Transurethral Renal Pelvic Denervation: A Feasibility Trial in Patients with Uncontrolled Hypertension

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BACKGROUND: Endovascular renal denervation reduces blood pressure (BP). We explored an alternative approach to renal denervation using radiofrequency energy delivered across the renal pelvis utilizing the natural orifice of the urethra and the ureters.

METHODS: This open-label, single-arm feasibility study enrolled patients with uncontrolled hypertension despite antihypertensive drug therapy. The primary effectiveness endpoint was the change in ambulatory daytime systolic BP (SBP) 2 months following renal pelvic denervation.

RESULTS: The 18 patients (mean age 56±12 years) enrolled were taking an average of 2.7 antihypertensive drugs daily. Renal pelvic denervation reduced mean daytime SBP by 19.4 mm Hg (95% CI, −24.9 to −14.0, P<0.001) from its baseline of 148.4±8.7 mm Hg. Mean nighttime (−21.4 mm Hg [95% CI, −29.5 to −13.3]) and 24-hour (−20.3 mm Hg [95% CI, −26.2 to −14.5]) SBP each fell significantly (P<0.001) as did the corresponding diastolic BPs (P<0.001). Office SBP decreased from 156.5±12.3 mm Hg by 22.4 mm Hg (95% CI, −31.5 to −13.3, P<0.001) by 2 months. Office SBP decreased over time (P=0.001 by linear trend test) starting by day 1 with a decrease of 8.3 mm Hg (95% CI, −16.9 to 0.3, P=0.057). There were no serious adverse events. Mild transitory back pain followed the procedure. Serum creatinine decreased by 0.08 mg/dL (P=0.02) and estimated glomerular filtration rate increased by 7.2 mL/min/1.73m² (P=0.03) 2 months following ablation procedure.

CONCLUSIONS: Based on these initial findings, a well-powered, sham-controlled trial of renal pelvic denervation to more fully establish its safety and effectiveness is now justified in patients with uncontrolled hypertension despite drug therapy.

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Uncontrolled hypertension remains a major public health problem. Among its causes are poor patient adherence to prescribed therapy and inadequate intensification of treatment by clinicians. The use of interventional procedures offers the advantage of sustained effects that do not depend on patient adherence.

One effective approach used decades ago for difficult-to-control hypertension was surgical sympathectomy, which demonstrated meaningful reductions in blood pressure (BP), but with considerable morbidity. More recently, catheter-based renal denervation administered through the renal arteries has been tested in clinical trials and has been demonstrated to be safe and...
Renal pelvic denervation reduces blood pressure when medications are not fully effective in treating hypertension. This article describes how techniques routinely used by urologists in their clinical practice can be adapted to ablate renal nerves and reduce blood pressure.

What is Relevant?
Uncontrolled blood pressure is a common problem that results in major adverse outcomes including stroke and myocardial infarction. This new urology procedure, termed renal pelvic denervation, could be a valuable treatment option in people with hypertension.

Clinical/Pathophysiological Implications?
In patients with uncontrolled hypertension despite medications, this procedure was effective in significantly reducing blood pressure.

Nonstandard Abbreviations and Acronyms

| BP          | blood pressure |

These procedures most commonly work by transmitting energy or injecting alcohol across the artery walls and destroying the renal nerve fibers situated closely parallel to the arteries. This treatment is already being used in an active registry program in some regions of the World, though gaining access to the renal arteries for this procedure requires experienced cardiovascular interventionalists.

Renal nerves also are profuse along the outer surface of the renal pelvis, which can be accessed through the natural orifice of the urethra and thence bilaterally through the ureters. Applying radiofrequency energy from inside the renal pelvis has been shown in a porcine model to reduce BP and renal tissue norepinephrine levels. A preliminary pilot experience using this approach in a very small group of hypertensive patients also suggested its clinical potential. This current study assessed the clinical feasibility of renal pelvic denervation in a cohort of patients with uncontrolled hypertension despite the prescription of antihypertensive drugs.

METHODS

Data Availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants
Adults between ages of 18 and 70 with uncontrolled hypertension were eligible for the study at either of 2 study sites in Tbilisi, Georgia. Although continuing to take their background antihypertensive therapy of up to 3 antihypertensive medications, mean daytime systolic BP measured by 24-hour ambulatory BP monitoring was required to be at least 135 mmHg <170 mmHg, with mean daytime diastolic BP <105 mmHg. For those not receiving medications, mean daytime systolic BP was required to be at least 140 mmHg and <170, with mean daytime diastolic BP less than 105 mmHg. However, although the protocol allowed for participation of both on-med and off-med patients, a decision was made early during the patient enrollment period to recruit only those patients receiving antihypertensive medications. This study report is based on the 18 patients on antihypertensive drug therapy, although data for the 2 patients studied while not taking medications are very briefly summarized separately in the Results Section.

Exclusion criteria included an estimated glomerular filtration rate under 45 mL/min/1.73m² (calculated via the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation, National Kidney Foundation), type 1 diabetes, clinically significant structural heart disease and secondary hypertension. The study was approved by the local Ethics Committee. Written informed consent was obtained from all patients before study enrollment.

Study Procedures
Baseline evaluation included measurement of automated office BP and 24-hour ambulatory BP monitoring along with laboratory assessment of serum and urine parameters. Following collection of blood and urine specimens, patients were seated and allowed to rest for 5 minutes prior to use of automated BP measurement device (HEM-907XL, Omron Healthcare, Bannockburn, IL) which recorded BP in each arm. Office BP measurement was recorded in triplicate with one-minute separations between measurements. The arm with higher BP at the baseline assessment was used for all subsequent measures. Study personnel would then witness the antihypertensive medication self-administration before positioning the arm cuff for ambulatory BP monitoring (ABP OnTrak 90227, Spacelabs Healthcare, Snoqualmie, WA) on the same arm as used for office BP measurements. BP was measured every 20 minutes during the day (0600-2159h) and every 30 minutes at night (2200-0559h). Patients would return the following day, at a time to assure at least 24 hours of BP recording time, for the device to be removed. Additional baseline assessments included a pregnancy test where relevant, computed tomographic urography, and renal ultrasound. Electrocardiograms and echocardiograms were also obtained, but these data will be provided in a future report of longer-term patient follow-up. Medication compliance was assessed by patient diaries, with witnessed pill-taking
being performed immediately prior to initiating the 24-hour ambulatory BP monitoring period.

For those patients meeting entry criteria, renal pelvic denervation was performed via the use of the Verve Medical Phoenix system. (Verve Medical, Paradise Valley, AZ). This system includes a radiofrequency generator and monopolar ablation device with 4 spherical electrodes. A dispersive electrical grounding pad was used (Universal Electrosurgical Pad with Cord, REF 9135-LP, 3M, Saint Paul, MN). The following procedure was used: The ablation device is placed into the renal pelvis following insertion of 0.035”-0.038” soft tip guidewire into the bladder under visual guidance via rigid cystoscope. The guidewire is then advanced under fluoroscopy past the ureteropelvic junction. A sheath (Destino Twist, Oscor, Inc, Palm Harbor, FL) is passed over that wire to allow for placement of the Phoenix ablation device into the pelvis, beyond the ureteropelvic junction. The generator delivers up to 30 watts of power via this ablation device which has 4 spherical conductors on a nitinol helix designed to expand into the renal pelvis and abut the uroepithelial lining. When activated, energy is delivered to increase the temperature to 60°C within 20 seconds and maintain 60°C for 2 minutes. Energy is delivered for a single cycle, then repeated in the other kidney. At the completion of the ablation, physicians were permitted to place ureteral stents at their discretion, which, when deployed, remained in place until the day 14 visit. The protocol required an overnight stay following the procedure.

Unless clinically necessary, physicians and subjects were strongly encouraged not to terminate or add antihypertensive medications following renal pelvic denervation until completing the month 2 assessments, with addition of medicines permitted thereafter if office BP continued to be uncontrolled. Post-treatment assessments were scheduled for day 1, day 14, and month 1 with the primary endpoints of safety and effectiveness performed at month 2. At each visit, subjects underwent clinical evaluation including pain assessment and office BP measurement. At day 14, month 1, and month 2, specimens were obtained for blood and urine testing. At baseline, month 1 and month 2, ambulatory BP monitoring was performed. At month 1, renal ultrasound and computed tomographic urography were repeated. Concomitant medications were recorded and adverse events elicited at every visit.

Safety events of interest were defined in the protocol as cardiovascular (including acute coronary syndrome, stroke, acute kidney injury, or death), device and procedure-related adverse events, urologic events (ie, infections, hematuria, pain, urinary incontinence and/or obstruction within 14 days of the procedure) and clinically significant changes in serum and urine biochemistry.

**Statistical Analysis**

The objectives of the study were to assess the safety and effectiveness of the Verve Medical Phoenix system. Safety was assessed through laboratory, urologic imaging, and clinical events, included adverse events, serious adverse events, and treatment-emergent adverse events. The primary effectiveness endpoint was the mean change in daytime systolic BP measured by ambulatory BP monitoring from baseline to 2 months. Additional endpoints included changes in 24-hour and nighttime ambulatory BP measurements and office BP.

Summary single timepoint measurements and baseline characteristics are expressed as mean±SD or percentages (%), although in the graphs showing the hourly BP data during the 24-hour ambulatory monitoring period, SEs rather than SDs are used to reduce the visual complexity of those figures. Changes in continuous variables from baseline are shown as mean difference with 95% CI. P values for individual time points are based on paired t tests with changes through the assessment at month 2, the primary endpoint, are based of mixed models (i.e., random effects models) using the Satterthwaite approximation for degrees of freedom for the overall F value (F statistic) and confidence intervals (t-statistic). Statistical analysis was performed using R version 4.1.3 (R Core Team 2022). A value of P<0.05 was considered significant. Analyses by age, sex, and diagnosis of isolated systolic hypertension were considered using P<0.10 as a threshold to investigate subgroup effects. Subgroup analysis first used Hotelling’s T test on all BP measurements (both ambulatory and office). If P<0.10 then the individual BP measurements were tested using t tests at P<0.05. D.H. had full access to all data from the clinical trial and was responsible for the integrity of the data used in the analysis.

**RESULTS**

**Baseline**

Of 41 patients who signed informed consents, 21 were excluded (Figure 1) including 10 who were disqualified for failing to meet the study’s BP entry criteria, 2 due to COVID-19 infection, 1 identified with ureteral stenosis on baseline imaging, and 1 with ureteral orifice too narrow to allow for the sheath to be advanced and in whom the option of ureteral pre-stenting to enable performance of renal pelvic denervation 1-2 weeks later was not employed.

The study population included 18 patients receiving antihypertensive medicines (Table 1) and 2 not receiving BP-lowering drugs. As explained in the Methods Section, the focus of this report is on those patients receiving antihypertensive therapy. Average age was 56±12 years, the cohort included 7 women and 11 men who, on average, were treated with 2.7 antihypertensive drugs, with 12 subjects receiving 3 drugs and 6 receiving 2 drugs. (Table 1). No patients were lost to follow-up and all study assessments were completed.

**Procedural Safety**

No serious intra-procedural adverse events were observed. Following renal pelvic denervation, bilateral double-J ureteral stents were placed at investigators’ discretion in 9 of 18 patients but were all removed in the office at the 14-day follow-up visit without any complications.

**Adverse Events**

There were no serious adverse events and no treatment-emergent adverse events. In the 9 subjects without stent
placement, 5 reported back/flank pain, while in the 9 patients who had stents placed 7 reported some pain or discomfort. By day 14, none of the 9 patients without stents had pain, whereas 3 patients with stents in place reported mild back or flank pain that persisted following hospital discharge but which resolved prior to or one day following removal of the stents (with average pain score of 3 out of 10) at day 14. In one subject, a renal stone 2.5 to 3 mm was evident 1 month after treatment and in whom the baseline study showed evidence of microoliths and calcifications indicating stone formation prior to treatment. The site reported that there was no stone evident on ultrasound imaging at month 6 or at month 12. The one subject with proteinuria on a scheduled urinalysis had a repeat study 4 days later with no evidence of proteinuria. No interventions or concomitant therapies were required for either of these two patients, and both were categorized as mild and resolved. Nonetheless, the investigator listed these as adverse events. One patient’s hemoglobin level dropped from 11.6 g/dL at baseline to 9.8 g/dL at month 1. There was no evidence of blood loss and iron supplementation was initiated. By month 2, the hemoglobin was 10.6 g/dL. The site reported resolution of anemia at month 6 follow-up. No adverse event is ongoing (Table 2).

**Effects on BP**

The primary effectiveness endpoint of daytime systolic BP at 2 months postprocedure was significantly reduced from its baseline of 148.4±8.7 by 19.4 mm Hg (95% CI, −24.9 to −14.0, *P*<0.001). Mean 24-hour systolic BP was reduced from its baseline of 146.6±8.9 mm Hg by 20.3 mm Hg (95% CI, −26.2 to −14.5, *P*<0.001), and nighttime systolic BP was reduced from 142.1±13.5

| Event | n (%) |
|-------|-------|
| Postprocedure back/flank pain* | 12 (67%) |
| Persistent back/flank pain | 0 (0%) |
| Urinary tract infection† | 2 (11%) |
| Cystitis | 0 (0%) |
| Proteinuria | 1 (6%) |
| Anemia | 1 (6%) |
| Renal stone | 1 (6%) |
| Perforation | 0 (0%) |
| Hypertensive crisis | 0 (0%) |
| Acute kidney injury | 0 (0%) |
| Renal failure | 0 (0%) |
| Acute coronary syndrome | 0 (0%) |
| Stroke | 0 (0%) |
| Hospitalization | 0 (0%) |
| Death | 0 (0%) |
| Treatment-emergent adverse event | 0 (0%) |
| Serious adverse event | 0 (0%) |

*Postprocedure back/ flank pain was evident by day 14 only in 3 subjects—each of whom had stents in place—with average score of 3 out of 10, with pain resolved within 1 day of stent removal.*

†Both urinary tract infections responded to treatment with oral antibiotics.
mm Hg by 21.4 mm Hg (95% CI, −29.5 to −13.3, \(P<0.001\)). The corresponding changes for diastolic BP were 9.7 mm Hg daytime (95% CI, −12.7 to −6.8), −9.2 mm Hg nighttime (95% CI, −13.3 to −5.0), and 9.6 mm Hg over 24-hour (95% CI, −12.5 to −6.6). All these diastolic BP changes were significant (\(P<0.001\)). (Figure 2A) The changes in ambulatory BP by 2 months following renal pelvic denervation were evident over the 24-hour monitoring period, including an effect during the time of the morning BP surge. (Figure 2B) BP measures at each timepoint are provided in Tables S1A and S1B, with scatterplots for changes from baseline to Month 2 in daytime systolic BP and 24-hour systolic BP in supplement Figures S1 and S2.

Office systolic BP was reduced from its baseline of 156.5±12.3 mm Hg by 22.4 mm Hg (95% CI, −31.0, −13.8, \(P<0.001\)) 2 months postprocedure (Figure 3). Office BP measurements showed reductions at each assessment following renal pelvic denervation, starting as early as 1 day postprocedure (Figure 3). However, the decreases in office systolic BP (\(P=0.002\)) and diastolic BP (\(P=0.023\)) at day one post renal pelvic denervation were statistically significant by \(t\)-test but not by mixed model analysis (\(P=0.057\) and \(P=0.083\) for systolic BP and diastolic BP respectively). By linear trend test from the time of the procedure to the 2-month endpoint, the progressive decrease in systolic BP over time was statistically significant (\(P=0.001\)), whereas the decrease in diastolic BP over time was not (\(P=0.07\)).

By 2 months postprocedure, mean daytime systolic BP fell in 17 of 18 (94%) subjects and was unchanged in the remaining subject; and mean 24-hour systolic BP fell in all 18 patients (Figure 4). Mean daytime systolic BP dropped by at least 5 mm Hg in 17 (94%) out of 18 subjects and in 16 (89%) out of 18 patients for 24-hour systolic BP. Mean systolic BP dropped at least 10 mm Hg in 16 (89%) of 18 patients during daytime systolic BP and in 15 (83%) of 18 patients over mean 24-hour systolic BP, and by at least 15 mm Hg in 12 (67%) of 18 patients during daytime systolic BP and in 15 (83%) of 18 patients over mean 24-hour systolic BP. No subjects experienced an increase in mean daytime or 24-hour systolic BP at month 2 postrenal pelvic denervation.

Office heart rate on the first day increased compared to baseline following renal pelvic denervation (\(P=0.03\)) but was lower at months 1 (\(P=0.069\)) and 2 (\(P=0.067\)). Renal pelvic denervation resulted in a significant reduction in office heart rate (\(P<0.001\)) at the 2-month timepoint, but no significant changes in heart rate were observed in mean daytime, nighttime or 24 hours values.

Exploratory analysis of the response in subjects with (\(n=8\)) compared to those without (\(n=10\)) isolated systolic hypertension did not suggest differences between these groups in systolic BP, diastolic BP or heart rate (\(P=0.08\) by Hotelling T statistic). Univariate analyses suggested smaller reduction in daytime and 24-hour diastolic BP for subjects with isolated systolic hypertension. Two months following ablation in these subjects with isolated systolic hypertension, 24-hour systolic BP was reduced by 16.8 mm Hg (95% CI, −25.8 to −7.7, \(P=0.003\) by \(t\) test) and diastolic BP by 6.1 mm Hg (95% CI, −9.6 to −2.6, \(P=0.004\) by \(t\) test).

At baseline, a nighttime dipping pattern (nighttime systolic BP at least 10% lower than daytime measure) occurred in three of the 18 subjects; by month 2, two additional patients met the definition of nighttime dipping.

The overall results of all analyses were not meaningfully changed by including the 2 off-med patients, whose 24-hour ambulatory BPs fell from 142/90 to 125/82 and from 155/100 to 140/93 by month 2.

Effects on Laboratory Assessments
There was a small but significant increase in estimated glomerular filtration rate (6.3 mL/[min·1.73m\(^2\)] at month 1 and 7.2 mL/[min·1.73m\(^2\)] at month 2. \(P=0.033\) by mixed model analysis) and a significant decrease in mean serum creatinine (0.08 mg/dL both at months 1 and 2, \(P=0.023\) by mixed model). Hemoglobin dropped by 0.5 g/dL by day 14, by 0.8 g/dL at month 1 and by 0.7 g/dL at month 2 (\(P=0.001\) by mixed model). Hematocrit dropped by 2.4% (\(P=0.007\) by mixed model) by month 2. No significant changes were noted in sodium and potassium levels.

DISCUSSION
This feasibility study has found that renal pelvic denervation significantly reduced BP in patients with uncontrolled hypertension who were taking an average of 2.7 antihypertensive drugs. By 2 months after the procedure, there was a reduction in the 24-hour ambulatory systolic BP of 20.3 mm Hg with similar reductions in the daytime and nighttime measurements, indicating a continuous and consistent 24-hour BP-lowering effect. Of note, 17 of the 18 patients had reductions in their daytime systolic BP (one had no change), and all 18 had reductions in their 24-hour systolic BPs. At baseline, only 3 of the 18 patients exhibited nighttime systolic BP averages at least 10% lower than their daytime values (physiologic dipping), which is probably typical for a cohort with relatively severe uncontrolled hypertension. By two months, two additional patients exhibited a dipping pattern.

Our findings are consistent with reports of earlier open-label feasibility studies of endovascular denervation in hypertensive patients receiving medications.13,14 However, subsequent experience with those interventions in randomized controlled trials reported effects that were significant but of lesser magnitude when compared with data from the sham-controlled patients.46 Thus, we acknowledge that caution should be used in interpreting the findings from the current uncontrolled feasibility.
study, although the robust technique of ambulatory BP monitoring has been used and the treatment effects across individual patients were consistent.

Automated measurements of office BP have been shown to provide consistency and to reduce white-coat effects.\textsuperscript{15,16} In the present study, office systolic BP was reduced within one day of the renal pelvic denervation procedure and was followed by progressively greater BP-lowering effects out to 2 months postprocedure. The early BP reduction achieved with renal pelvic denervation observed in the present study is consistent with our preclinical studies in a porcine model that reported meaningful BP reductions within hours of denervation that were associated with substantial reductions in renal tissue norepinephrine concentrations.\textsuperscript{11} And although we cannot exclude the possibility that variable medication adherence by patients might partly explain the observed changes in BP, it is a reasonable speculation that the continuing reductions observed in office BP by the 2-month primary endpoint may reflect the contribution of afferent renal nerve fiber ablation. Such an effect has been considered previously in renal denervation studies as an explanation for delayed BP effects that presumably reflected central adaptations of sympathetic outflow caused by diminished renal afferent input.\textsuperscript{6,17} This possibility is supported by the findings that renal denervation can lead to a sustained and significant reduction in systemic sympathetic activity as measured by microneurography.

Figure 2. Effect of renal pelvic denervation on ambulatory blood pressure (BP).

\textbf{A}, Changes 1 and 2 months after ablation (*indicates }p<0.001\textit{ by t test; overall effects for changes in systolic and diastolic blood pressure [SBP] through month 2 by linear mixed model at }p<0.001\textit{ with (B) persistent 24-hour effects on SBP and diastolic blood pressure (DBP) from baseline to month 2 (means with standard errors calculated by averaging all blood pressures taken during that hour).
studies. Since both efferent and afferent renal nerve fibers are concentrated in close proximity to the renal pelvis, it appears likely that ablation energy applied to that area should effectively reduce activity of both fiber types. As reviewed elsewhere, the efferent and afferent renal nerve fibers play key roles in BP control and appear to mediate both the vasoconstrictor and volume components of hypertension.

Overall, this new intrarenal approach to denervation was well-tolerated. There were no serious adverse events, and none of the patients experienced cardiovascular, cerebrovascular, or renal adverse outcomes. Back pain in the region of the kidneys occurred in about two-thirds of patients, but in general, was mild in severity and resolved by the day 14 follow-up visit. Transient proteinuria was observed in one patient and 2 patients were diagnosed with urinary tract infections that responded promptly to oral antibiotics. There were significant improvements in indices of renal function over 2 months of observation, similar to those reported in previous denervation studies. Sodium and potassium levels were not affected, and there were the small but significant reductions in hemoglobin and hematocrit that are expected when BP is reduced.

Much of the likely future use of renal denervation will be for the treatment of hypertensive patients whose BP remains uncontrolled despite treatment with antihypertensive drugs. The available clinical data do not allow for rigorous comparisons of effectiveness and safety among the different anatomical approaches or devices used to achieve renal denervation. Still, unique features of renal pelvic denervation are that it is performed through the natural orifice of the urethra and uses techniques that are performed routinely in clinical urology practice. Further, this trial included patients with isolated systolic hypertension, a group that has been excluded from
previous renal denervation trials\textsuperscript{5–7} and observed effective BP reductions.

As a trial enrolling 18 patients, the current report cannot be regarded as definitive. Even so, it could be noted that virtually all patients experienced reductions in both systolic and diastolic BPs, and no patients experienced any increases in BP following the procedure. An additional limitation to this study is that it was conducted as an open-label trial without a control group, just as in other feasibility studies of renal denervation.\textsuperscript{12,21} Still, the use of ambulatory BP for assessment of the primary effectiveness endpoint in this study provided a bias-free technique since during the monitoring period both patients and investigators were blinded to the BP values. The lack of major adverse events is reassuring, although the patient numbers are small.

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