Original Article

High-frequency irreversible electroporation ablation for the prostate in Beagle dogs

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Background: Ablation procedures have garnered significant attention as a minimally invasive treatment of prostate diseases. However, the feasibility and safety of applying high-frequency irreversible electroporation (H-FIRE) to ablate the Beagle prostate for benign prostatic hyperplasia (BPH) treatment have not been thoroughly explored, the appropriate range of parameters has not been determined. In order to ensure the feasibility and safety of prostate ablation surgery, we conducted a study using Beagle dogs as subjects to investigate prostate tissue.

Methods: We utilized a composite steep pulse therapy device to perform ablations on 26 lateral lobes of the prostate in 13 Beagles, employing various parameters for different needle distances. The effectiveness of this device was assessed through the observation of the ablation area, intraoperative muscle tremors, postoperative hematological examination, and gross inspection.

Results: The findings of our study revealed that 1,000 to 2,000 v/cm in electric field strength, combined with 5 µs pulse width and pulse number 100, is a safe parameter range for ablation of prostate tissue. At the same time, the large electric field strength (2,000 v/cm) has the best ablation effect with the biggest continuous and thorough ablation area. All parameters of H-FIRE were safe for Beagles.

Conclusions: H-FIRE ablation for prostate is safe and effective in dogs, which has the potential to be a useful addition to the range of minimally invasive treatments available for the treatment of BPH against this backdrop of increasing surgical practice.

Keywords: Prostate; benign prostatic hyperplasia (BPH); irreversible electroporation (IRE); Beagle dogs; high-frequency IRE (H-FIRE)

Submitted Feb 28, 2024. Accepted for publication Aug 16, 2024. Published online Sep 26, 2024.
doi: 10.21037/tau-24-108
View this article at: https://dx.doi.org/10.21037/tau-24-108

Introduction

Benign prostatic hyperplasia (BPH) ranks among the most prevalent conditions affecting elderly men, and the conventional treatment of choice remains transurethral resection of the prostate (TURP) (1). However, TURP comes with a plethora of complications, particularly urinary and sexual dysfunction, encompassing issues like urethral stricture, retrograde ejaculation, and erectile dysfunction. These complications significantly impact the patients' quality of life (2,3). In recent years, minimally invasive surgical approaches have gained prominence in the management of BPH and localized prostate cancer (PCa), with ablation procedures taking center stage. Notable ablative treatments include high-intensity focused ultrasound (HIFU), cryotherapy, and photodynamic therapy (PDT), water vapor thermotherapy (WVTT), transurethral microwave thermotherapy (TUMT), among others. The widespread utilization of these treatments serves as a viable alternative to address the complications associated with TURP (4,5). Nonetheless, these ablation techniques generate substantial thermal energy during application, potentially causing harm to adjacent normal tissues and vascular nerves and introducing unpredictable complications. This limitation significantly restricts the application of these ablation techniques in the treatment of prostate disease. Irreversible electroporation (IRE) ablation emerges as a solution to these shortcomings, offering a non-thermal ablation. IRE relies on the application of high-voltage pulse voltage under specific conditions, inducing the formation of voids in the cell membrane, ultimately leading to the demise of tumor or normal cells. Presently, IRE has found success in the treatment of liver cancer, pancreatic cancer, kidney cancer, and PCa (6).

Compound steep pulse therapy involves the application of high-frequency IRE (H-FIRE), which employs a compound pulse characterized by microsecond pulse width, positive/negative bipolarity, and high intensity, to target solid tissue. It works by applying ultra-short, high-voltage electric pulses to the target area through a fine probe to create a strong external electric field. This causes the cell membrane to become electroporated, or to form nano-pores that are permeable to ions, which causes the cell membrane to lose its physiological function and undergo apoptosis (7). In the context of treating prostate enlargement, ablating periurethral tissue theoretically alleviates the pressure exerted by hyperplastic tissue on the urethra, thereby ameliorating symptoms associated with prostate enlargement. This approach holds promise as a potentially superior form of ablative treatment for BPH. To our best knowledge, this is the first study to evaluate feasibility and safety of H-FIRE for BPH treatment in animal model. By establishing a Beagle prostate ablation model, we aim to investigate the feasibility and safety of applying H-FIRE to ablate the Beagle prostate and to determine an approximate range of parameter for BPH. This research endeavor serves as a foundational step towards future clinical investigations into BPH treatment. We present this article in accordance with the ARRIVE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-108/rc).

Highlight box

Key findings
- High-frequency irreversible electroporation (H-FIRE) ablation for prostate is safe and effective in dog.

What is known and what is new?
- H-FIRE is widely used in many organs.
- Safety and effectiveness of H-FIRE ablation for prostate in dog is still unknown.

What is the implication, and what should change now?
- H-FIRE has the potential to be a useful addition to the range of minimally invasive treatments available for the treatment of benign prostatic hyperplasia against this backdrop of increasing surgical practice.

Methods

Grouping

We employed a pulse with fixed pulse width parameter of 5 µs and fixed needle depth of 10 mm, with various electric field strength and needle distance (10, 14, and 18 mm). Three sets of parameters were defined: small (1,000 v/cm), medium (1,500 v/cm), and large parameter groups (2,000 v/cm). And 100 pulses were performed for each treatment in each group. When the electric field strength was 2,000 v/cm and the needle distance = 18 mm, the required voltage value was too large, which was beyond the limitation the equipment, so the 2,000 v/cm parameter was not set for the 18 mm needle distance group. Dogs were purchased from the Shanghai Jiaotong University Agriculture and Biology Experimental Company. All dogs were randomly assigned to each group, with their prostate as the target (refer to *Figure 1* for the detailed experimental animal group design). In the prostate of each experimental dog, two ablation areas were established, one in each of the left (marked as L) and right (marked as R) lobes. The control group of Beagles underwent only the lancet procedure without ablation, whereas the experimental group of Beagles received H-FIRE ablation under various parameter settings. The range of treatment parameters used referred to the previous study of PCa treatment (6). Animal experiments were performed under a project license (No. 20230302) granted by the institutional ethics board of Shanghai Jiaotong University Agriculture and Biology Experimental Company, in compliance with the institutional guidelines for the care and use of animals. A protocol was prepared before the study without registration.

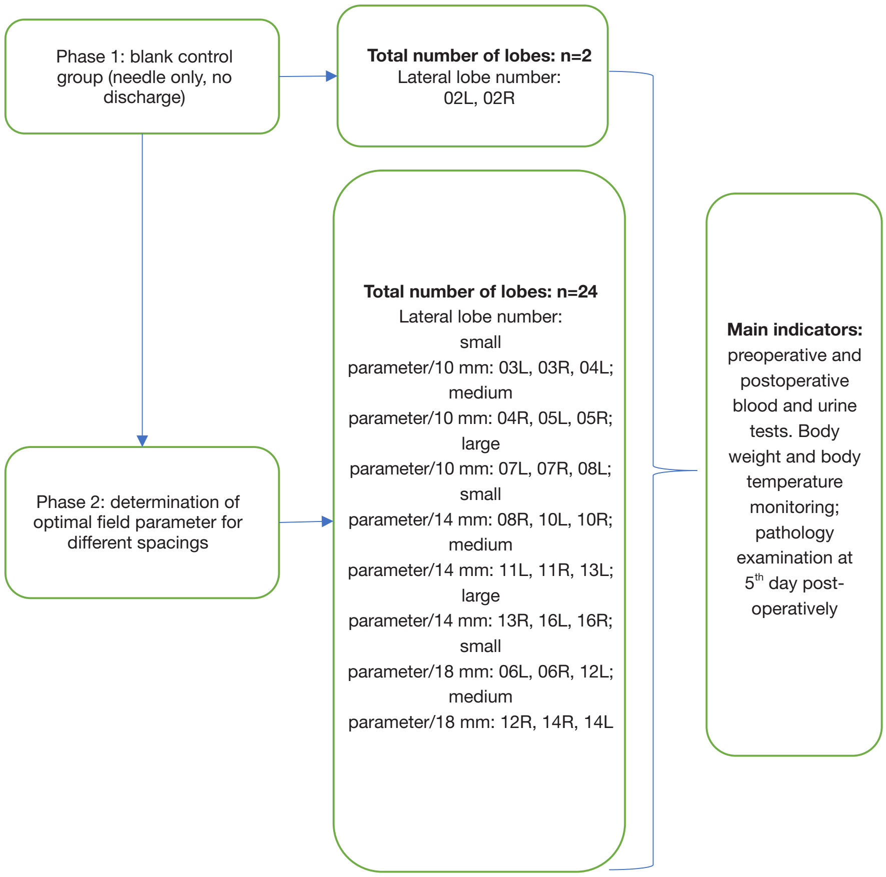


Figure 1 Grouping of experimental animals and procedures. Three sets of parameters were defined: small (1,000 v/cm), medium (1,500 v/cm), and large parameter groups (2,000 v/cm). L, left; R, right.

Ablation treatment

The Beagles were administered intravenous Zoletil for anesthesia and positioned on the operating table in the supine posture, connected to a respiratory anesthesia system and cardiac monitor. A catheter was carefully inserted into the Beagle's bladder to secure the urethra. The lower abdominal region was meticulously shaved, cleansed, and sterilized, followed by making an incision along the side of the penis to expose the prostate. The electrode needle was then inserted into the designated position within the prostate gland. For the blank control group, muscle tremors exhibited by the Beagle were monitored and recorded without H-FIRE ablation. For other groups, H-FIRE ablation was performed under different parameters, and muscle tremors were also monitored concurrently. Upon completion of the treatment, the electrode needle was withdrawn and sutured. Subsequently, the animals were roused from anesthesia, administered antibiotics to prevent postoperative infections, and placed in the sterile animal laboratory room for continued care. H-FIRE facilities were performed using a composite steep-pulse therapeutic apparatus (Shanghai Nortion Medical Technology Co., Ltd., Shanghai, China).

Material collection

Prior to surgery, blood was collected from the forelimbs of the experimental dogs for routine blood tests; the lower abdomen of the experimental dogs was pressed, and urine was collected and sent for examination; and the indicators were measured: red blood cells, hemoglobin, white blood cells, and platelets; and leukocytes, occult blood, and so on.

Sample observations

Before the ablation procedure, a comprehensive assessment was conducted, encompassing general observations,

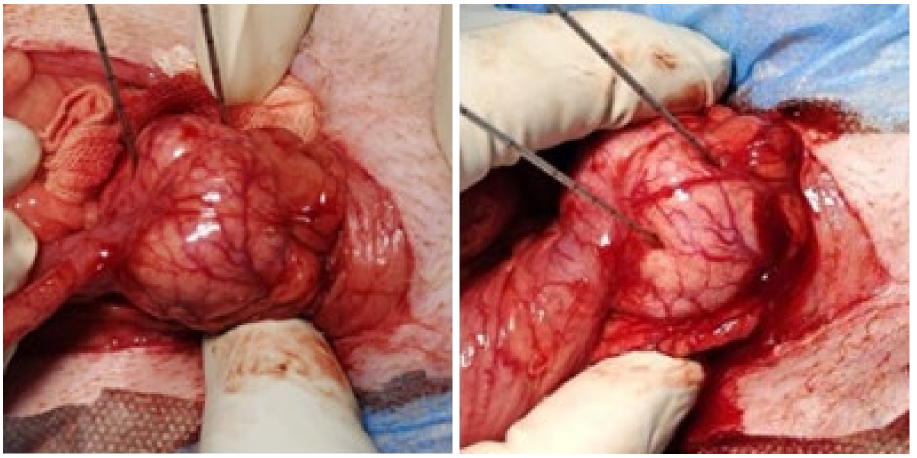


Figure 2 Gross observation of the ablation site of the prostate in intraoperative Beagle dogs.

hematology, and routine urinalysis. On the fifth day after the operation, prior to sampling, these assessments were repeated. Any adverse events that occurred during the experiment were meticulously documented.

Pathological examination

On the fifth day after the operation, all dogs were executed and the prostates were used for pathological analysis. Following tissue sampling, it was immersed in a 10% formalin solution for a minimum of 24 hours to facilitate paraffin embedding. Subsequently, the wax block was affixed to the sample holder of the sectioning machine. The thickness was adjusted to 10 µm, and the slicing process commenced to remove any excess paraffin and tissue from the wax block, thus revealing the maximum tissue surface. The slice thickness was then fine-tuned to 4 µm, and 5–10 consecutive slices were generated perpendicular to the path of the electrode needle. The cut-off wax membrane was submerged in warm water to facilitate the spreading of the slices. From this batch, 1–2 pieces of wax membranes featuring intact tissues, uniform slice thickness, flatness, devoid of knife marks, cracks, or folds, were meticulously chosen. Hematoxylin and eosin (HE) staining was conducted using an Olympus BX53 microscope and Jiangfeng digital section scanning software for the purpose of observing the ablation.

Statistical analyses

Statistical analyses for this study were conducted using SAS 9.4 software. Continuous variables underwent statistical analysis through Chi-squared or *t*-tests when they met the normality assumption. For variables not meeting normality, the Kruskal-Wallis test or Wilcoxon rank-sum test was employed. Within-group before-and-after comparisons were evaluated using paired *t*-tests or Wilcoxon signed-rank tests. Categorical variables were subject to statistical analysis using the Chi-square test or Fisher's exact probability method, while hierarchical data were assessed using the Wilcoxon rank-sum test or the Cochran-Mantel-Haenszel (CMH) test. Post hoc two-by-two comparisons underwent P value corrections using the Bonferroni method.

Results

Effectiveness evaluation

Observation

Gross observation: the gross examination of the ablation site during the operation is depicted in *Figure 2*. Following the completion of the experimental procedures, the prostate was exposed and examined visually without the aid of magnification. It exhibited normal size, color, and texture, with no discernible anomalies such as effusion, edema, or tissue adhesion both in the blank control group and the experimental animal group.

Pathologic findings

Based on the pathological findings, we outlined the completely ablated areas with lines. In the blank control group, no ablation was observed. However, in other Beagles received H-FIRE ablation under various parameter, nuclear fragmentation and disintegration in prostate tissues were observed with different extent. The ablation zones showed flaky necrosis and the area sizes were calculated. The area sizes results revealed that the mean ablation areas in the small, medium, and large parameter groups were 39.74±43.45, 175.46±94.08, and 228.49±41.26 mm^2, respectively. Among these, both the medium and large parameter groups exhibited significantly larger ablation areas compared to the small parameter group (both P<0.05). However, there was no statistically significant difference when comparing the medium and large parameter groups (P=0.66) (refer to *Tables 1-3* for detailed data).

Safety assessment

General postoperative observation

No abnormalities in feeding, drinking, defecation, or other behaviors were noted both before and after the operation. Furthermore, there were no signs of redness, swelling, or abnormal blood oozing from the wounds post-operation. Throughout the observation period, the body temperature and body weight of all animals remained stable without significant fluctuations, staying within the normal physiological range. No visible hematuresis was found in any dogs.

Muscle tremor level monitoring

Throughout the treatment, the extent of muscle tremors exhibited by each animal in the control groups or under varying ablation parameters was meticulously documented by observation and graded accordingly (ranging from very mild, mild, moderate, to severe). No muscle tremors were found in the control group. A progressive increase in the degree of muscle tremors across the small, medium, and large parameter groups. However, even in the large parameter group, there was no more than moderate tremor, and there was no muscle tremor that could cause the electrode needle to shift.

Laboratory test results

Blood test

Statistically significant differences were observed in the preoperative and postoperative values of erythrocytes and hemoglobin when employing the three ablation parameter sets (P<0.05). However, it is worth noting that these values of erythrocytes and hemoglobin remained within the normal range both before and after the procedure. In contrast, there was no significant difference in the preoperative and postoperative values of platelets across the three ablation parameter sets. As for leukocyte counts, there was a statistical difference observed (P<0.05), but these values were either within or very close to the normal range. Importantly, in the large parameter group, there was no statistically significant difference between preoperative and postoperative leukocyte counts (P>0.05).

Urine test

No statistically significant difference was observed in leukocyte counts between the preoperative and postoperative periods across the three sets of ablation parameters (P>0.05). As for occult blood, there was no statistically significant difference between the preoperative and postoperative periods in the small-parameter and large-parameter groups (P>0.05). However, a statistically significant difference was noted between the preoperative and postoperative periods in the medium-parameter group (P<0.05). It is important to note that despite this statistical difference, all of these values were quite close to falling within the normal range, and there was no notable impact on the animals' behavior.

Discussion

Many ablation procedures are traditionally based on thermal ablation principles; however, these techniques are susceptible to the heat sink effect, potentially leading to incomplete ablation and damage to surrounding normal tissue. IRE addresses the limitations of conventional thermal ablation methods (6). While the primary management approach for localized PCa remains radical prostatectomy, it often results in urinary incontinence and sexual dysfunction, significantly impacting patients' quality of life (8). Local therapies offer an alternative option, providing tumor control while preserving urinary and erectile function. Localized treatments encompass modalities such as HIFU, focused laser ablation, focal cryotherapy, IRE, and PDT (9). Among these, IRE has demonstrated promising outcomes in PCa treatment. Its tissue selectivity enables it to ablate the target area without damaging the vessels and nerves. However, the first-generation IRE technique had limitations, including a reduction in electric field strength near blood vessels, resulting in a tumor residual rate of up to 31% in patients with localized PCa treated with IRE (10). In contrast, high-frequency electroporation therapy not only eradicates PCa cells but also preserves surrounding

Table 1 Ablation of the prostate in Beagle dogs at various parameters

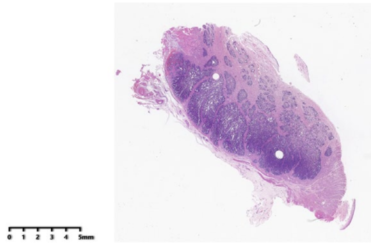
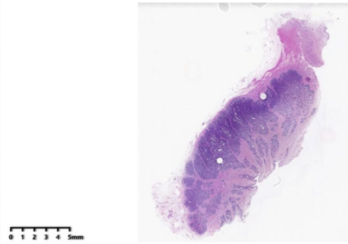
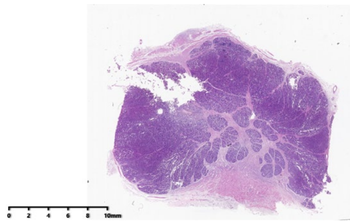
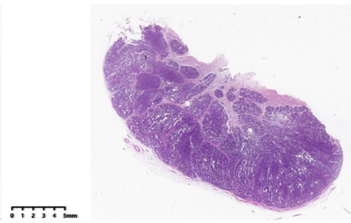
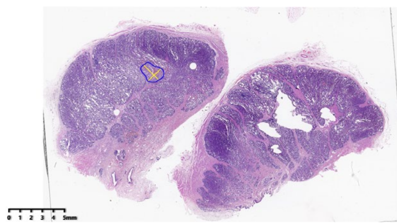
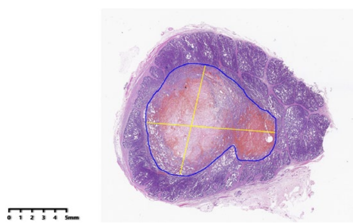
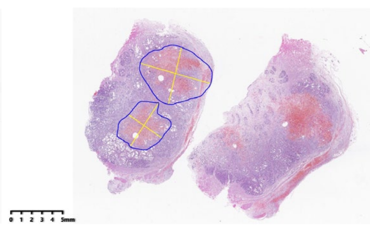
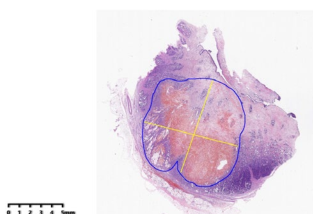
Grouping	Animal No.	Histopathological manifestations	Ablation area (mm^2)
Blank control group	02L, 02R	 	No ablation observed
Small parameter (1,000 v/cm); needle distance: 10 mm	03L, 03R, 04L	  	1.03±1.78
Medium parameter (1,500 v/cm); needle distance: 10 mm	04R, 05L, 05R	  	83.93±25.31

Table 1 *(continued)*

Table 1 *(continued)*

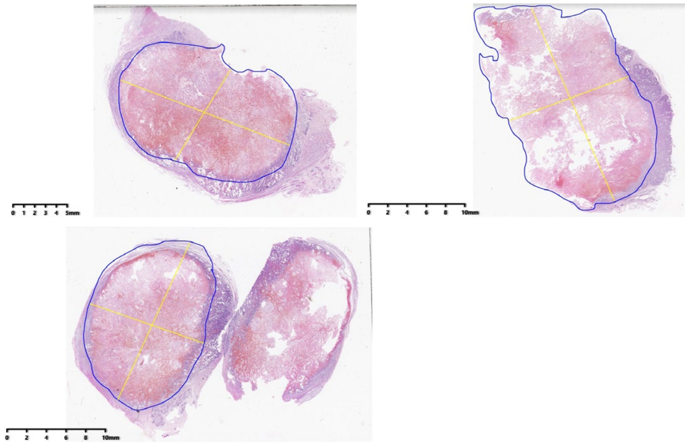
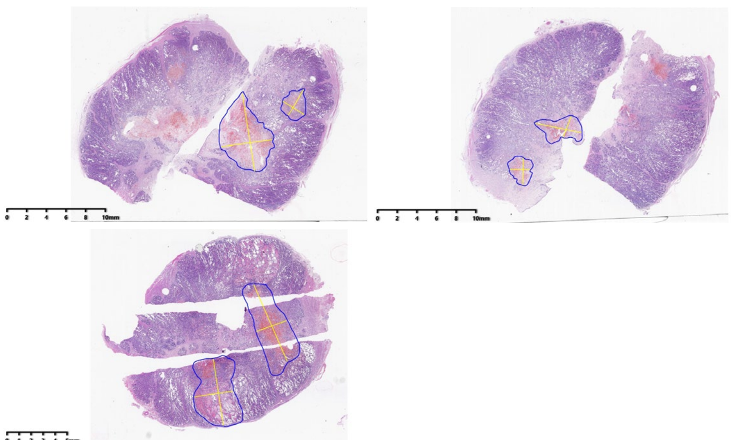
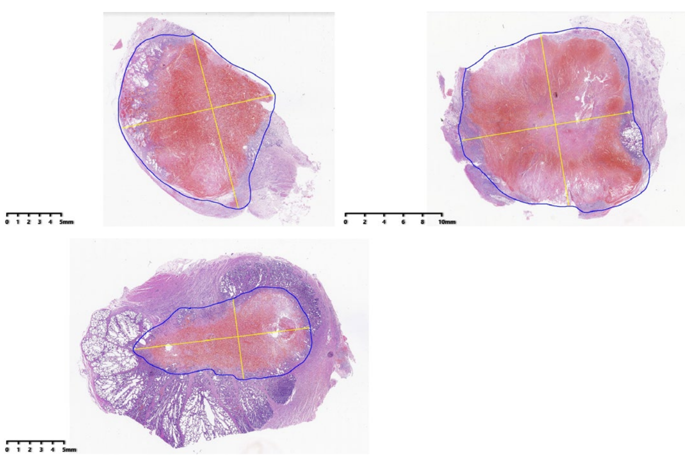
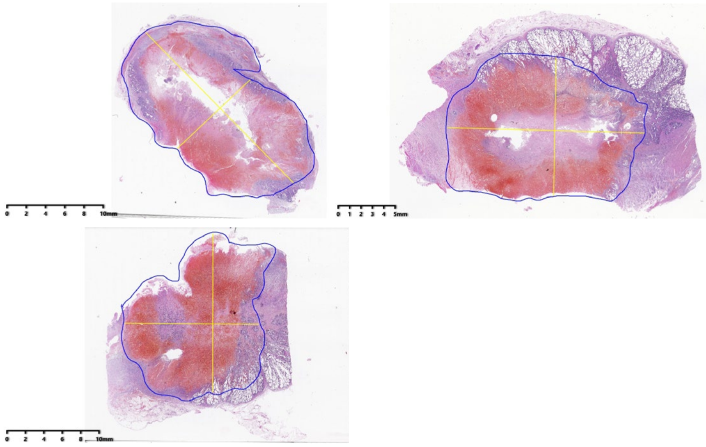
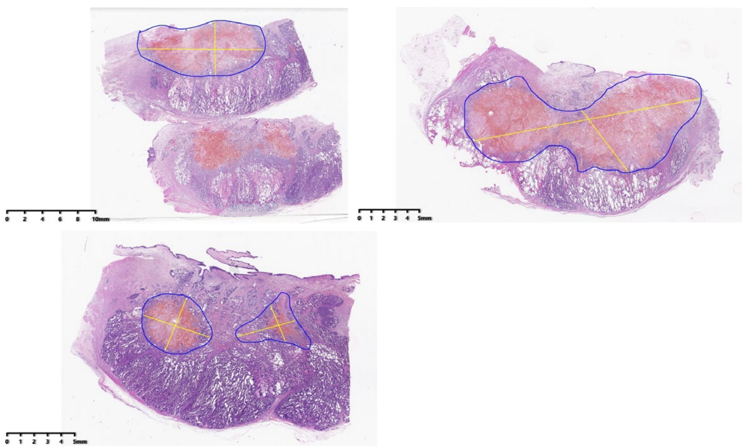
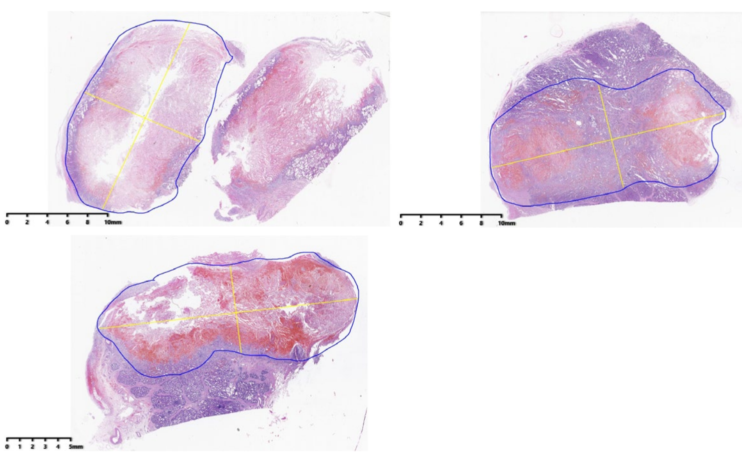
Grouping	Animal No.	Histopathological manifestations	Ablation area (mm^2)
Large parameter (2,000 v/cm); needle distance: 10 mm	07L, 07R, 08L		224.79±61.62
Small parameter (1,000 v/cm); needle distance: 14 mm	08R, 10L, 10R		34.92±16.73
Medium parameter (1,500 v/cm); needle distance: 14 mm	11L, 11R, 13L		226.25±108.25

Table 1 *(continued)*

Table 1 *(continued)*

Grouping	Animal No.	Histopathological manifestations	Ablation area (mm^2)
Large parameter (2,000 v/cm); needle distance: 14 mm	13R, 16L, 16R		232.20±20.44
Small parameter (1,000 v/cm); needle distance: 18 mm	6L, 6R, 12L		83.28±46.31
Medium parameter (1,500 v/cm); needle distance: 18 mm	12R, 14L, 14R		216.20±64.17

Data are presented with mean ± SD. HE staining was performed. Detailed scale is presented in the figure. L, left; R, right; SD, standard deviation; HE, hematoxylin and eosin.

Table 2 Results of multiple comparisons of the three parameters

Projects	Small parameter group	Medium parameter group	Large parameter group
Ablation zone			
N [missing]	9 [0]	9 [0]	6 [0]
Mean ± SD	39.74±43.45	175.46±94.08	228.49±41.26
Median	35.35	142.28	224.46
Q1, Q3	3.09, 50.27	110.22, 248.68	211.92, 252.80
Min, max	0.00, 127.77	59.73, 325.37	167.40, 289.91
Comparison between groups			
Test statistic	H=14.05		
P value	<0.001		

SD, standard deviation.

Table 3 Results of two-by-two comparison of three parameters

Comparison group	Test methods	Statistic	Calibration P value
Small *vs.* medium parameters	Rank-sum test	*Z*=3.00	0.01
Small *vs.* large parameters	*t*-test	*t*=8.40	<0.001
Medium *vs.* large parameters	*t*-test	*t*=1.29	0.66

nerves and blood vessels. A clinical study revealed that patients treated with high-frequency electroporation experienced a significantly lower 6-month clinical recurrence rate compared to other localized treatments, with minimal impact on urinary and sexual function (11). Traditional IRE employs unipolar pulses characterized by extended pulse widths, which translates to reduced ablation efficiency, necessitating a larger number of pulses and potentially leading to incomplete ablation. In contrast, H-FIRE utilizes a technique that employs short-pulse-width bipolar (alternating polarity) composite pulses for ablation. This approach offers several advantages, including heightened ablation efficiency, improved safety, and reduced muscle contractions (12,13). Particularly, H-FIRE showed less recurrence rates than other novel surgical treatments, such as radiofrequency ablation (RFA), cryoablation (CA), microwave ablation (MWA) (14). Because of non-thermal effect, tissue selectivity, preserving urinary and erectile function, IRE has been proven to have good safety and effectiveness when it comes to tumors that are near big vessels (14) in PCa. If applied in the treatment of prostate hyperplasia, IRE can also reduce the damage of sexual function and urinary control function while ablating prostate gland hyperplasia cells. Additionally, an increasing number of novel surgical treatments are becoming more widely used despite their greater costs, which is indicative of an increasing understanding of their advantages—which in some circumstances include a lower need for retreatment than with TURP (15). Given its non-thermal approach, which may protect erectile and urinary functioning, H-FIRE has the potential to be a useful addition to the range of minimally invasive treatments available for the treatment of BPH against this backdrop of increasing surgical practice. Therefore, we verified the feasibility and safety of its treatment of BPH in animal trials for the first time. The results of this experiment support that it is a promising treatment for prostate hyperplasia.

As we know, the electric field parameter is critical for the IRE ablation effect, different parameters can yield varying outcomes; IRE treatment does not produce thermal effects during the treatment process, which basically does not cause damage to peripheral nerves, blood vessels and other tissues, and better preserves the sexual function of patients, which is its greatest advantage. Excessively high voltage may lead to muscle contractions and patient discomfort, whereas overly low voltage can compromise the ablation efficacy (16). Therefore, establishing appropriate yet effective and safe ablation parameters is paramount for successful tumor suppression. Consequently, in this study, no matter the needle distance was 10, 14, or 18 mm, we found that these three sets of electric field parameters were safe. There was no change of clinical significance found in both animals' behavior and laboratory tests in all groups. Meanwhile, the ablation areas of the medium and large parameter groups were significantly larger than that of the small parameter group, and there was no significant difference in the area between the medium and large parameter groups. However, the medium and small parameter groups were similarly resulting in interrupted and incomplete ablation area as the pathological results demonstrated, while the ablation areas of large parameter group were continuous and complete. Therefore, we believe that 1,000–2,000 v/cm, 5 μs, is a safe parameter range for ablation of prostate tissue. At the same time, the large electric field strength (2,000 v/cm) has the best ablation effect of which the ablation area is complete and thorough.

For the animal model, Beagle dog is internationally acknowledged as one of the most suitable model animals, characterized by a moderate body size, robust self-resistance, and reliable response consistency. Beagles have found widespread utilization in prostate tissue ablation models, encompassing studies involving IRE, radiofrequency, and various other ablation techniques (17). In the current experiments, Beagles served as the primary subjects, and the outcomes of these experiments hold the potential to bolster the foundational knowledge for subsequent investigations, including clinical trials. In this study, H-FIRE ablation was performed on prostate of Beagles which was similar to the structure of prostate of humans (17). We found that H-FIRE ablation was safe and effective in prostate of Beagles, providing a further use in prostate of human beings. By employing Beagles as experimental subjects to ascertain the optimal ablation parameters, we provide a robust experimental foundation for the selection of parameters in future IRE procedures for clinical prostate diseases.

The study also had some limitations. This was a preliminary study that had only studied a small number of animals; therefore, a large number of experiments were needed to further optimize the parameters and enhance their reliability. Additionally, the follow-up period was only 5 days, which required a longer period for further evaluations.

Conclusions

In this study, although our range of parameters is not too large and the grouping is not refined enough, based on the histopathology results, laboratory examinations, animals' behaviors, we believe that from 1,000 to 2,000 v/cm in electric field strength, combined with 5 µs pulse width and pulse number 100, is a safe parameter range for ablation of prostate tissue. At the same time, the large electric field strength (2,000 v/cm) has the best ablation effect with biggest continuous and thorough ablation area. It can provide reference for further animal and clinical studies.

Acknowledgments

We are really grateful to Shanghai Jiaotong University Agriculture and Biology Experimental Company for providing animals and facilities.
Funding: The study was supported by the Pudong New Area Science and Technology Development Fund (No. PKX2020-S11).

Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-108/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-108/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-108/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-108/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Animal experiments were performed under a project license (No. 20230302) granted by the institutional ethics board of Shanghai Jiaotong University Agriculture and Biology Experimental Company, in compliance with the institutional guidelines for the care and use of animals.

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Cite this article as: Xing R, Ji S, Li X, Gong T, Jiang Q. High-frequency irreversible electroporation ablation for the prostate in Beagle dogs. Transl Androl Urol 2024;13(9):2016-2026. doi: 10.21037/tau-24-108

