LABORATORY INVESTIGATION

Feasibility of Catheter-Directed Intraluminal Irreversible Electroporation of Porcine Ureter and Acute Outcomes in Response to Increasing Energy Delivery

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ABSTRACT

Purpose: To evaluate the feasibility of focal intraluminal irreversible electroporation (IRE) in the ureter with a novel electrode catheter and to study the treatment effects in response to increasing pulse strength.

Materials and Methods: Five IRE treatment settings were each evaluated twice for the ablation of normal ureter in five Yorkshire pigs (n = 1–4 ablations per animal; total of 10 ablations) with the use of a prototype device under ultrasound and fluoroscopic guidance. Animals received unilateral or bilateral treatment, limited to a maximum of two ablations in any one ureter. Treatment was delivered with increasing pulse strength (from 1,000 V to 3,000 V in increments of 500 V) while keeping the pulse duration (100 μs) and number of pulses (n = 90) constant. Ureter patency was assessed with antegrade ureteropyelography immediately following treatment. Animals were euthanized within 4 hours after treatment, and treated urinary tract was harvested for histopathologic analysis with hematoxylin and eosin and Masson trichrome stains.

Results: IRE was successfully performed in all animals, without evidence of ureteral perforation. Hematoxylin and eosin analysis of IRE treatments demonstrated full-thickness ablation at higher field strengths (mucosa to the adventitia). Masson trichrome stains showed preservation of connective tissue at all field strengths.

Conclusions: Intraluminal catheter-directed IRE ablation is feasible and produces full-thickness ablation of normal ureters. There was no evidence of lumen perforation even at the maximum voltages evaluated.

ABBREVIATIONS

H&E = hematoxylin and eosin, IRE = irreversible electroporation, MT = Masson trichrome

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Irreversible electroporation (IRE) has been evaluated in multiple preclinical studies (1–6) for focal ablation of renal parenchyma adjacent to the renal pelvis and the ureter in large animal models. Results from these studies indicate that IRE may be safe for the focal ablation of tissue near such heat-sensitive structures (1,2). IRE of the renal parenchyma causes cell death with preservation of the extracellular matrix and other collagenous structures within the treated region (1,5). Acute loss of urothelium in the collecting system was reported (6), with complete recovery within 2–3 weeks after treatment. Studies have also reported the absence of clinically significant remodeling or disruption of the urinary collecting system (1,2). Long-term clinical and imaging

follow-up after renal IRE in animals showed preservation of normal urinary function and flow characteristics (6). IRE has also been evaluated for the focal ablation of renal tumors in humans in a treat-and-resect trial (7). Results from this study (7) suggest that IRE may be a safe and feasible technique and may offer advantages over thermal ablation, including greater sparing and rapid recovery of normal renal tissues and shorter treatment duration. Further evaluation of IRE in humans (8) has provided feasibility and safety data for treatment of tumors adjacent to bile ducts (9), pancreatic ducts (10,11), or nerves (12).

Ureteroscopic and percutaneous management of urothelial cancer is typically used with patients who are contraindicated for surgical treatment because of existing conditions such as poor renal function, bilateral cancer, or presence of chronic kidney conditions. Treatment is mostly used in patients with low-grade disease. However, clinically used ablative approaches of electrodiathermy or laser treatment are associated with high complication rates (14%) and high rates of disease recurrence (52%) (13). The inability to safely perform deep treatment may be a key factor limiting the wider use of ablative therapy. Sparing of the renal collecting system from injury and posttreatment urothelial regeneration may make IRE an alternative for the treatment of early-stage urothelial cancers. The development of a new catheter-mounted electrode has enabled image-guided focal IRE for endoluminal treatment of urothelial tumors that could preserve urinary tract form and function. In the present study, we examine feasibility, acute safety, and tissue response to catheter-mounted endoluminal IRE in swine ureters with the use of a clinically relevant range of increasing energy delivery settings.

MATERIALS AND METHODS

Prototype Catheter

A flexible electrode catheter was created by winding 22-gauge (0.025-inch diameter) medical-grade stainless-steel tubing (316 LVM) at the distal tip of a straight-tip catheter (65 cm, 5 F, Soft-Vu; AngioDynamics, Latham, New York) to create an electrode with a working length of 15 mm (**Fig 1**). The wiring for the passage of current was passed along the body of the catheter, leaving the inner lumen open for guide wire access. The electrode was sized to be 2.5 mm in external diameter to allow the gentle dilation of the ureter and achieve uniform contact between the electrode coil and the tissues. The external diameter of the modified device was approximately 7 F.

Experimental Procedure

The goal of the experiments was to evaluate IRE delivered at five different voltage values. Treatment at each voltage was attempted twice, once each in the proximal or distal ureter. As the study involved a new technique (ie, IRE) and a new type of procedure (ie, fluoroscopy-guided ablation of ureter wall) and device, the experiments had to be performed in an incremental fashion. The first two animals received a single treatment each at voltages that were expected to evoke a definite response in the tissue (2,500 V and 2,000 V). The experience gained from the first two studies was used to perfect the experimental procedure. The next two animals received two treatments each, and the last animal received four treatments. In animals 3 and 4, choice of treatment location was also dictated by the ability to establish percutaneous access to the ureter and the reach of the catheter device inside the lumen. Treatment was limited to a maximum of two ablations in any one ureter. A total of 10 treatments were completed among five animals. The chronologic sequence of experiments and treatment parameters evaluated in each animal can be seen in **Table 1**.

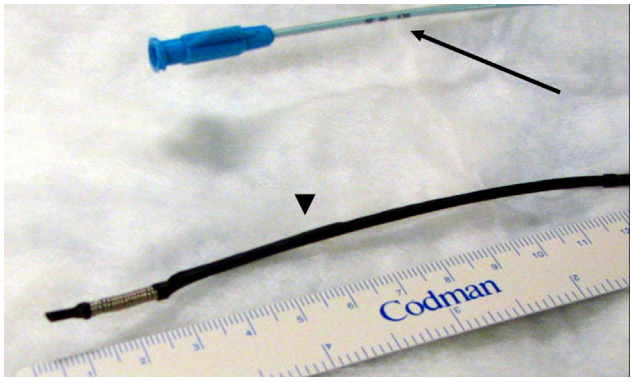

Figure 1. Prototype catheter-mounted electrode used for intraluminal IRE of swine ureter. The catheter hub and body are blue (arrow), and the insulated portions of the catheter overlying the wiring are black (arrowhead). (Available in color online at *www.jvir.org*.)

Following an experimental protocol approved by our institutional animal care and use committee, five female Yorkshire swine (weight range, 35–50 kg) were sedated with intravenous tiletamine hydrochloride and zolazepam hydrochloride (6 mg/kg, Telazol; Fort Dodge Animal Health, Fort Dodge, Iowa), and general anesthesia was maintained with inhaled isoflurane (2%–3% AErrane; Baxter, Deerfield, Illinois). Pigs were positioned in prone position on a fluoroscopy table and were prepared and draped in a sterile fashion. Access to the ureter was obtained via direct calyceal puncture by using a 21-gauge needle under ultrasound guidance (Prosound; Hitachi-Aloka, Wallingford, Connecticut). Location in the collecting system was confirmed by injection of dilute iohexol contrast medium (Omnipaque 300; GE Healthcare, Milwaukee, Wisconsin) under fluoroscopic visualization (Innova; GE Healthcare). After serial dilation over a wire, a 9-F, 10-cm-long sheath (Pinnacle; Terumo, Somerset, New Jersey) was inserted into the proximal ureter on one side.