CLINICAL STUDY

First-in-Man Experience with a Novel Catheter-Based Renal Denervation System of Ultrasonic Ablation in Patients with Resistant Hypertension

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ABSTRACT

Purpose: To report results of renal denervation (RDN) with the first catheter-based, non–balloon occlusion ultrasonic system in patients with resistant hypertension.

Materials and Methods: In a multicenter, single-arm trial, 39 patients with resistant hypertension (defined as uncontrolled hypertension while taking ≥ 3 antihypertensive medications) were treated. The cohort consisted of 4 groups: severe resistant hypertension (office systolic blood pressure [OSBP] $\geq$ 160 mm Hg) treated with a unidirectional catheter (group 1; n = 14); severe resistant hypertension treated with a multidirectional catheter (group 2; n = 18); moderate resistant hypertension (OSBP 140–159 mm Hg) treated with a multidirectional catheter (group 3; n = 5); and recurrent severe resistant hypertension, after an initial response to RF RDN (group 4; n = 2). Blood pressure monitoring was performed for 6 months.

Results: Severe adverse events were not noted immediately after the procedure or during follow-up. Treatment time was longer with unidirectional than with multidirectional catheters (36.7 min ± 9.6 vs 11.9 min ± 5.8; $P < .001$). Mean reductions in office blood pressure (systolic/diastolic) at 1, 3, and 6 months were −26.1/−9.6 mm Hg, −28.0/−9.9 mm Hg, and −30.6/−14.1 mm Hg ($P < .01$ for all). Per-group analysis showed significant OSBP reduction for groups 1 and 2. Patients with isolated systolic hypertension had a significantly smaller reduction in OSBP after 6 months compared with patients with combined systolic/diastolic hypertension (−16.2 mm Hg ± 18.5 vs −9.9 mm Hg ± 33.4; $P < .005$).

Conclusions: Use of the RDN system was feasible and safe in this phase I study. Significant blood pressure reductions were observed over 6 months, although less in patients with isolated systolic hypertension.

ABBREVIATIONS

ABPM = ambulatory blood pressure monitoring, ADBP = ambulatory diastolic blood pressure, ASBP = ambulatory systolic blood pressure, CH = combined systolic/diastolic hypertension, eGFR = estimated glomerular filtration rate, ISH = isolated systolic hypertension, ODBP = office diastolic blood pressure, OSBP = office systolic blood pressure, RDN = renal denervation

Resistant hypertension is defined as uncontrolled hypertension while taking at least 3 antihypertensive medications, of which one is a diuretic (1). In recent years, percutaneous catheter-based renal denervation (RDN) has emerged as a potential treatment for resistant hypertension (2). Radiofrequency (RF) catheters, ultrasound energy-emitting catheters, cryoenergy

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catheters, and chemical denervation catheters have been developed to achieve RDN (2–5). A noninvasive approach to RDN using externally delivered ultrasound (Surround Sound; Kona Medical, Inc, Bellevue, Washington) failed to reduce blood pressure in a double-blind, randomized, sham-controlled study of patients with uncontrolled hypertension (6). The Therapeutic Intra Vascular UltraSound (TIVUS; Cardiosonic Ltd, Tel Aviv, Israel) system is a novel RDN technology (7). This system uses a high-intensity, nonfocused ultrasound catheter system to generate a remote, controlled, thermal effect to sympathetic nerves along the renal artery, without the need for an occlusion cooling balloon. The present study reports the first experience of this system in patients with resistant hypertension.

MATERIALS AND METHODS

The TIVUS I and II trials (ClinicalTrials.gov Identifier: NCT01835535) were prospective, multicenter, nonrandomized, open-label clinical studies that evaluated the safety and efficacy of a therapeutic intravascular ultrasound system in patients with resistant hypertension. An advisory committee of the sponsor was responsible for the clinical study design. The studies were reviewed and approved by the ethics committees of all participating medical centers, and all enrolled participants gave informed consent. To reduce intraoperator bias, the studies were performed after a training session that familiarized site operators with the RDN system. All 11 operators were interventional radiologists or cardiologists with $>$ 10 years of post-fellowship experience in renal angiography. All data were collected using an electronic data collection system (MedNet Solutions, Minnetonka, Minnesota). Data entry and development of the primary database for the study were managed by Prairie Education and Research Cooperative (Springfield, Illinois). Prairie Education and Research Cooperative was also responsible for the quality control of the database and for confirming the overall integrity of the data. All statistical analyses were performed by independent statisticians. The decision to publish the data was made by the authors. The authors also analyzed the data and wrote the article independent of the sponsor.

Study Endpoints

The primary endpoint was change in office systolic blood pressure (OSBP) from baseline to 6 months. The primary safety endpoint was the occurrence of adverse events during the 30 days after RDN. Secondary outcome measures were (*a*) procedural complications during the 30 days after RDN, (*b*) major adverse events, (*c*) eGFR change, and (*d*) cardiovascular complications during the first year following RDN.

RDN System Procedure

The device and procedure were previously described in detail (7). Briefly, the system consisted of a console, connecting leads, and single-use 6-F (unidirectional, steerable or multidirectional), over-the-wire ultrasound catheter (**Fig 1a**, **b**). Local protocols were applied at each participating center for sedation and analgesia. A 6-F renal sheath (HEARTRAIL; Terumo Corp, Tokyo, Japan) and 6F renal guiding sheath (Morph; BioCardia, Inc, San Carlos, California) or guiding catheter (VISTA BRITE TIP; Cordis Corp, Milpitas, California) were introduced percutaneously via femoral access to insert the catheter over a 0.014-inch standard wire throughout the renal arteries. Depending on the length and anatomy of the renal artery, ultrasound RDN was administered in the renal artery circumference, from distal to proximal along the arteries. A minimal renal artery length of 20 mm allows several treatment sites (approximately 10 mm per site). The length of the renal artery defines the number of times the catheter can be retrieved. The intensity of each treatment, in both the unidirectional catheter and the multidirectional catheter, was up to 35 W/cm^2. Following the procedure, hemostasis of the femoral access site was achieved using standard techniques. RDN procedure time was defined as the time from initiation to completion of the ultrasonic energy delivery including catheter retrieval.

Participant Screening and Selection

Patients were eligible to participate if they had a diagnosis of resistant hypertension as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (1). Patients were excluded if they (*a*) were $<$ 18 years of age; (*b*) were pregnant or breastfeeding; (*c*) were allergic to contrast media; (*d*) had eGFR $\leq$ 45 mL/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease equation; (*e*) had a known cause for secondary hypertension; (*f*) had had a myocardial infarction, unstable angina pectoris, or cerebrovascular accident within 6 months of screening; (*g*) had hemodynamically significant valvular heart disease for which reduction of blood pressure would be considered hazardous; or (*h*) had comorbidities limiting life expectancy to $<$ 1 year.

Screening involved 3 steps (**Fig 2**): (*i*) assessment of inclusion and exclusion criteria, medication compliance and resistance to hypertension based on OSBP at 2 visits, and a 2-week period of home blood pressure measuring; (*ii*) 24-hour ambulatory blood pressure monitoring (ABPM) with evidence of uncontrolled hypertension, defined as ambulatory systolic blood pressure (ASBP) $\geq$ 135 mm Hg and/or ambulatory diastolic blood pressure (ADBP) $\geq$ 85 mm Hg (2); (*iii*) renal angiography in patients found eligible at this point that evaluated anatomy eligibility before RDN. Patients with main renal arteries $<$ 4 mm in lumen diameter or $<$ 20 mm in length were excluded from participation; also excluded were patients with hemodynamically or anatomically significant renal artery calcification or with abnormality or stenosis in either renal artery, which, in the operator's opinion, would interfere with safe cannulation of the renal artery or which meets local standards for surgical repair or interventional dilation. Patients found ineligible for