treatment volume in these subjects did not communicate with the urethra. Sixteen prostatic tissue volumes treated with histotripsy did not communicate with the urethra: 7 in subjects harvested acutely, 4 followed until POD7, and 5 followed to POD56.

On serial ultrasound examination, urethral sparing histotripsy progressed from characteristic acute hypoechoic changes in the targeted lateral lobes of the prostate immediately following treatment, to more heterogeneous hypoechoic regions lateral to the urethra on POD7. TRUS on POD28 revealed that three of the five cavities that did not communicate with the urethra had minimal internal echoes and the other two had layering debris. On POD56, 4/5 intact cavities had minimal internal echoes on TRUS suggesting the presence of only simple fluid. The remaining cavity had persistent layering debris. The cavity that was found to communicate with the urethra on cystourethroscopy on POD28 was without internal echoes on TRUS examination performed immediately prior to urethral instrumentation cystourethroscopy, suggesting drainage of homogenized material prior to endoscopic assessment. Among subjects survived to POD56, there was a small reduction in TRUS estimated prostate stepper volume with a mean volume decrease of 4.6 ± 3.1 cc on POD 28 vs preop and 3.0 ± 5.3 cc on POD 56 vs preop.

Laboratory Tests

On post-procedure laboratory examination, a mild leukocytosis developed peaking on POD3 and resolving by POD14 (mean WBC K/mcL was 7.1 ± 1.4 (preop) vs 11.7 ± 1.8 (POD3) vs 6.9 ± 2.9 (POD14)) (Figure 2). Hemoglobin was stable throughout the perioperative period. LDH rose from baseline to peak on POD7 (228 ± 30.5 vs 428.3 ± 179.1 U/L) and approached baseline by POD14 (285.8 ± 149.9 U/L) and was at baseline by POD28. CRP peaked from baseline of 2.3 ± 0.9 to 30.3 ± 13.9 mcg/mL on POD3 and subsequently trended down, achieving baseline by POD56 (1.79 ± 1.13 mcg/mL).

Pathology and Histology

On gross examination, acute specimens demonstrated homogenized material with punctate hemorrhage within targeted prostate with sparing of the urethra and periurethral stroma. Examination of one week chronic prostates revealed siderin stained fractionated material within a well-defined intact treatment cavity with a region of normal appearing periurethral stroma separating the urethra from the treatment cavity. Examination of POD56 prostates revealed that 4/5 intact urethral sparing cavities contained clear lightly straw colored “simple” fluid (Figure 3). The fifth intact cavity contained similar fluid with a settled layer of fractionated necrotic debris. All POD56 intact cavities had a collar of normal periurethral tissue.

On histologic examination acute prostates demonstrated complete loss of cellular architecture consistent with histotripsy cellular homogenization in the central regions of the targeted volume (Figure 4). The periphery of the targeted volume transitioned from cellular fractionation to normal parenchyma with small areas of hemorrhage. The urethra appeared completely intact without evidence of treatment effect in all examined slides in 7/7 acute treatments suggesting successful urethral sparing. At POD7, histology revealed sharp delineation between normal viable tissue and evolving fractionated necrotic debris with focal inflammatory infiltrate consisting of lymphocytes and macrophages at the periphery of the treatment cavity. The urethra appeared histologically normal in 4/4 treatments. At POD56, histologic examination revealed epithelial lined periurethral cavities in all subjects. Minimal fragmented cellular debris were observed in 4/5 treatment cavities, with the remaining cavity containing dependent layering necrotic debris. There was minimal focal inflammation in all subjects survived to 8 weeks irrespective of cavity status.

Complications

Complications related to histotripsy occurred in 1 subject: an episode of transient urinary retention managed with indwelling urethral catheterization for 48 hours with subsequent return of voiding. Additionally, complications related to the TRUS positioner occurred in 3 subjects: 2 superficial (1 each acute and 1 week chronic) and 1 partial thickness (1 week chronic) rectal pressure ulcers. In all cases there was no evidence of histotripsy effect in the adjacent posterior prostate or rectum suggesting pressure necrosis resulting from the TRUS transducer positioner sheath.

Discussion

While the optimal treatment strategy for prostate histotripsy is currently unknown, previously we had hypothesized that achieving urethral disintegration may be necessary for prompt drainage of fractionated BPH adenoma to facilitate adequate tissue debulking and creation of a TURP-like defect^{13, 15, 16} based on the observation of retained fractionated debris in non-urethral communicating cavities at 14–21 days post-histotripsy.¹⁷ However, the observation that urethral sparing procedures in humans such as TUMT and TUNA offer significant improvement in BPH symptoms, with less risk of complications compared to the traditional TURP^{5–7} led us to hypothesize that urethral sparing histotripsy might also result in therapeutic benefit more quickly and with delivery of less acoustic energy than “TURP-like histotripsy” strategies that require urethral homogenization.

In the present study, urethral sparing was accomplished in 16/18 targeted volumes demonstrating the feasibility of urethral sparing prostate histotripsy in a canine model. One of the failed urethral sparing treatments had observable urethral treatment effect acutely indicating mistargeting during histotripsy treatment. In the other subject, however, the urethra appeared normal until POD7 when a unilateral pale area of urothelium was seen on

cystourethroscopy and subsequently progressed to small punctate fenestrations by POD28. This observation was unexpected based on previous work (targeting the urethra) demonstrating failure to achieve urethral disintegration in the absence of acute endoscopic evidence of urethral treatment effect when targeting the urethra.¹⁷ Consequently, the development of urethral fenestrations in this subject may have resulted from the close proximity of the treatment cavity to the urethra, resulting in necessitation of fractionated debris through the urethra or focal urethral ischemia as opposed to direct mechanical treatment effect on the urethra.

Although we cannot assess therapeutic benefit in a canine model, our data suggest that most of the fractionated cellular material in intact urethral sparing histotripsy treatment cavities are resorbed by 8 weeks post treatment in a canine model, with ~80% of cavities containing nearly simple fluid. This suggests relatively prompt tissue remodeling. Further, although only small tissue volumes were targeted with histotripsy to minimize the possibility of urethral disintegration and facilitate ultrasound and histologic assessment of the treated volume over time, there was a modest prostate volume loss of ~12.4% at 8 weeks. We expect urethral sparing histotripsy to result in greater relative volume loss in larger prostates due to the higher percentage of non-urethral tissue available for targeted histotripsy induced homogenization and resultant debulking. Additionally, further volume reduction may occur following urethral sparing histotripsy as the treatment cavities continue to evolve beyond 8 weeks post-histotripsy, in particular if the cavities completely reabsorb as has been observed in porcine kidney.¹⁸ By avoiding urethral irritation and tissue destruction not possible with any of the existing technologies, it is possible that urethral sparing histotripsy could allow for the greater reduction in BPH symptoms with the less convalescence than existing treatment modalities.

One concern with a urethral sparing approach is the theoretical possibility that undrained non-viable fractionated adenoma tissue could facilitate infection and abscess formation with associated significant inflammatory response as the host attempts to remodel the undrained necrotic tissue. As a result, we tried to assess the inflammatory host response by monitoring laboratory markers of inflammation including WBC, LDH and CRP. Interestingly, only mild elevation occurred in WBC and LDH peaking at POD 3 and returning to baseline by POD 14. Elevation in CRP followed a similar curve but took longer to return to baseline POD56. These data suggest that urethral sparing histotripsy produced a modest acute inflammatory response that subsequently resolved without significant ongoing chronic inflammatory activity. This is further supported by the limited focal inflammation seen on histology.

While the optimal prostate histotripsy treatment strategy remains to be determined, the generalizability of these results from canine to human prostate is uncertain. Structurally the canine prostate is bi-lobed without zonal structures, whereas the human prostate is subdivided into several different zones with the transition zone being most relevant to BPH.¹⁹ Different prostatic zones may have different histotripsy treatment thresholds which could alter the ease of urethral sparing in human prostates. Additionally, the intraperitoneal location of the canine prostate lends itself to a transabdominal histotripsy approach, whereas structural modeling suggests that the human prostate will likely be more amenable to a transperineal approach²⁰ or transrectal approach. Ultimately, human studies are needed to determine both the clinical efficacy and optimal treatment algorithm for prostate histotripsy, including urethral sparing approaches.

Conclusion

In a canine model of BPH, urethral sparing during prostate histotripsy appears possible and well tolerated, with modest volume reduction at 8 weeks post-treatment. Further studies are

needed to optimize histotripsy treatment parameters and strategies in preparation for trials evaluating the clinical utility/feasibility of prostate histotripsy in humans.

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References

1. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol.* 2005; 173:1256–1261. [PubMed: 15758764]
2. Ahyai SA, Lehrich K, Kuntz RM. Holmium laser enucleation versus transurethral resection of the prostate: 3-year follow-up results of a randomized clinical trial. *Eur Urol.* 2007; 52:1456–1463. [PubMed: 17499427]
3. Ruszat R, Seitz M, Wyler SF, et al. GreenLight laser vaporization of the prostate: single-center experience and long-term results after 500 procedures. *Eur Urol.* 2008; 54:893–901. [PubMed: 18486311]
4. Larson TR. Current treatment options for benign prostatic hyperplasia and their impact on sexual function. *Urology.* 2003; 61:692–698. [PubMed: 12670545]
5. McVary, KT.; Roehrborn, CG.; Avins, AL., et al. [Accessed April 5, 2011, 2011] Guidline on the Managment of Benign Prostatic Hyperplasia (BPH). 2010. <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=bph>
6. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol.* 2011; 185:1793–1803. [PubMed: 21420124]
7. Bouza C, Lopez T, Magro A, et al. Systematic review and meta-analysis of Transurethral Needle Ablation in symptomatic Benign Prostatic Hyperplasia. *BMC Urol.* 2006; 6:14. [PubMed: 16790044]
8. Lake AM, Hall TL, Kieran K, et al. Histotripsy: minimally invasive technology for prostatic tissue ablation in an in vivo canine model. *Urology.* 2008; 72:682–686. [PubMed: 18342918]
9. Xu Z, Raghavan M, Hall TL, et al. High speed imaging of bubble clouds generated in pulsed ultrasound cavitation therapy--histotripsy. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2007; 54:2091–2101. [PubMed: 18019247]
10. Xu Z, Fowlkes JB, Rothman ED, et al. Controlled ultrasound tissue erosion: the role of dynamic interaction between insonation and microbubble activity. *J Acoust Soc Am.* 2005; 117:424–435. [PubMed: 15704435]
11. Tran BC, Seo J, Hall TL, et al. Microbubble-enhanced cavitation for noninvasive ultrasound surgery. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2003; 50:1296–1304. [PubMed: 14609069]
12. Kieran K, Hall TL, Parsons JE, et al. Refining histotripsy: defining the parameter space for the creation of nonthermal lesions with high intensity, pulsed focused ultrasound of the in vitro kidney. *J Urol.* 2007; 178:672–676. [PubMed: 17574617]
13. Hempel CR, Hall TL, Cain CA, et al. Histotripsy fractionation of prostate tissue: local effects and systemic response in a canine model. *J Urol.* 2011; 185:1484–1489. [PubMed: 21334667]
14. Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol.* 2007; 178:2314–2330. [PubMed: 17993339]
15. Wheat JC, Hall TL, Hempel CR, et al. Prostate histotripsy in an anticoagulated model. *Urology.* 2010; 75:207–211. [PubMed: 19931897]
16. Hall TL, Hempel CR, Wojno K, et al. Histotripsy of the prostate: dose effects in a chronic canine model. *Urology.* 2009; 74:932–937. [PubMed: 19628261]

17. Schade GR, Styn NR, Hall TL, et al. Endoscopic assessment and prediction of prostate urethral disintegration after histotripsy treatment in a canine model. *J Endourol.* 2012; 26:183–189. [PubMed: 22050511]
18. Lake AM, Xu Z, Wilkinson JE, et al. Renal ablation by histotripsy--does it spare the collecting system? *J Urol.* 2008; 179:1150–1154. [PubMed: 18206166]
19. Evans, HE. *Miller's Anatomy of the Dog.* Philadelphia, PA: W. B. Saunders; 1993. p. 514-516.
20. Hall TL, Hempel CR, Sabb BJ, et al. Acoustic access to the prostate for extracorporeal ultrasound ablation. *J Endourol.* 2010; 24:1875–1881. [PubMed: 20677990]

Figure 1.

Transrectal ultrasound appearance of the prostate during urethral sparing histotripsy (upper left panel) and post-treatment in the same subject on post-procedure (POD) 0, 28, and 56. The histotripsy induced cavitation bubble cloud (white circle) results in progressive loss of tissue echogenicity and the appearance of heterogenous prostatic parenchyma acutely (POD 0). By POD 28 treatment urethral sparing treatment cavities (seen on transverse view) contain sparse internal echoes and virtually no internal echoes by POD56 bilaterally.

Figure 2.

Graphical depiction of mean serial perioperative laboratory results (error bars = standard deviation) for serum white blood cell count (A), hemoglobin (B), LDH (C), and CRP (D).

Figure 3. Cystoscopic appearance of intact urethra (A) and corresponding gross (B) and low-power micrograph (C) demonstrating intact urethral sparing histotripsy treatment cavities at 8 weeks post-histotripsy.

Figure 4.

Histologic appearance of acute (A), 1 week chronic (B) and 8 week chronic (C) successful urethral sparing histotripsy treatment (hematoxylin and eosin, 20x magnification). Acutely histotripsy resulted in homogenization of central portion of targeted volume with per homogenization focal hemorrhage (A). At 1 week there is focal acute inflammatory infiltration of the surrounding stroma and homogenized tissue with resolving focal hemorrhage (B). At 8 weeks the homogenized contents of the targeted volume have been nearly completely resorbed (right hand side) with resolution of inflammation and normal appearing parenchyma between the urethra (left hand side) and the intact treatment cavity.