LABORATORY INVESTIGATION

Renal Sympathetic Denervation System via Intraluminal Ultrasonic Ablation: Therapeutic Intravascular Ultrasound Design and Preclinical Evaluation

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ABSTRACT

Purpose: To assess the safety and performance of a nonfocused and nonballooned ultrasonic (US) catheter–based renal sympathetic denervation (RDN) system in normotensive swine.

Materials and Methods: RDN with the therapeutic intravascular US catheter was evaluated in 3 experiments: (*i*) therapeutic intravascular US RDN vs a control group of untreated animals with follow-up of 30, 45, and 90 days (n = 6; n = 12 renal arteries for each group); (*ii*) therapeutic intravascular US RDN vs radiofrequency (RF) RDN in the contralateral artery in the same animal (n = 2; n = 4 renal arteries); and (*iii*) therapeutic intravascular US RDN in a recently stent-implanted renal artery (n = 2; n = 4 renal arteries).

Results: In the first experiment, therapeutic intravascular US RDN was safe, without angiographic evidence of dissection or renal artery stenosis. Neuronal tissue vacuolization, nuclei pyknosis, and perineuronal inflammation were evident after RDN, without renal artery wall damage. Norepinephrine levels were significantly lower after therapeutic intravascular US RDN after 30, 45, and 90 days compared with the control group (200.17 pg/mg ± 63.35, 184.75 pg/mg ± 44.51, and 203.43 pg/mg ± 58.54, respectively, vs 342.42 pg/mg ± 79.97). In the second experiment, deeper neuronal ablation penetrance was found with therapeutic intravascular US RDN vs RF RDN (maximal penetrance from endothelium of 7.0 mm vs 3.5 mm, respectively). There was less damage to the artery wall after therapeutic intravascular US RDN than with RF RDN, after which edema and injured endothelium were seen. In the third experiment, denervation inside the stent-implanted segments was feasible without damage to the renal artery wall or stent.

Conclusions: The therapeutic intravascular US system performed safely and reduced norepinephrine levels. Deeper penetrance and better preservation of vessel wall were observed with therapeutic intravascular US RDN vs RF RDN. Neuronal ablations were observed in stent-implanted renal arteries.

ABBREVIATIONS

H&E = hematoxylin and eosin, RDN = renal sympathetic denervation, RF = radiofrequency, TTC = triphenyl tetrazolium chloride

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The renal sympathetic nervous system plays a key role in the pathogenesis of hypertension. Activation of the efferent renal nerve fibers leads to salt and water retention and activation of the renin–angiotensin–aldosterone system, thereby promoting blood pressure elevation (1). In addition, renal afferent sympathetic nerve activation may promote blood pressure elevation by an increase in global sympathetic outflow (1). Surgical renal sympathetic denervation (RDN) reduced blood pressure in animal models and was suggested as an aid in the treatment of resistant hypertension (1). Percutaneous catheter-based RDN is a potential treatment for resistant hypertension (2,3). Radiofrequency (RF) catheters, ultrasound (US) energy–emitting catheters, and chemical

denervation catheters have been developed to achieve RDN (2,3). The Symplicity catheter system (Medtronic, Minneapolis, Minnesota), which uses RF ablation energy, is currently the most studied catheter-based RDN treatment in resistant hypertension (3–6). RDN with the Symplicity system reduced blood pressure in patients with resistant hypertension in small randomized, nonblinded studies (5). However, the most rigorously designed randomized sham-control study (3,6) failed to meet the efficacy endpoints. Therefore, catheter-based RDN is currently an investigational treatment. Ongoing clinical trials may provide definitive answers regarding its efficacy in resistant hypertension (3). A new method of noninvasive RDN that uses externally delivered US (Surround-Sound; Kona Medical, Bellevue, Washington) was recently tested in patients with resistant hypertension (7).

The therapeutic intravascular US RDN system (TIVUS^{TM}; Cardiosonic, Tel Aviv, Israel) uses a high-intensity, nonfocused US nonocclusive catheter system. The present report evaluates the safety and the effect on renal tissue norepinephrine levels of RDN treatment with the therapeutic intravascular US RDN device and an RF RDN device.

MATERIALS AND METHODS

The protocols for all described studies were reviewed and approved by the ethics committees of the test facilities. All studies were performed on healthy normotensive domestic swine under good laboratory practice protocol.

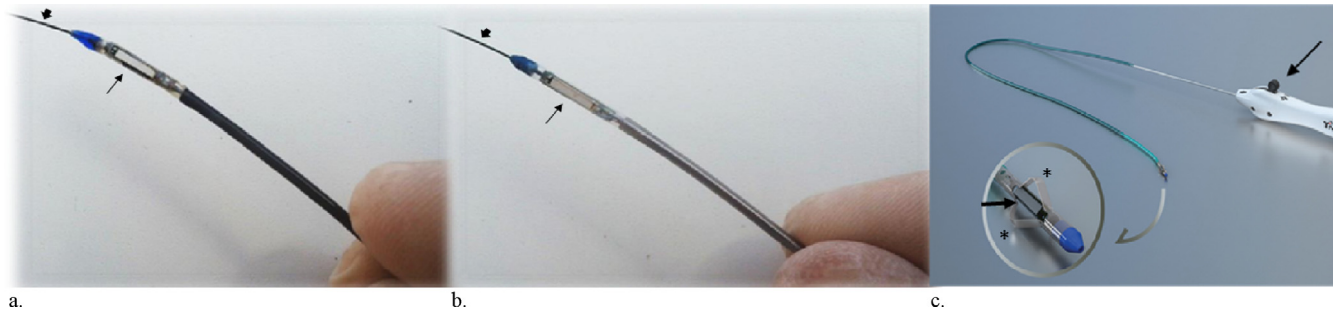
Device Overview

The therapeutic intravascular US RDN system consists of a console, connecting leads, and a single-use 6-F over-the-wire US catheter (unidirectional, steerable, or multidirectional; Fig 1). The unidirectional and steerable catheters are composed of a single flat US transducer mounted on a 5-F shaft. The unidirectional catheter can be delivered through a guiding catheter or a sheath (Fig 1a). The steerable therapeutic intravascular US catheter (Fig 1b) is composed of a single US transducer with a steerable and "torqueable" mechanism, such that the user can use the catheter handle to control tip navigation to the desired location in the renal artery and rotate the catheter to treat different locations circumferentially and along the vessel.

The multidirectional therapeutic intravascular US catheter (Fig 1c) is composed of three US elements, enabling emission of circumferential US energy simultaneously. A gradual distancing mechanism is operated via a designated lever on the multidirectional catheter handle. The lever deploys three petals surrounding the US elements. Each stop of the lever results in additional opening of the petals, moving the catheter further away from the artery wall. Real-time feedback consisting of blood temperature and catheter position within the artery may provide a safety mechanism and minimizes the need for contrast agent injections. The real-time temperature measurement represents the highest temperature of the transducer at its point of contact with blood. The flowing blood cools the transducer and keeps it from becoming too hot while also helping to protect the artery from direct thermal injury.

Therapeutic Intravascular US RDN Procedure

A flowchart of the therapeutic intravascular US RDN procedure is shown in Figure 2. Domestic swine (weight, 70–80 kg) were treated under anesthesia, with induction with xylazine (2 mg/kg) and ketamine (20 mg/kg) and maintenance with isoflurane (1.5%–3%). A 6-F renal sheath and 6-F renal guide catheter were introduced percutaneously via femoral access to insert the therapeutic intravascular US catheter over a 0.014-inch standard wire throughout the renal arteries. Depending on the length and anatomy of the renal artery, four to eight points were treated with the therapeutic intravascular US catheter throughout the renal artery circumference at one or two sites, from distal to proximal, along the artery.



a. b. c.

Figure 1. The therapeutic intravascular US RDN catheter system. **(a)** Unidirectional catheter: the guide wire and US transducer are marked with short and long arrows, respectively. **(b)** Steerable catheter: the guide wire and US transducer are marked with short and long arrows, respectively. **(c)** Multidirectional catheter: the long arrow indicates the catheter's mechanical lever. In the circle is an open position of two of the three distancing petals (asterisks). The short arrow indicates 1 of the 3 US transducers.