New Hope for Resistant Hypertention

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Abstract:

Hypertension is a major public health problem. Despite the increasing awareness of hypertension and its implications among patients and treating physicians, the prevalence of resistant hypertension remains high.

Resistant hypertension define as blood pressure that remains elevated above treatment goals despite administration of an optimal three drug regimen that include a diuretic[1] The prevalence of resistant hypertension is projected to increase, owing to the aging population and increasing trends in obesity, sleep apnea, and chronic kidney disease. It is estimated that at least 10% of all patients with hypertension are resistant to existing drugs. Management of resistant hypertension must begin with a careful evaluation of the patient to confirm the diagnosis and exclude factors associated with "pseudo-resistance," such as improper BP measurement technique, the white-coat effect, and poor patient adherence to life-style and/or antihypertensive medications. Despite the use of the appropriate dose and type of diuretic to overcome the management of resistant hypertension, we can't achieve our goal. But there is at least two devices namely Baroreflex Activation Therapy and Catheter-based renal sympathetic denervation make the new hope for the patient with resistant hypertension.

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Introduction:

Hypertension is the most common chronic disease in developed and developing countries, affecting 25% of adults.[2] Meta analyses have demonstrated a linear relationship between level of blood pressure (BP) and risk for cardiovascular events.[3-5] Suboptimal BP control is, consequently, the most common attributable risk for death worldwide, responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease as well as an estimated 7.1 million deaths a year.[4] In the U.S., both the net and age-adjusted prevalence ratios of hypertension continue to increase. Recent data suggest that a slight improvement in hypertension awareness, treatment, and control.[6] The rates of hypertension treatment and control in Europe are much lower than in the U.S.[7] and no data is available in our country. Several large hypertension outcome trials also demonstrate a failure to achieve BP goals in spite of protocol-defined treatment regimens. In these trials, 20% to 35% of participants could not achieve BP control despite receiving 3 antihypertensive medications (Fig. 1).[8–10] This article provides the clinician with an overview of the patient characteristics associated with resistant hypertension, the diagnostic evaluation to assess the problem, the treatment strategies for optimizing BP control and new drugs and devices for the management of resistant hypertension.

Definition and Prevalence of Resistant Hypertension-

The Joint National Committee 7 defines resistant hypertension as failure to achieve goal BP (140/90 mm Hg for the overall population and 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic.[11] This definition does not apply to patients who have been recently diagnosed with hypertension.[12] Moreover, resistant hypertension is not synonymous with uncontrolled hypertension. Uncontrolled includes all hypertensive patients who lack BP control under treatment, namely, those receiving an inadequate treatment regimen, those with poor adherence, and those with undetected.

secondary hypertension, as well as those with true treatment resistance. By this definition, patients with resistant hypertension may achieve BP control with full doses of 4 or more antihypertensive medications.[13,14] Although the definition of resistant hypertension is arbitrary

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relative to the number of antihypertensive medications required, the patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high BP levels, may benefit from special diagnostic or therapeutic considerations.[13] The prevalence of resistant hypertension in the general population is unknown because of an inadequate sample size of published studies as well as the feasibility of doing a large enough prospective study that would answer the question.[15,16] Small studies, however, demonstrate a prevalence of resistant hypertension that ranges from 5% in general medical practice to 50% in nephrology clinics [15]. Based on data from the National Health and Nutrition Examination Survey, 2003 to 2004, 58% of people being treated for hypertension achieve BP levels 140/90 mm Hg;[6] control rates among those with diabetes mellitus or chronic kidney disease are 40% [(6,17)]. In Europe, the situation is worse, with control rates among treated hypertensive patients between 19% and 40% in 5 large countries.[7] Such data suggest that resistant hypertension is more common than appreciated; however, accurate estimates are not possible, as control rates under treatment are affected by many factors.

"Pseudo-Resistance"

The term "pseudo-resistance" refers to lack of BP control with appropriate treatment in a patient who does not have resistant hypertension. Several factors contribute to elevated BP readings and produce the perception of resistant hypertension (Table 1).[12-16] Such factors include the following: 1) suboptimal BP measurement technique; 2) the white-coat effect; and 3) poor adherence to prescribed therapy.[13,14] Several common mistakes often produce falsely elevated BP readings. Such mistakes include (1) not allowing the patient to sit quietly for adequate time, (2) taking single instead of triple readings, (3) using cuffs that are too small for the arm, (4) recent smoking, and (5) not fully supporting the arm at heart level.[12,13,16] In older patients, the presence of heavily calcified or arteriosclerotic arteries that cannot be fully compressed is common and results in overestimation of intra-arterial BP.[12,16] The "white-coat effect," defined as an elevation of BP during a clinic visit resulting in higher office readings than at home or ambulatory BP readings,[17] is another cause of pseudo-resistance.

Table-I

Causes of Pseudo-Resistant Hypertension

Improper blood pressure measurement
Heavily calcified or arteriosclerotic arteries that are difficult to compress (in elderly persons)
White-coat effect
Poor patient adherence
Side effects of medication
Complicated dosing schedules
Poor relations between doctor and patient
Inadequate patient education
Memory or psychiatric problems
Costs of medication
Related to antihypertensive medication
Inadequate doses
Inappropriate combinations
Physician inertia (failure to change or increase dose regimens when not at goal)

How to rule out pseudo-resistance hypertension

A careful evaluation to exclude these factors before labeling someone as having resistant hypertension should be performed. The first step to rule out resistant hypertension is confirmation of the diagnosis:

I. With reliable office BP readings; II. The observer should strictly follow the relevant BP measurement guidelines;[18] III. Patient's posture IV. Environment V. Triple BP readings with adequate intervals between; VI. Use of appropriate cuffs and devices is mandatory.

Identification of patients who have the white-coat effect either having qualified nonphysician personnel (i.e., nurses), perform office measurements or using an automated device with the patient alone in the room is useful, determination of BP under treatment with home or ambulatory measurements

Table-II

Factors Contributing to Resistant Hypertension

A. Drug-induced
   1. Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors)
   2. Sympathomimetics (decongestants, anorectics)
   3. Cocaine, amphetamines, other illicit drugs
   4. Oral contraceptive hormones
   5. Adrenal steroid hormones
   6. Erythropoietin
   7. Cyclosporine and tacrolimus
   8. Licorice (included in some chewing tobacco)
   9. Over-the-counter dietary and herbal supplements (e.g., ginseng, yohimbine, ma huang, bitter orange)
B. Excess alcohol intake
C. Volume overload
D. Excess sodium intake
E. Volume retention from kidney disease
F. Inadequate diuretic therapy
G. Associated conditions
   1. Obesity
   2. Diabetes mellitus
   3. Older age
H. Identifiable causes of hypertension
   1. Renal parenchymal disease
   2. Renovascular disease
   3. Primary aldosteronism
   4. Obstructive sleep apnea
   5. Pheochromocytoma
   6. Cushing's syndrome
   7. Thyroid diseases
   8. Aortic coarctation
   9. Intracranial tumors

Management of Resistant Hypertension

A. Pharmacological Treatment of Resistant Hypertension

Suboptimal dosing regimens or inappropriate antihypertensive drug combinations are the most common causes of resistant hypertension.[19,20] Recommendations on the modification and intensification of antihypertensive regimens for a given patient taking 3 or more drugs is based on pharmacological principles in the context of the underlying pathophysiology that portends hypertension, clinical experience, and available treatment guidelines. The present rationale for intervention in resistant hypertension (Fig. 2) is to ensure that all possible mechanisms for BP elevation are blocked.

Table-III

Step-by-Step Physician Guide for Evaluation and Management of Patients Appearing to Have Resistant Hypertension

A. Become familiar with and adhere to the most recent hypertension guidelines.

B. Identify and reverse "pseudo-resistance."
   1. Perform proper measurements of BP in the office, following the relevant guidelines, to confirm the diagnosis of resistant hypertension.
   2. Exclude the "white-coat effect" with the use of home or ambulatory BP measurements.
   3. Evaluate patient's adherence to the treatment regimens; in case of poor adherence, determine the causes of it. Educate the patient on the risks of uncontrolled hypertension and the benefits of drug treatment and motivate the patient to work toward an appropriate BP goal.
   4. Closely follow-up non-adherent patients to ensure their compliance.

C. Identify and reverse factors contributing to true resistance.
   1. Specifically ask the patient about use of any pharmacological agents that may increase BP; in case of identification of such a substance, discontinue or minimize its use.
   2. Evaluate the amount of alcohol intake and counsel the patient on the benefits of ceasing alcohol consumption.
   3. Perform a reliable evaluation of dietary salt intake and recommend sodium restriction to 100 mmol (2.4 g) per day.
   4. Assess the degree of obesity, abdominal obesity, and physical activity and recommend weight reduction and regular aerobic exercise (at least 30 min/ day, most days of the week).
   5. Evaluate the level of renal function with estimation of glomerular filtration rate and modify treatment accordingly.
   6. Perform a thorough search for secondary hypertension; if an identifiable cause is present, treat accordingly or refer the patient to a hypertension center.

D. Treat aggressively with optimal doses of appropriate antihypertensive medications (including drug combinations) according to patient characteristics.

E. Refer the patient to a hypertension specialist if BP control is not achieved.

B. Management of resistant hypertension beyond pharmacotherapy

Despite the all above mentioned pharmacological measures a good number of patients failed to achieve the BP goal, 20-30% of patients continue to have resistant hypertension even while on optimal medical regimens. There is no approved therapy for patients with resistant hypertension. But the good news is that there are two devices therapy namely I. Baroreflex activation therapy and II. Renal denervation therapy open the new era for achieving BP goal in resistant hypertension.

I. Baroreflex activation therapy

What Is the Baroreflex?

Carotid Baroreceptors Stimulation

Baroreflex or baroreceptor reflex are the terms used to describe the body's rapid response system for dealing with changes in blood pressure. The human body has its own physiologic mechanisms for sensing changes in blood pressure and controlling blood pressure. This natural system is largely located in the brain, as well as the walls of the carotid arteries, the vessels in the neck that supply blood to the brain. Pressure sensors, called baroreceptors, are found on the carotid artery and in the carotid sinus. These sensors measure and report blood pressure to the brain, which compares it to the needs of the body. For example, higher blood pressure is good for exercising, while lower blood pressure is appropriate during sleep or other periods of reduced activity. How do the Baroreceptors Control Blood Pressure? If the sensors report higher-than-needed blood pressure to the brain, the brain sends signals to other parts of the body to lower blood pressure, including the heart, vessels and kidneys.

Rheos Hypertension (HT) Therapy is a new medical device-based treatment for drug resistant hypertension. The Rheos HT System uses the CVRx patented Baroreflex Activation Therapy technology to trigger the body's own natural blood pressure regulation system. The system was designed to significantly reduce blood pressure in patients who cannot control their hypertension with drug treatments and lifestyle modifications (resistant hypertension). It is considered unique because it uses the body's own natural blood pressure sensors (baroreflex) to control blood pressure. Initially, Rheos HT Therapy will serve as an adjunct to existing therapies.

The Rheos HT System includes:

1) The Rheos Implantable Pulse Generator (about size of an iPod) is placed under the skin below the collarbone in a minimally invasive surgical procedure to control and deliver the system's activation energy.

2) The Rheos Carotid Sinus Leads are thin wires with electrical contacts that conduct activation energy from the Rheos generator to the left and right carotid arteries, located in the neck.

3) The Rheos Programmer System is an external device that allows physicians to noninvasively regulate the electrical activation according to individual patient needs.

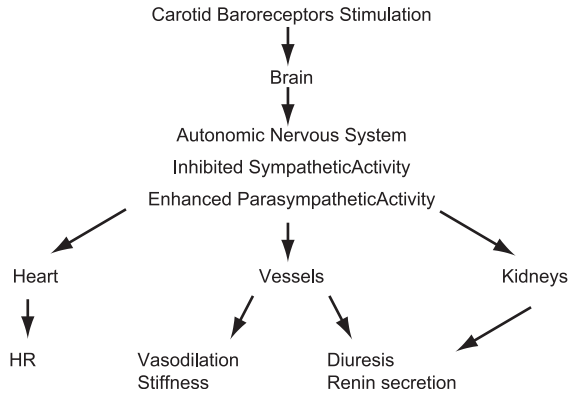

Fig. I: *Mechanism of BP control by Baroreceptors system.*

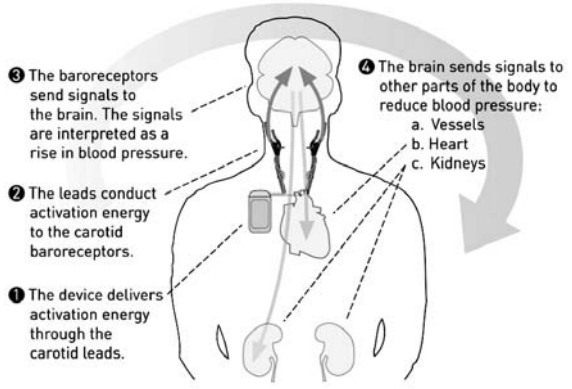

Fig. 2: *Rheos Baroreflex system and its mechanism*

Mechanism:

The device requires surgical implantation under collar bone[21] and two electrodes are placed in both carotid sinuses under general anesthesia, and are fully programmable after implantation to allow adjustment of stimulation parameters. The device delivers a stimulus to trigger the body's own natural blood flow regulation system to treat high BP and heart failure. The device is intended for patients with type 2 hypertension who do not respond to BP-lowering drugs. The system works in a similar fashion to a pacemaker. The activation energy is delivered from the device to the left and right carotid arteries. The Rheos device provides control and delivery of the activation energy through the Rheos carotid sinus leads. The leads conduct activation energy from the Rheos device to the left and right carotid arteries. The Rheos programmer system provides the ability to non-invasively regulate the activation energy therapy from the device to the leads. The therapy can be adjusted to meet each patient's individual needs as they change over time, providing personalized treatment (Fig. 1). The Rheos System works by electrically activating the baroreceptors, the body's natural blood flow regulation sensors, sensors that regulate cardiovascular function (Fig. 2). These baroreceptors are located on the carotid artery and in the carotid sinus. When activated by the Rheos System, signals are sent through neural pathways to the brain. The brain responds by modulating autonomic nervous activity and thereby lowering BP. The brain sends signals to other parts of the body to treat high BP and heart failure.

Studies:

17 patients enrolled in a multicenter study showed prior mean BP of the cohort was 189.6 ± 27.5/110.7 ± 15.3 mm Hg despite stable therapy (5.2 ± 1.8 antihypertensive drugs). The mean procedure time was 202 ± 43 minutes. No perioperative strokes or deaths occurred. System tests performed one or up to three days post-operatively resulted in significant (all $p < 0.0001$) mean maximum reduction, with standard deviations and 95% confidence limits for systolic BP, diastolic BP and heart rate of 28 ± 22, mm Hg, 16 ± 11[22] mm Hg and 8 ± 4 [23,24] mean BP, respectively. Repeated testing during three months of therapeutic electrical activation demonstrated a durable response.

The outcomes of the US-European clinical trial [24,25] are even more encouraging: 33 subjects (18 male, 15 female, age 52.4 ± 10.4 years, body mass index 33.0 ± 7.3 kg/m2) were implanted at five centers. The Rheos System improved cardiac structure and function while reducing BP. Although change in arterial compliance was correlated ($r = –0.53$, $p < 0.01$) with change in systolic BP at month three, no other relationships were observed between changes in cardiac structure and BP, suggesting alternative mechanisms for these effects. Reduced mitral A-wave velocity, coupled with decreased left atrial dimension and left ventricular mass index, suggests that the therapy reduces left ventricular diastolic filling pressure. No unanticipated adverse events occurred. These promising results indicate that this has the potential to become a useful tool in the treatment of drug resistant hypertension.

Rheos Pivotal trial- It is a Prospective randomized double-blind trial included 322 patients from 49 sites 55 roll-in patients / 265 randomized (2:1) to observe the 1. Short Term Acute Response 2. Long Term Sustained Response 3. Short Term Procedural Adverse Events 4. Short Term Hypertension Therapy Adverse Events 5. Long Term Device Adverse Events.

Patients are divided in group A (Device ON) and group B (Device OFF) in first 6 months and device on in 2nd 6 months with Key Inclusion Criteria are Systolic Blood Pressure ≥160 mmHg, Diastolic Blood Pressure ≥80 mmHg ?24-hour Average Ambulatory Blood Pressure ≥135 mmHg ?At least one month of maximally tolerated therapy with at least three appropriate antihypertensive medications, including a diuretic. Baseline characteristics and medications are almost same in two groups.

Results showing:

At 6 month SBP reduced ≥10 mm of Hg in 54% (N=181) in group A (Device On) and 46% (N=94) in

group B (Device Off), at 12 m in 88% patient reduced SBP ≥10 mm of Hg (P<0.001). At 30 days 75% of patients in both groups have no adverse effect and at 12 m 87% having no adverse events. At 6 m 40% reduction of hypertensive crisis and 23% reduction of others events (p<0.001). 42% patients achieved SBP ≤140 mm of Hg at 6m in group A and 24% in group B (p=0.005) whereas at 12 m when device on in both groups 53% in group A and 51% in group B achieved SBP d" 140 mm of Hg (p=0.70). LV mass index reduced to 102gm/m^2 at 12 months from 117gm/m^2 at baseline (p=0.01). Post-hoc analysis showing 81% patients were responder that is SBP ≤140 mm of Hg at 12 month and beyond.

Summary

3 primary endpoints achieved: long term efficacy, long term device safety, and short term therapy safety. 2 primary endpoints not achieved: short term efficacy and procedure adverse events. Weight of overall evidence suggests long term efficacy of BAT to reduce blood pressure in resistant hypertension. These data justify further development of BAT.

Conclusions

Preliminary data suggests an acceptably safe procedure with a low rate of adverse events and supports further clinical development of baroreflex activation as a new concept to treat resistant hypertension. Reduction in BP is associated with a reduction in the risk of death, stroke, heart attack, heart failure and kidney disease. In addition to sustained BP reduction, chronic Rheos therapy in early-stage heart failure patients remodels left atrial and ventricular chambers and improves systolic function. Benefits are incremental to those achieved with aggressive medical therapy. A feasibility study is now under way to assess the potential benefit of Rheos therapy in patients with more advanced heart failure.[24,26]

II. RENAL DENERVATION THERAPY

Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. Renal sympathetic nerves contribute to development and perpetuation of hypertension, and sympathetic

outflow to the kidneys is activated in patients with essential hypertension.[27] Efferent sympathetic outflow stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow.[28] Afferent signals from the kidney modulate central sympathetic outflow and thereby directly contribute to neurogenic hypertension.[29-31] Non-selective surgical sympathectomy was effectively used as a treatment of severe hypertension before antihypertensive drugs became generally available.[32,33]

Recently developed endovascular catheter technology enables selective denervation of the human kidney, with radiofrequency energy delivered in the renal artery lumen, accessing the renal nerves located in the adventitia of the renal arteries. A first-in-man study of this approach[34] showed successful renal denervation with reduction of sympathetic activity and renin release in parallel with reductions of central sympathetic outflow. Safety and feasibility trials of this procedure identified substantial reductions of blood pressure without substantial procedure-related complications.[35]

Procedures

Symplicity catheter method:

For patients randomly assigned to undergo renal denervation, the femoral artery was accessed with the standard endovascular technique and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator[35] . Four-to-six discrete, low-power radio frequency treatments were applied along the length of both main renal arteries. Participants were given heparin to achieve an activated clotting time of more than 250 sec. Intra procedural diffuse visceral pain that was restricted to the duration of energy delivery was managed with intravenous anxiolytics and narcotics.

Other methods: Renal sympathetic denervation can also be done by others methods like 1. Vessix V2 Renal Denervation System™ where Bipolar RF systems deliver energy using the electrical phenomena of ohmic resistive heating to the adjacent tissue and deliver electrical energy between two electrodes, which in the case of the V2 catheter are within a few millimeters of each other. The V2 confines its energy delivery to an area very close to the two electrodes and moreover, thermistors mounted at each electrode pair allow for precise monitoring and temperature control at each independent electrode pair. This delivery of energy causes thermal heat to perfuse through the artery wall into the adventitia layer of the artery and results in denervation of the target renal sympathetic nerves.

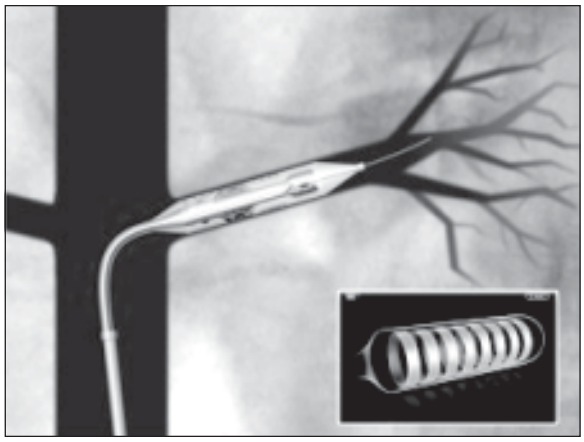

Fig.-3: *Vessix V2 Renal Denervation System™*

Fig.-4: *EnligHTN system for renal sympathetic denervation*

2. EnligHTN Renal Denervation System by St Jude Medical: The EnligHTN has multiple electrodes which potentially saves time during the ablation procedure, as four ablations can be performed without catheter repositioning

Studies about renal denervation therapy

Studies on Renal Denervation Therapy

Name of study	Study population	Results	Conclusions/ References
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study[36]	50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems).	Baseline mean office blood pressure was 177/101 mm Hg with mean 4.7 antihypertensive medications; Office blood pressures after procedure were reduced by -14/-10, -21/-10, -22/-11, -24/-11, and -27/-17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/-2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months, respectively. One perprocedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae and no other renovascular complications.	Renal denervation effectively reduces the BP in multidrug resistant hypertensive patient.
Symplicity HTN-1: Trial[37](NB: It is extension of previous study)	Expanded cohort of patients (n=153)-24-month follow-up	Baseline BP (mmHg) 176/98 ± 17/15, number of anti-HTN medicine (mean) 5.0 ± 1.4 Ï%Average of 4 ablations per artery• No major complications• Minor complications 4/153:– 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae, 3 access site complications, treated without further sequelae.Results showing significant sustained BP reduction:at 6m -25/-11mm Hg , N=86; at 12m -23/-11 mm Hg, N=64 and at 24m -32/-14mm Hg, N=18	Symplicity HTN-1: Trial[37]Showing significant BP reduction by renal denervation.

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Symplicity HTN-1: Trial[37] (NB: It is extension of previous study)	Expanded cohort of patients (n=153) -24-month follow-up	Baseline BP (mmHg) 176/98 ± 17/15, number of anti-HTN medicine (mean) 5.0 ± 1.4 Ï%Average of 4 ablations per artery • No major complications • Minor complications 4/153: – 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae, 3 access site complications, treated without further sequelae. Results showing significant sustained BP reduction: at 6m -25/-11mm Hg , N=86; at 12m -23/-11 mm Hg, N=64 and at 24m -32/-14mm Hg, N=18	Symplicity HTN-1: Trial[37] Showing significant BP reduction by renal denervation.
The Symplicity HTN-2 Trial): multicentre, prospective, randomized trial[38]	Out of 190 patients 106 were randomly assed and eligible for renal denervation were n=52 and control were n=54. Sample taken between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renaldenervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months in 24 participating centers.	Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of178/96 mm Hg, p<0û00001), whereas in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0û077 systolic and p=0û083 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0û00001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0û00001). There was no serious procedure-related or device-related complications; one patient who had renal denervation had possible progression of an underlyingatherosclerotic lesion, but required no treatment.	Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment resistant hypertensive patients.
Renal Denervation in Patients with Uncontrolled Hypertension (SYMPLICITY HTN-3)[39] **Phase 3This study is currently recruiting participants. (Verified May 2012 by Medtronic Vascular)**	It is a multi-center, prospective, single-blind, randomized, controlled study and subjects with uncontrolled hypertension. Bilateral renal denervation will be performed.Estimated Enrollment: 530 Study Start Date: Sept 2011, Estimated Primary Completion Date: March 2013	*Purpose:* **Primary Outcome Measures:** Ï%Change in Office Systolic Blood Pressure (Time Frame: Baseline to 6 months) Ï%Primary Effectiveness Outcome MeasureÏ%Incidence of Major Adverse Events through 1 month post-randomization (Renal artery stenosis measured at 6 months) **Secondary Outcome Measures:** Change in average 24-hour Systolic Blood Pressure by ambulatory blood pressure monitoring [Time Frame: Baseline to 6 months]	It is a trial approved by USFDA. As per we know investigators think results will be encouraging for renal denervation.

Name of study	Study population	Results	Conclusions/ References
Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study[40]	50 patients with resistant hypertension among them 37 underwent bilateral renal denervation, and 13 patients were assigned to a control group. Systolic and diastolic BP, fasting glucose, insulin, C peptide, hemoglobin A(1c), calculated insulin sensitivity were assessd.	Three months after renal denervation, fasting glucose was reduced from 118±3.4 to 108±3.8 mg/dL (P=0.039). Insulin levels were decreased from 20.8±3.0 to 9.3±2.5 ìIU/mL (P=0.006) and C-peptide levels from 5.3±0.6 to 3.0±0.9 ng/mL (P=0.002). After 3 months, homeostasis model assessment-insulin resistance decreased from 6.0±0.9 to 2.4±0.8 (P=0.001). There were no significant changes in blood pressure or metabolic markers in the control group.	Renal denervation improves glucose metabolism and insulin sensitivity in addition to a significantly reducing blood pressure. This novel procedure may therefore provide protection in patients with resistant hypertension and metabolic disorders at high cardiovascular risk.

Summary

Trans-catheter Renal Denervation resulted in significant reductions in BP. No major complications occurred. Trans-catheter Renal Denervation is beneficial for patients with treatment resistant essential hypertension.

Conclusions

Hypertension is a major public health problem and the prevalence of resistant hypertension remains high with available drugs with good compliance and optimal doses. But recently developed intervention and device therapies mitigate the problems of resistant hypertension. One is Baroreflex activation therapy and another one is Renal denervation therapy. It is very important to rule out the 'pseudoresistant' hypertension and confirm the diagnosis of resistant hypertension before treating by these methods. In Baroreflex activation therapy BP was reduced by altering the body's own physiological regulatory system for hypertension by implanting a device (The Rheos HT System) like a pace maker. As it does not release any drug therefore no or very minimum procedure related adverse events. Renal denervation therapy where sympathetic nerves along the both renal arteries are denervated by catheter based low dose radio-frequency ablation. Both the procedures are safe and effective. They not only reduce the BP but also reduce the hypertensive related complications.

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