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PERIPHERAL

Externally Delivered Focused Ultrasound for Renal Denervation

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ABSTRACT

OBJECTIVES The aim of this study was to assess clinical safety and efficacy outcomes of renal denervation executed by an externally delivered, completely noninvasive focused therapeutic ultrasound device.

BACKGROUND Renal denervation has emerged as a potential treatment approach for resistant hypertension.

METHODS Sixty-nine subjects received renal denervation with externally delivered focused ultrasound via the Kona Medical Surround Sound System. This approach was investigated across 3 consecutive studies to optimize targeting, tracking, and dosing. In the third study, treatments were performed in a completely noninvasive way using duplex ultrasound image guidance to target the therapy. Short- and long-term safety and efficacy were evaluated through use of clinical assessments, magnetic resonance imaging scans prior to and 3 and 24 weeks after renal denervation, and, in cases in which a targeting catheter was used to facilitate targeting, fluoroscopic angiography with contrast.

RESULTS All patients tolerated renal denervation using externally delivered focused ultrasound. Office blood pressure (BP) decreased by 24.6 ± 27.6/9.0 ± 15.0 mm Hg (from baseline BP of 180.0 ± 18.5/97.7 ± 13.7 mm Hg) in 69 patients after 6 months and 23.8 ± 24.1/10.3 ± 13.1 mm Hg in 64 patients with complete 1-year follow-up. The response rate (BP decrease >10 mm Hg) was 75% after 6 months and 77% after 1 year. The most common adverse event was post-treatment back pain, which was reported in 32 of 69 patients and resolved within 72 h in most cases. No intervention-related adverse events involving motor or sensory deficits were reported. Renal function was not altered, and vascular safety was established by magnetic resonance imaging (all patients), fluoroscopic angiography (n = 48), and optical coherence tomography (n = 5).

CONCLUSIONS Using externally delivered focused ultrasound and noninvasive duplex ultrasound, image-guided targeting was associated with substantial BP reduction without any major safety signals. Further randomized, sham-controlled trials will be needed to validate this unique approach. (J Am Coll Cardiol Intv 2016;9:1292–9)

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Up to 65% of patients with hypertension have untreated and/or uncontrolled blood pressure (BP) and about 10% have treatment-resistant hypertension (TRH) (1). In an effort to address this clinical need, attention has been focused on addressing BP control by disrupting the nerves running along the renal arteries (2). Patients with primary hypertension generally have increased efferent sympathetic nerve drive to the kidneys as well as increased systemic drive resulting from afferent nerves, as evidenced by elevated rates of renal norepinephrine spillover (2) and globally increased sympathetic nerve activity (3).

Disruption of the renal nerves has been shown to diminish the development of hypertension and to reduce elevated BP in TRH (4-7).

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Several intravascular methods have been developed to denervate the renal artery, with intravascular radiofrequency ablation to safely and effectively attenuate renal sympathetic nerve activity, resulting in a significant reduction in renal norepinephrine spillover (2,4) and substantial and sustained decreases in BP in patients with TRH (4,5).

Despite the success of catheter-based renal denervation systems, a number of limitations exist. Perhaps the most important limitation is the inability of radiofrequency catheter systems to deposit energy uniformly in the nerves, which are located both circumferentially and at varying depths around the vessel wall (8,9). Furthermore, because the radiofrequency energy is highly concentrated at the tip of the catheter, more energy is deposited in the arterial wall adjacent to the catheter tip than in the outer adventitial layer, resulting in injury to the endothelium and surrounding tissue and reduced range of neurolysis. The catheter devices are also invasive and require the use of fluoroscopy and contrast agents, which pose increased risks to patients (10).

A new, noninvasive approach for renal denervation has been developed for the treatment of hypertension using externally delivered focused ultrasound. In this paper, we present the initial clinical experience with externally delivered focused ultrasound renal denervation using the Surround Sound System (Kona Medical, Bellevue, Washington).

METHODS

From June 2012 to July 2014, 3 consecutive multicenter, prospective, single-arm, nonrandomized studies (waves I, II, and III) (NCT01926951 and NCT01704170) were conducted. The Surround Sound System in the wave I and wave II studies used an intra-arterial targeting catheter with small ultrasound transducer (beacon) in its distal tip to facilitate targeting of the intended renal artery treatment sites. In the wave III study, the targeting catheter was substituted by a duplex ultrasound imaging technology to enable noninvasive treatment targeting.

A total of 69 eligible patients with uncontrolled TRH provided written consent and underwent treatment at 4 different centers (St. Vincent's Hospital, Melbourne, Australia; Homolka Hospital, Prague, Czech Republic; St. Anne Hospital, Brno, Czech Republic; and Mercy Angiographic Institute, Auckland, New Zealand). All 3 studies (waves I, II, and III) were approved by each institution's respective ethics committee. An independent data and safety monitoring board was engaged to monitor the safety and efficacy outcomes from the 3 studies. Patients were screened in 2 sets of baseline visits 2 weeks apart. At each visit, 3 office BP measurements were performed, and the average systolic BP was calculated. To be included in the study, systolic BP >160 mm Hg at each baseline visit was required. In addition, 24-h ambulatory BP monitoring was performed at baseline in all patients but was not pre-defined as an inclusion criterion in the protocols. All subjects underwent pre-treatment work-up to exclude secondary causes of hypertension that involved renal artery ultrasound and magnetic resonance imaging (MRI) to further confirm eligibility.

TREATMENT. All patients were treated using the Surround Sound System (**Figure 1**). The device is designed to generate and deliver an annular pattern of ellipsoid-shaped ultrasound foci to the renal nerves noninvasively while automatically tracking and correcting in real time for motions associated with breathing and other patient movements. In case of excessive motion beyond trackable boundaries, the treatment is paused automatically until accurate targeting and tracking functions have been reestablished. In all 3 studies, only a single artery was treated per side, regardless of whether multiple renal arteries

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

ECG = electrocardiogram

MRI = magnetic resonance imaging

TRH = treatment-resistant hypertension

conduct of the study. Dr. Schmieder received grants and personal fees from Kona Medical during the conduct of the study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Neuzil and Ormiston contributed equally to this work.

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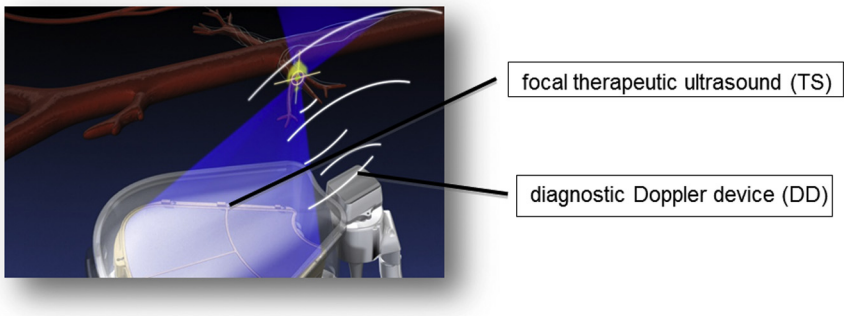
FIGURE 1 Illustration of Externally Delivered Focused Ultrasound to the Renal Artery and Surrounding Nerves



After visualizing the renal artery with the diagnostic duplex ultrasound device, and tracking of the kidney, the focal therapeutic ultrasound is delivered in a robotic way (14 spots around the kidney) within a 3-min time frame.

were present. A site within 1 cm of the bifurcation of the main renal artery was targeted for treatment, and only a single treatment pattern was administered at each site and per side.

In the wave I and wave II studies, a targeting catheter was placed to ensure safe and accurate delivery of the focused ultrasound prior to implementation of the duplex ultrasound image-guided targeting function. Of the 27 subjects enrolled in the wave III study, the first 5 patients enrolled were treated using both a targeting catheter and image-guided targeting to validate the performance and accuracy of the noninvasive targeting and tracking method. The final 22 subjects enrolled were all treated completely noninvasively using duplex ultrasound image guidance only.

FOLLOW-UP. Patients in all 3 studies were examined at 3, 6, 12, 24, and 52 weeks following treatment to assess short- and long-term safety and long-term efficacy. The 24-h ambulatory BP monitoring was scheduled at 24 and 52 weeks post-treatment. In the wave I study, patients underwent at 24 weeks and in waves II and III at 3 and 24 weeks post-treatment contrast-enhanced renal magnetic resonance angiography and MRI. In the first 48 patients through the waves I, II, and III trials, angiographic examinations were performed immediately prior to and following investigational treatment. In addition, the 24 patients in wave I and 5 in wave II underwent angiography at 6 weeks. Each angiogram was examined for the presence of spasm, thrombosis, stenosis, dissection, aneurysm, pseudoaneurysm, fistula, and any other vascular abnormalities. To the extent possible, each angiogram was also scrutinized to assess for renal perfusion defects. Additionally, optical coherence tomography was performed on 5 patients in Prague.

Subjects were instructed to remain on current antihypertensive medications up to the 12-month follow-up evaluation. Adjustments to hypertension medications were allowed as medically necessary to treat elevated BP (i.e., >180 mm Hg systolic) or significantly reduced BP (i.e., <120 mm Hg systolic).

STATISTICAL ANALYSIS. All analyses were performed using SPSS version 19.0 (SPSS, Chicago, Illinois). Normal distribution of data was confirmed by the Kolmogorov-Smirnov test. Data were compared using paired Student *t* tests and Wilcoxon and McNemar tests as appropriate. Data are presented as mean ± SD or as number (percentage). In the figures, the mean ± 1.96 SEM are provided.

RESULTS

OVERVIEW OF STUDY PATIENTS. The average age of the patient population was 62 years. Patients were receiving an average of 4.57 antihypertensive medications. Baseline office BP was 180.0 ± 18.5/97.7 ± 13.7 mm Hg. In 3 of 27 patients in wave III, treatment of a contralateral renal artery was prevented as a result of inadequate image quality to visualize the target site.

Details of the aggregate waves I to III study population (n = 69) are given in Table 1.

BP RESPONSE FOR WAVES I, II, AND III. After 6 months, BP was reduced by 24.6 ± 27.6/9.0 ± 15.0 mm Hg (n = 69) and after 1 year by 23.8 ± 24.1/10.3 ± 13.1 mm Hg (n = 64) (Figure 2). Of the 27 subjects in wave III, 22 were treated using noninvasive duplex ultrasound image guidance, and BP reductions in this cohort were 18.0 ± 18.6/8.8 ± 10.0 mm Hg at 3 weeks, 29.6 ± 20.6/11.8 ± 13.8 mm Hg at 12 weeks, 19.8 ± 17.9/6.2 ± 14.7 mm Hg at 6 months, and 28.6 ± 18.5/11.3 ± 9.9

TABLE 1 Waves I to III Clinical Characteristics of All 69 Patients

Age (yrs)	61.7 ± 10.9
Male/female	41 (59.4)/28 (40.6)
Caucasians	66 (96)
Body mass index (kg/m^2)	31.2 ± 4.8
Type 2 diabetes	15 (21.7)
Coronary artery disease	4 (5.8)
Hypercholesterolemia	29 (42.0)
eGFR (ml/min/1.73 m^2)	78.9 ± 14
Heart rate (beats/min)	68.7 ± 12
Baseline systolic BP (mm Hg)	180 ± 18
Baseline diastolic BP (mm Hg)	98 ± 14
Number of antihypertensive medications	4.57 ± 1.1
Patients on antihypertensive medications for >5 yrs	57 (82.6)
Patients on ≥5 antihypertensive medications	34 (49.2)
Number of patients receiving each drug class	
ACE inhibitors	43 (62.3)
Angiotensin receptor blockers	32 (46.3)
Beta-blockers	46 (66.7)
Calcium-channel blockers	52 (75.4)
Diuretic agents	52 (75.4)
Aldosterone antagonists	13 (18.8)
Vasodilators	1 (1.4)
α-1 blockers	21 (30.4)
Centrally acting sympatholytic agents	32 (46.4)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; BP = blood pressure; eGFR = estimated glomerular filtration rate.

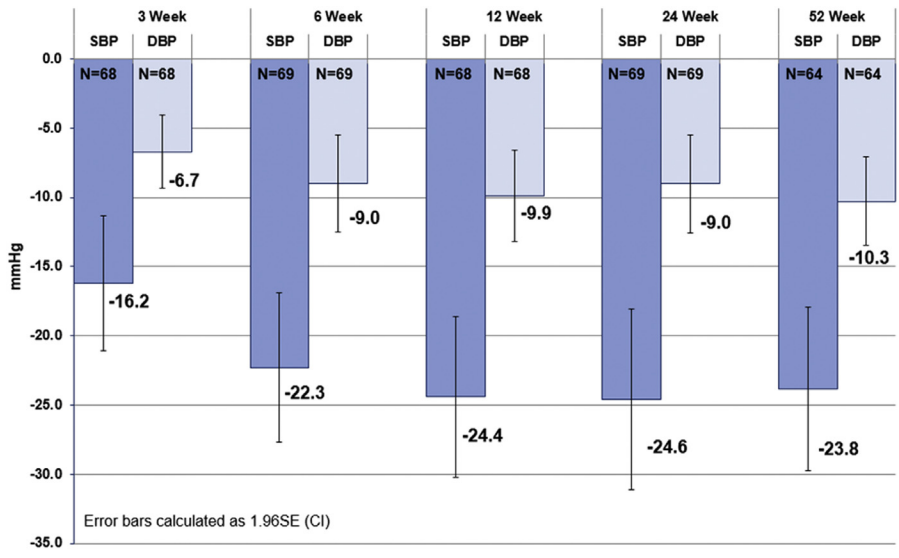
(n = 21) at 12 months (Figure 3). Response rates of at least 10 and 20 mm Hg office systolic BP decrease were observed in 75% and 55% of the 69 patients at 6 months and 77% and 56% at 1 year.

Twenty-four-hour ambulatory BP dropped by 2.2 ± 20.6/2.6 ± 10.9 mm Hg at 6-month follow-up (n = 38). If 24-h ambulatory BP is categorized by its baseline value (note that 24-h ambulatory BP was not required to be elevated as an inclusion criterion), the magnitude of effect at 24 weeks increased with increasing baseline ambulatory BP; for example, for 24-h ambulatory BP >140 mm Hg, the decrease in BP was 7.6 ± 20.9/4.8 ± 11.3 mm Hg (Figure 4).

During the course of the waves I to III studies, the number of antihypertensive medications being taken at 6 months increased in 7% of patients and decreased in 23%. Additionally, the doses of antihypertensive medications were increased in 7% and decreased in 13% of patients during the first 6 months of follow-up (Table 2). In patients with no changes in medication and dose (n = 43), office BP decreased by 23.7 ± 27.1/8.7 ± 12.5 mm Hg ($p < 0.05$ for both) after 6 months.

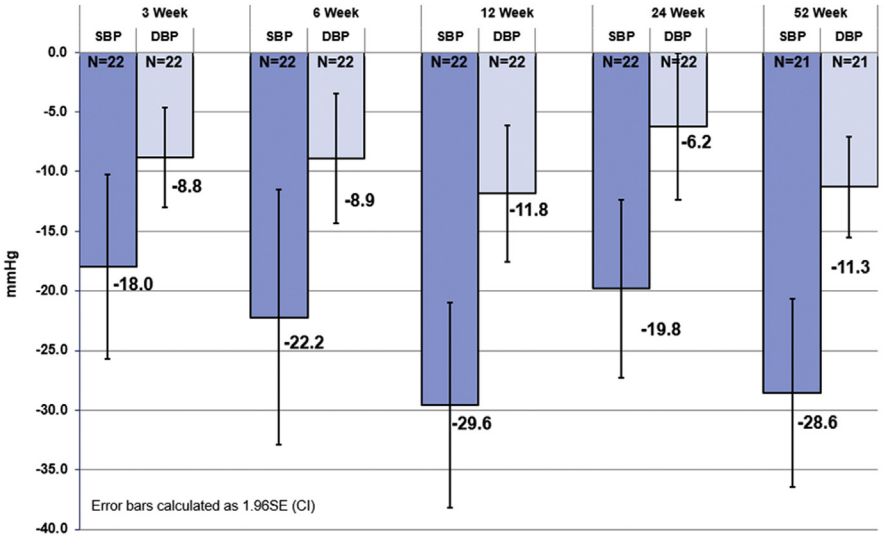
ADVERSE EVENTS. Nine serious adverse events were reported in the wave I study, 6 in the wave II study, and none in the wave III study. In wave II, 3 intervention-related serious adverse events were reported, consisting of 2 cases of hypertension and 1 case of hypotension that each required hospitalization. All 3 cases resolved completely. There was 1 death (in wave

FIGURE 2 Waves I to III Study Aggregate Office Blood Pressure Response (n = 69)



CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure; SE = standard error.

FIGURE 3 Wave III Study Average Office BP Response for Patients With Noninvasive Image Guidance (n = 22)



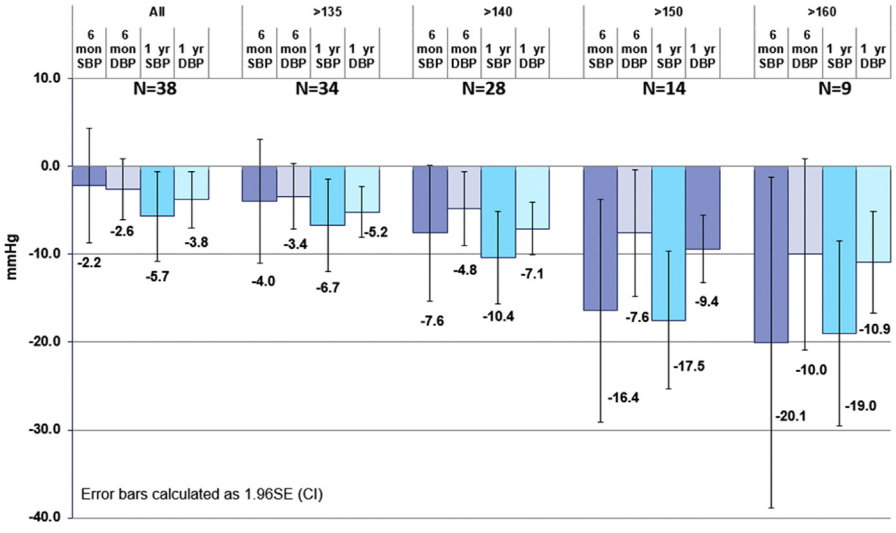
CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure; SE = standard error.

III), which was unrelated to the investigational treatment.

The most common adverse event reported across the 3 studies was post-treatment back pain, which was reported in 32 of 69 subjects (Table 3). Fifty percent of subjects reported post-treatment back pain in waves I and II, and 41% of subjects reported post-treatment back pain in wave III. No cases of back pain were associated with motor or sensory deficits, and no cases were noted to affect daily activities of living for subjects.

In the wave III study, creatinine phosphokinase increased from 139 to 253 U/l after 24 h but returned to 122 U/l after 3 weeks and to 144 U/l after 6 weeks.

FIGURE 4 Aggregate Ambulatory Blood Pressure 6-Month Response Stratified by Baseline Ambulatory Blood Pressure Over 135, 140, 150, and 160 mm Hg



CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure; SE = standard error.

TABLE 2 Waves I to III Overview of Medication Changes

	Baseline	6 Months
Average number of anti-HTN medications per patient	4.57 ± 1.09	4.33 ± 1.22
Patients with changes to medications	6 months (n = 69)	
Number of patients with number of medication changes		
Number of patients with medication number increases	5 (7)	
Number of patients with medication number decreases	16 (23)	
No change	50 (72)	
Number of patients with dosage changes		
Dose increases	5 (7)	
Dose decreases	9 (13)	
No change	55 (80)	

Values are mean ± SD or n (%).
HTN = hypertension.

Two patients with back pain had elevation in enzymes at 24 h post-treatment but never exceeded more than 3 times baseline levels, and all values returned to baseline within 3 weeks.

The frequency and intensity of MRI-detected abnormalities decreased from wave I to wave III in parallel with the clinical improvement in back pain as the dose of delivered energy was reduced and the placement of the treatment module was improved (Table 4).

Short- and long-term effects on renal function were assessed by serum creatinine and estimated glomerular filtration rate measurements. No significant differences in post-treatment estimated glomerular filtration rate values from baseline (78.7 ± 14.7 ml/min/1.73 m^2) were noted at the 3-week (80.4 ± 20.5 ml/min/1.73 m^2), 6-week (79.3 ± 16.0 ml/min/1.73 m^2), 12-week (78.9 ± 14.8 ml/min/1.73 m^2), 24-week (79.6 ± 16.7 ml/min/1.73 m^2), and 52-week (76.1 ± 16.2 ml/min/1.73 m^2) follow-up time points, supporting preservation of renal function. No increase in serum creatinine of 0.3 mg/dl or 1.5 times that at baseline was observed, thereby ruling out acute kidney injury. No hematuria was observed after the procedure.

ASSESSMENT OF VASCULAR SAFETY. No short- or long-term effects were seen on the renal vasculature in any of the 69 subjects treated with the Surround Sound System. Comparison of the baseline, 3-week, and 24-week follow-up magnetic resonance angiographic images revealed no evidence of spasm, stenosis, thrombosis, dissection, aneurysm, pseudoaneurysm, fistula, or any other vascular abnormalities at 3 and 24 weeks post-treatment. Neither were any filling defects detected.

No kidney pathology or vascular abnormalities were detected in any of the follow-up magnetic resonance images that were not present at the baseline examination. All kidneys examined were found to be within normal limits at the time of each examination, aside from some incidental renal cysts and common variations in developmental anatomy.

In 5 patients, renal artery optical coherence tomographic imaging was performed both at baseline and immediately following renal denervation. Comprehensive review of the images demonstrated no evidence of injury such as spasm, endothelial damage, or dissection to the renal artery (Figure 5).

TABLE 4 Overall Incidence and Severity of Treatment-Related MRI Findings at 3 Weeks Post-Treatment

	Within Normal Limits		Edema and/or Hyperemia		Hypoenhancement or Necrosis	
Wave I*	13/21	62%	5/21	24%	3/21	14%
Wave II	1/17	6%	9/17	53%	7/17	41%
Wave III	20/25	80%	5/25	20%	0/24	0%

*Performed at 24 weeks only; 3-week surveillance with MRI began in wave II.
MRI = magnetic resonance imaging.

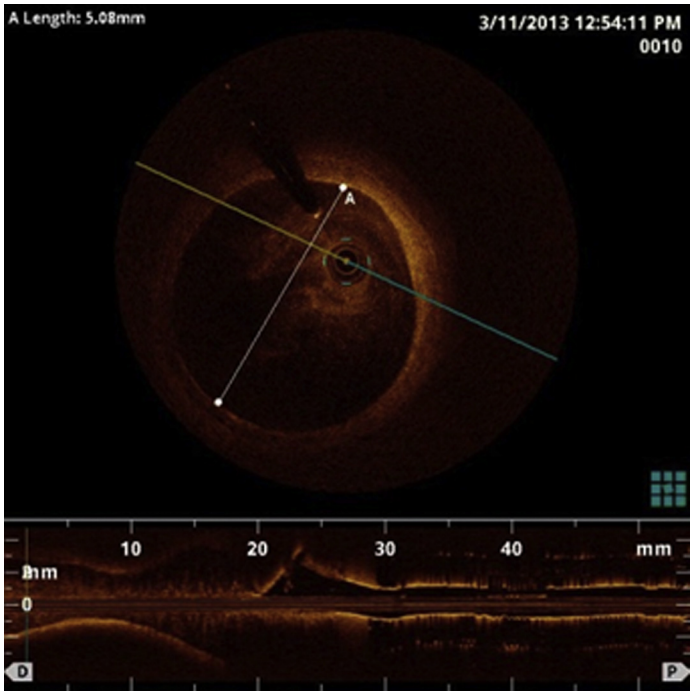
DISCUSSION

The Surround Sound System provides a unique approach for delivering externally focused ultrasound specifically targeting the peri-renal artery tissue. Evidenced by a series of experiments in 225 swine, the application of acoustic energy creates a thermal field sufficient to ablate renal nerves around the renal artery up to 1 cm beyond the lumen. The effectiveness of this novel, noninvasive approach in humans has now been studied in 3 clinical studies

TABLE 3 Composite Assessment of Back Pain in the Waves I, II, and III Studies

	Patients with Back Pain	Distribution		Duration of Back Pain					Pain Medications Required		Visit for Back Pain Outside Study Follow-Up	Affecting Daily Life Activities	Sensory Deficits	Motor Deficits
		Bilateral	Unilateral	<24 h	1-3 days	4-7 days	8-30 days	>30 days	Non-narcotic	Narcotic				
Wave I	12/24 (50%)	9	3	3	0	4	3	2	5	2	1	0	0	0
Wave II	9/18 (50%)	6	3	2	1	1	1	4	4	3	0	0	0	0
Wave III	11/27 (41%)	7	4	5	2	1	2	1	3	0	0	0	0	0

FIGURE 5 **Representative Optical Coherence Tomographic Image Obtained on the Treatment Day Immediately Following the Renal Denervation Treatment With the Surround Sound System and Targeting Catheter in the Wave I Study**



in patients with severe TRH. Office BP dropped, in the aggregate, from 180/98 mm Hg after 6 months by 25/9 mm Hg and after 12 months by 24/10 mm Hg. In these initial studies, more than 75% of subjects experienced a 10 mm Hg or more response, and more than 50% experienced a 20 mm Hg or more response. These in-line results (2,4,5,11) support the potential for delivering externally generated acoustic energy to induce neurolysis in the peri-renal artery tissue without the need for invasive vascular instrumentation. The value to patients is not only a reduction in treatment-related risks related to invasiveness, radiation, and contrast medium associated with the conventional invasive approach but also the opportunity for renal denervation in patients with contraindications to invasive catheterization due to other comorbidities. The major limitation of the device in its current state of development is the occasional less than optimal visualization of the renal arteries, mainly in patients with severe obesity. At this time, patients with body mass index under 35 kg/m^2 are best suited for the procedure. The noninvasive approach shares also the limitation with the invasive procedures that no physiological data (i.e., noradrenaline spillover measurements) are available to confirm complete interruption of afferent and efferent renal nerve traffic to and from the central nervous system.

The 24-h ambulatory BP was not an inclusion criterion in these 3 early studies because at the time these studies were designed, there was no clear demand for it (2). The changes in 24-h ambulatory BP were lower than expected, because of the inclusion of patients with white-coat hypertension. Previously the change in 43 pseudoresistant patients was +1.2 mm Hg (from 120 mm Hg) systolic at 6 months post-treatment (12), whereas severely resistant patients (n = 303) showed a decrease of 10.2 mm Hg (from 154 mm Hg) systolic at baseline. In our patients with 24-h ambulatory BP >135 and 140 mm Hg with a baseline of 152 and 155 mm Hg, the reductions in BP were 4.0 and 7.4 mm Hg, respectively. Not surprisingly, the greater the baseline value, the greater the BP decrease in our patients and across the various published studies (13,14).

Our pre-clinical data as well as waves I, II, and III suggest that externally delivered focused therapeutic ultrasound may be safe. No major device-related adverse events were reported. Although acute low back pain was experienced by one-half the patients following treatment in early studies, significant improvements to the investigational device and to the dosing scheme yielded substantial reductions in the incidence, intensity, and duration of discomfort in later study (**Table 3**). The etiology of the back pain was most likely related to enhanced energy deposition in the treatment path at interfaces where paraspinal muscles and adjacent bones intersect, consistent with findings on post-treatment MRI scans that demonstrated transitory inflammatory responses in these regions. Follow-up MRI scans at 24 weeks demonstrated complete or nearly complete resolution of findings. Even in the most severe cases in wave I, low back pain was not associated with any motor or sensory findings and did not affect ambulation or subjects' daily activities of living. Further review of post-treatment imaging also supported safety, with preservation of normal tissue within the kidney parenchyma, collecting system and vasculature, and surrounding organs. Renal function was well preserved, and no sign of acute kidney injury was observed in any of the patients.

This completely noninvasive approach to renal denervation is associated with BP reductions in patients with resistant hypertension. If confirmed by sham-controlled trials, this unique approach may be an attractive treatment for clinicians seeking treatment solutions for hypertensive patients with uncontrolled hypertension.

CONCLUSIONS

These 3 single-arm studies provide a first clinical experience with externally delivered focused ultrasound using the Kona Medical Surround Sound System. These initial studies form a strong foundation to support investigating noninvasive renal denervation using externally delivered focused ultrasound in a randomized phase 3, sham-controlled trial to further evaluate its safety and efficacy.

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PERSPECTIVES

WHAT IS KNOWN? In case of ineffectiveness of drug treatment, renal denervation represents an attractive treatment option for TRH, but so far only invasive procedures have been tested.

WHAT IS NEW? In 69 subjects with TRH who underwent renal denervation with externally delivered focused ultrasound, a reduction in BP of 24/10 mm Hg after 6 months was observed, without any major safety signals.

WHAT IS NEXT? Phase 3 sham-controlled randomized trials are now needed to evaluate safety and efficacy of this unique approach.

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