

HYPERLIPIDEMIA & HYPERTENSION UPDATE

Interventional Therapies for Resistant Hypertension

Nikolaos Sakellaris, MD, Maria Misailidou, MD

First Department of Cardiology,
Evangelismos General Hospital of
Athens, Athens, Greece

KEY WORDS: *resistant hypertension;
autonomic nervous system; baroreflex;
carotid sinus stimulation; renal
sympathetic denervation*

ABBREVIATIONS

AHA = American Heart Association
BAT = baroreflex activation therapy
BP = blood pressure
eGFR = estimated glomerular filtration
rate
HTN = hypertension
LVH = left ventricular hypertrophy
PG = pulse generator
SNS = sympathetic nervous system
RFA = radiofrequency ablation
RSD = renal sympathetic denervation

Correspondence to:

Nikolaos Sakellaris, MD, First
Department of Cardiology,
Evangelismos Hospital, Athens,
Greece;
E-mail: nikolaos.sakellaris@hotmail.com

ABSTRACT

Resistant hypertension represents a major health problem despite the plethora of antihypertensive drugs. Activation of the sympathetic nervous system is considered to be the basis of its pathogenesis. Two novel invasive therapeutic strategies for the treatment of resistant hypertension have recently emerged, namely catheter based renal sympathetic denervation and carotid baroreceptor stimulation. Both are effective in reducing elevated blood pressure values and display a good tolerability profile without the occurrence of any major untoward effect.

INTRODUCTION

Hypertension (HTN) has a prevalence of 26.4% in the age group 30-60, rising to 65% in those over 60 years of age¹ affecting nearly 72 million people in the USA, and 1 billion worldwide. It is a major risk factor for cardiovascular disease, stroke, heart failure, and premature renal failure, and a major cause of morbidity and mortality, responsible for 7 million deaths annually.² Yearly costs to treat hypertension in the United States are estimated to be \$69.4 billion; nevertheless only 25-35% of hypertensive patients achieve a blood pressure <140/90 mmHg.

Hypertension is defined as resistant or refractory to treatment when a therapeutic plan that has given attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) at their maximum or highest tolerated doses has failed to lower systolic and diastolic blood pressure <140/90 mmHg in general (130-139/80-85 mmHg in patients with diabetes mellitus and <130/80 mmHg in chronic renal disease).³

PREVALENCE AND HEALTH BURDEN

Resistant hypertension has a reported prevalence as high as 13%-18% in men and 22% among women (AHA 2010).⁴ The high prevalence of hypertension in the general population renders this small percentage significant in terms of actual patient numbers.

The most common causes of resistant hypertension is poor compliance or limitations in drug therapy (inadequate dosing, polypharmacy, adverse drug effects) or non-adherence to recommended lifestyle changes (particularly elimination of alcohol abuse). Other not infrequent causes of resistant hypertension are obstructive sleep apnea,

Conflict of Interest: none declared

renal artery stenosis, volume overload due to progressive renal insufficiency, hyperaldosteronism, excessive salt intake, and most often, insufficient diuretic therapy. Rare causes include pheochromocytoma, Cushing syndrome, hyperparathyroidism, and coarctation of the aorta. Finally pseudohypertension must be excluded.^{4,5} All these forms of HTN have a significant neurogenic component which is initiated and sustained in part by activation of the sympathetic, and inhibition of the parasympathetic, system, resulting in vasoconstriction, increased cardiac output, renin secretion, reduction in renal blood flow and sodium and water retention (Fig. 1).

In the 50's, non selective surgical sympathectomy was the last option for malignant hypertension but it was driven to total obscurity due to serious adverse effects, despite its efficacy in reducing blood pressure and a long-term duration of the results and also due to the development of new antihypertensive drugs.^{10,11} Recently, other approaches have been used to decrease sympathetic outflow, the electrical activation of the carotid baroreceptors using an implantable device (the Rheos System, CVRx Inc., Minneapolis, Minnesota) and the selective renal sympathetic denervation (RSD) carried out by endovascular, catheter-based, radiofrequency ablation (RFA) of the renal afferent nerves.

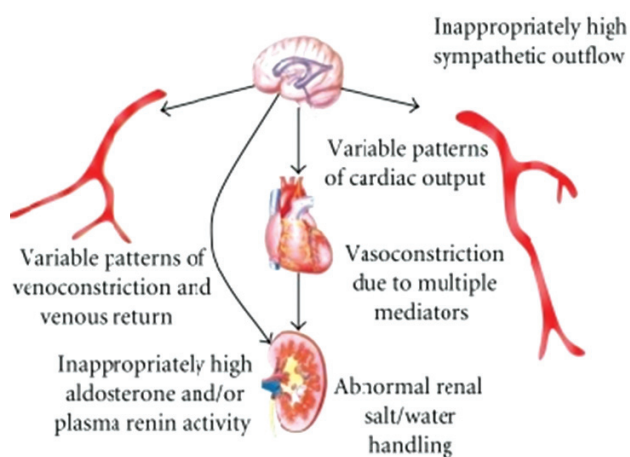


FIGURE 1. Pathophysiology of resistant hypertension (Papademetriou V, Int J Hypertens 2011).¹⁰

CAROTID SINUS STIMULATION

Neural control of the circulation is regulated by numerous hormonal and neural reflexes. The most important of these are the arterial baroreflexes which first respond to arterial pressure changes, regulate heart rate, cardiac contractility and vasomotor tone and participate in short and long term control of blood pressure (BP). The baroreflex is initiated by stretch receptors

(baroreceptors) located in the adventitia of the large systemic arteries, mainly the aortic arch and carotid sinuses. They encode mean arterial pressure (P) and its derivative (dp/dt) in action potentials that are transmitted along sensory fibers to the nucleus tractus solitarius (NTS) and sensory nucleus of the IXth (i.e. glossopharyngeal) and Xth (i.e. vagus) cranial nerves. The final result is inhibition of the sympathetic cardiovascular drive and stimulation of the vagal influences on the heart (negative feedback). However, baroreceptor response adapts over minutes to days, and a new threshold for activation is established (baroreceptors become less sensitive to any given change in blood pressure) as in the case of chronic hypertension, where this homeostatic function is impaired leading to vasoconstriction and tachycardia (Fig. 2)- an effect attributed to altered activity in the brain portion of the reflex.⁶⁻⁸ Recent evidence, however, calls into question the notion that the baroreflex is blunted in long-term BP control⁹ and therefore prolonged activation of the baroreflex produces sustained hypotension.¹²

Preliminary studies in experimental animals, conducted to restore the baroreceptor function, showed that carotid sinus stimulation (interpreted by the brain as a rise in BP) is able to lower blood pressure and reduce circulating levels of norepinephrine.¹³ Voltage-response curves are consistent, apparent and high linear (Fig. 3).^{14,15}

DEVICE AND TECHNIQUE

The Rheos CVRx Baroreflex Hypertension Therapy System resembles a pacemaker; it has three components: 1) The Rheos pulse generator (PG). This consists of a battery and a

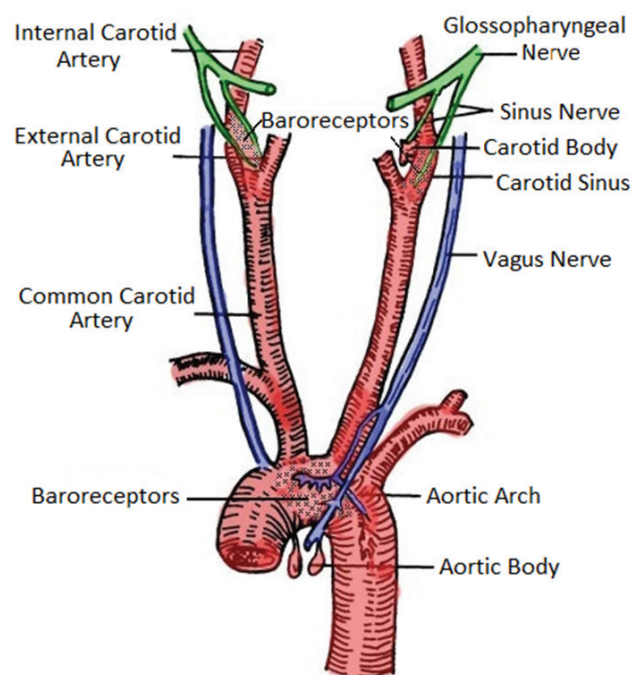


FIGURE 2. Aortic and carotid receptors.

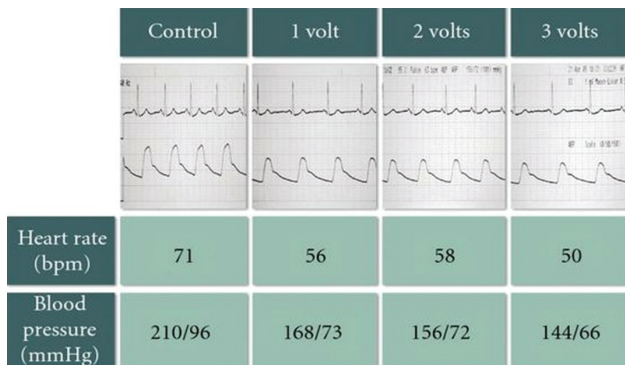


FIGURE 3. Blood pressure and heart rate reduction using baroreflex activation therapy from 1 to 3 volts. Note that acutely blood pressure was reduced from 210/96 to 144/66 and heart rate from 71 to 50 beats per minute (Courtesy of CVRX.com).

circuit system which delivers 1 to 7.5 V of activation energy; 2) Two bilateral carotid sinus leads that are connected to the pulse generator via flexible wires and to the carotid sinus by an electrode with an insulative backer and; 3) The Rheos Programmer System that allows control of the generator via radiofrequency coup (Fig. 4).¹³ The device is surgically implanted. The operation can be divided into three phases: phase 1, induction of anesthesia and exposure of the carotid bifurcations; phase 2, carotid sinus mapping, electrode fixation, and testing; and phase 3, tunneling and wound closure. In general, inhalation anesthetics should be minimized or avoided during the first two phases, to preserve the reflex but conventional anesthesia can be used during phase 3. The PG is implanted in a pocket created infraclavicularly usually on the right side (to avoid confusion with the typical left-sided pacemaker or implantable defibrillator placement).¹⁷

Recently, a second-generation implantable device, the Barostim neo™ CVRx received CE mark approval for hyper-

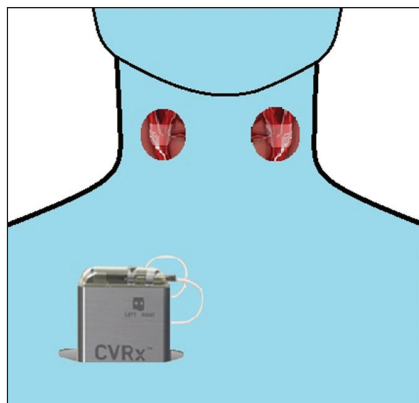


FIGURE 4. Position of the carotid sinus leads and impulse generator.

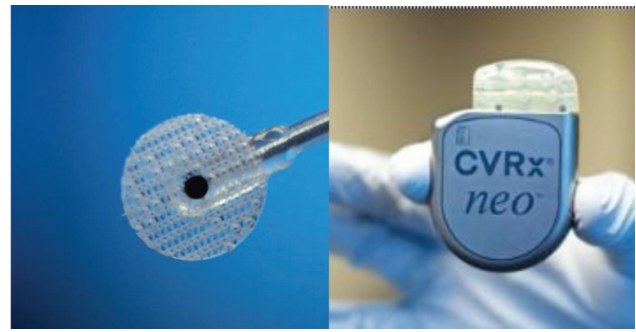


FIGURE 5. The Barostim neo CVRx system (Courtesy of CVRx.com).

tension. It features a new unilateral, 1mm electrode and a new smaller, more advanced stimulator to allow for more focused and efficient delivery of therapy. These improvements have led to shorter procedure times and extended longevity (Fig. 5). The Barostim neo is CE marked and approved for sale for hypertension patients in Europe.

STUDIES

The European DEBuT-HT (Device Based Therapy in Hypertension) study, and the US Rheos Feasibility Trial (2010),¹⁸ were two small, prospective, multicenter, nonrandomized, phase II, single-arm, open-label, feasibility studies, to assess whether Rheos System therapy could safely lower BP. A total of 45 patients with BP $\geq 160/90$ mmHg, despite at least three antihypertensive drugs, were enrolled and followed up for as long as 2 years. Mean BP was reduced by 21/12 mmHg after 3 months of device therapy and by 33/22 mmHg ($p=0.001, 0.002$) in 17 pts after 2 years of follow up. In addition heart function was improved, left ventricular hypertrophy (LVH) significantly regressed and kidney function was preserved after one year of follow up.¹⁹ However, 19% (8 of 42 implantations) were followed by severe complications (e.g., stroke, glossoplegia, device displacement or infection [5.5%]). Two generators had to be changed for planned battery replacement in patients requiring high voltages for blood pressure control.²⁰ Four-year results of the DEBuT-HT Investigators (2011)²⁴ showed mean BP reduction by 53 /30 mmHg (p -value <0.001 , p -value = 0.002) and pulse rate reduction by -5 ± 14 bpm \pm SD (p -value = 0.03).

The recently published Rheos Pivotal Trial (2011)²⁵ is a double-blind, randomized, prospective, multicenter, placebo-controlled, phase III clinical trial, in the US, to assess the safety and efficacy of the baroreflex activation therapy (BAT) delivered through the Rheos System in 265 pts with resistant HTN. The main enrollment criterion was resistant HTN (defined as at least one, out-patient, in-office BP $\geq 160/80$ mmHg), with additional enrollment criteria ambulatory SBP ≥ 135 mmHg for 24 hours in the absence of clinical significant orthostatic BP changes. Patients were implanted and randomized (2:1) one month after implantation. Subjects received either BAT for the first 6 months

(Group A) or delayed BAT initiation after this period (Group B). The five co-primary endpoints were two for efficacy and three for safety, as follows: 1) acute systolic BP efficacy at 6 months, 2) sustained efficacy at 12 months, 3) procedure safety, 4) BAT safety and 5) device safety. The trial showed significant benefit for the endpoints of sustained efficacy (88% responders), BAT safety (Group A 91.7%, Group B 89.3%; $p < 0.001$) and device safety (event-free rate 87.2%; $p < 0.001$). However, it did not meet the endpoints for acute efficacy (at 6 months Group A 54% responders, Group B 46%; $p = ns$) or procedural safety (event-free rate 74.8% which is less than the pre-specified objective performance criterion of 82%; $p = 1.00$). A protocol-specified ancillary analysis showed 42% (Group A) versus 24% (Group B) achieving systolic BP ≤ 140 mmHg ($p = 0.005$) with both groups achieving over 50% at 12 months, at which point Group B had received 6 months of BAT.

The adverse events were procedure-related: transient (4.4%) or permanent (4.8%) nerve injury at the time of implant, general surgical complication, respiratory complaint or a wound complication (2.6%); BAT-related: hypertensive crisis (Group A 5%; Group B 8.3%); device-related: hypertension-related stroke (2.3%). The authors explained that nerve injury was the main contributor to the adverse events, and that performing a unilateral implant may reduce the complexity and duration of the procedure.

Recently, Barostim neo CVRx, the new technology for delivering BAT system, showed systolic BP reductions by 28.7 mmHg, in 12 resistant hypertension patients, 3 months after activation, comparable to the results of the Rheos System (systolic BP reduction -29.1 mmHg) (Husenfuss, European Society of Hypertension, 2011).

In conclusion, BAT seems to achieve effective lasting reduction of blood pressure with relative safety. However, its clinical application is limited by the necessity of vascular surgery of the carotid artery, under general anesthesia, the need for frequent replacement of the device and the risk of infection entailed by device implantation. Future clinical trials will address the limitations of this study and further define the therapeutic benefit of the method. Today it represents a specific treatment in selected patients with severe resistant hypertension.⁵ The Barostim neo is CE marked and approved for sale for hypertension patients in Europe.

RENAL SYMPATHETIC DENERVATION (RSD)

The autonomic control of the kidney is predominantly sympathetic. Renal nerves run alongside the renal artery and enter the hilus of the kidney. Thereafter, they divide following the blood vessels, and penetrate the cortical and juxtamedullary areas (Fig. 6).

Efferent renal sympathetic nerve activation, when weak,

enhances noradrenaline production or spillover and renin secretion from the granular juxtaglomerular cells, via beta1 adrenergic receptors. Stronger sympathetic nerve stimulation, via alpha1 adrenergic receptors, enhances sodium reabsorption from the tubules and renal vasoconstriction, resulting in renal blood flow reduction. Afferent renal sympathetic nerves originate mostly from the renal pelvic wall (with mechanoreceptors responding to stretch and chemoreceptors detecting renal ischemia) whose cell bodies lie in the ipsilateral dorsal root ganglia (T6-L4). From there ascending signals travel to the renal cardiovascular centers in the central nervous system, mainly in the hypothalamic area, and promote vasopressin and oxytocin release from the neurohypophysis. Overall, afferent sympathetic fibers have important contribution in regulation of systemic vascular resistance and BP control. Complete renal denervation effectively inhibits ascending afferent stimuli without functional regeneration or reinnervation contributing in the BP therapy.^{3,30,35}

HISTORICAL PERSPECTIVE OF SYMPATHETIC DENERVATION

Non-selective surgical sympathectomy has been applied mainly in patients with severe or malignant hypertension as well as in patients with cardiovascular deterioration despite relatively good blood pressure reduction by other means. After the introduction of antihypertensive drugs, sympathectomy was reserved for patients who failed to respond to antihypertensive therapy or could not tolerate it. Total sympathectomy (from 8th to 12th dorsal vertebra) is impractical and poorly tolerated by humans. It was performed only in a few selected centers, in either 1 or 2 stages, and required a prolonged hospital stay (2 to 4 weeks). Adverse events were common and included postural hypotension and tachycardia, palpitation, breathlessness, anhidrosis, cold hands, intestinal, bowel and sexual dysfunction, thoracic duct injuries and atelectasias. However,

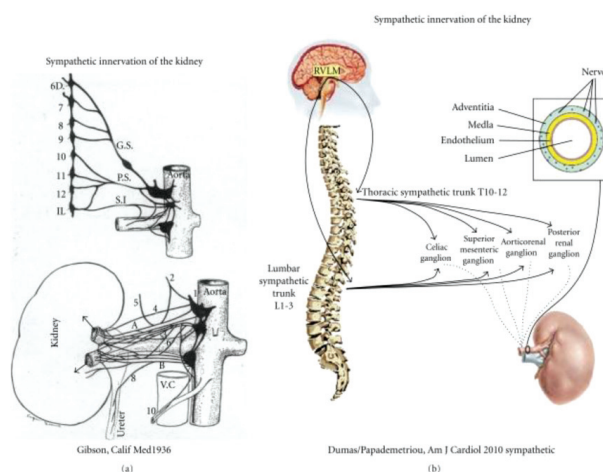


FIGURE 6. Sympathetic innervation of the kidney (Papademetriou V, Int J Hypertens 2011).

sympathectomy was associated with higher survival rates, more than doubled, in patients who underwent the procedure (Fig. 7).²⁶ Percutaneous renal sympathectomy (RSD) has several advantages over the radical sympathectomy; it is localized, minimally invasive, without systematic side effects and with short procedural and recovery times.

TECHNIQUE

Renal artery angiography is performed to assess anatomic eligibility for the procedure and to confirm the absence of significant renal artery stenosis. A flexible ablation catheter (Simplicity TM Catheter System, Ardian/Medtronic Inc., California, USA) is then introduced percutaneously via the femoral artery and advanced to the distal segment of the renal artery. The proximal end of the catheter is connected to a radiofrequency (RF) generator to apply a discrete RF ablation lasting 2 minutes. Up to six ablations are performed in each artery, separated both longitudinally (of at least 5 mm) and rotationally to achieve circumferential coverage of the renal artery. Catheter tip temperature (50-70 °C) and impedance are constantly monitored during ablation and RF energy delivery (maximum 8 Watts) is regulated according to a predetermined algorithm (Fig. 8).²⁷ The heating of the wall ablates the sympathetic nerve fibers in the adventitia. Bilateral percutaneous RSD can be accomplished in 40-60 minutes. The ablation procedure is accompanied by

diffuse visceral non-radiating abdominal pain which does not persist beyond the RF energy application and can be managed by intravenous narcotics and sedatives.

RECENT STUDIES

Renal sympathetic denervation (RSD) is evaluated in the multicenter proof-of-concept Simplicity HTN-1 study and the randomized controlled Simplicity HTN-2 trial. In the Simplicity HTN-1 Study,²⁸ 50 patients with resistant hypertension were studied and resulted in impressive blood pressure reductions. After only one month systolic and diastolic BP decreased significantly by 14/10 mm Hg respectively and after a 12-month follow up period by 27/17 mm Hg (Fig. 9) without subsequent increase in BP in the original study period or in the recently published follow up (153 patients) of a period of 24 months.²⁹

The reduction in BP at 6 months after RSD was accompanied by a significant decrease (-47%) in the renal norepinephrine spillover rate. Only two adverse events occurred, one renal artery dissection and one femoral artery pseudoaneurysm.²⁸ This study demonstrated, for the first time in humans, that RSD can reduce blood pressure in a safe way with long acting results. However, the study created several concerns and many questions. It lacked a proper control group (not randomized), it was small, the group of patients recruited was not clearly defined, predictors of blood pressure response had not been

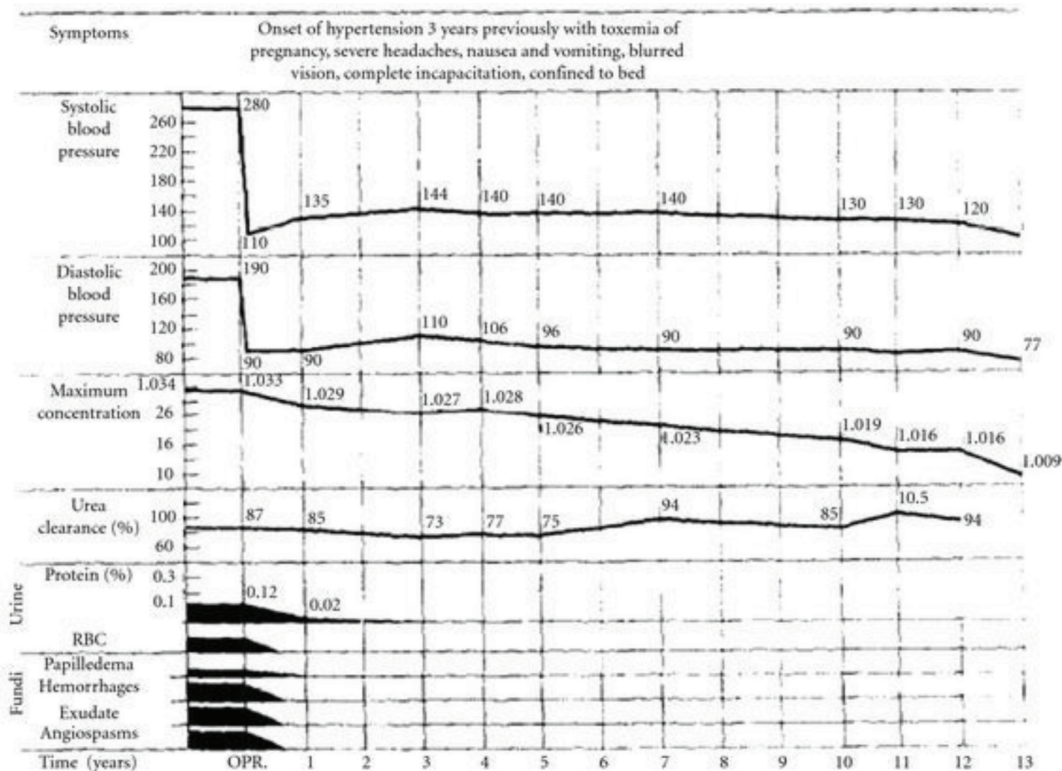


FIGURE 7. Long-term blood pressure control following surgical sympathectomy (Papademetriou V, Int J Hypertens 2011).

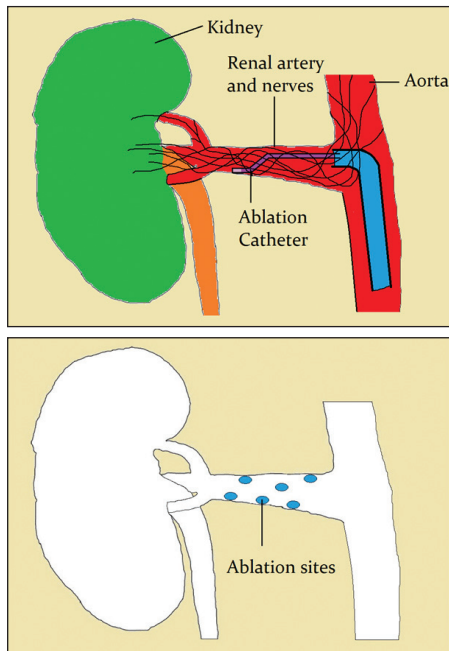


FIGURE 8. Percutaneous catheter-based renal sympathetic denervation (schematic representation)

identified, the potential for tissue damage (that will result in structural changes of the renal artery) was not defined.^{30,31}

Recently, a second catheter-based RSD study, the multicenter, prospective, randomized Symplicity HTN-2 Trial³² was published confirming the initial results in a controlled sample. A total of 106 patients with resistant hypertension (systolic BP ≥ 160 mmHg; for patients with diabetes mellitus type 2 ≥ 150 mmHg) were enrolled between June 2009 and January 2010. The primary effectiveness end point was the between-group change in average office-based measurements in systolic BP from baseline to 6 months post randomization. Secondary end points included a) acute and chronic procedural safety (reduction of eGFR $>25\%$ or new stenosis $>60\%$ confirmed by angiography at 6 months), b) a composite cardiovascular endpoint (myocardial infarction, sudden cardiac death, etc) and additional BP reduction at 6 months after randomization (systolic BP - 10 mmHg or more, achievement of target systolic BP, and change in home-based BP measurements). An initial 2-week observation period was followed by randomization 1:1 into a treatment group (52 patients) and a control group (continuation of drug treatment) (54 patients). Six months after renal denervation, mean BP in the treatment group had decreased significantly by 32/12 mmHg (Fig. 10) ($p < 0.0001$), while the BP in the control group remained unchanged. Home BP also decreased by 20/12 mmHg ($p < 0.0001$, $n = 32$) in the RSD group compared with a slight increase of 2/0 mmHg ($n = 40$) in the control group. In 20% of patients the reduction in BP permitted a decrease in the number or dosage of

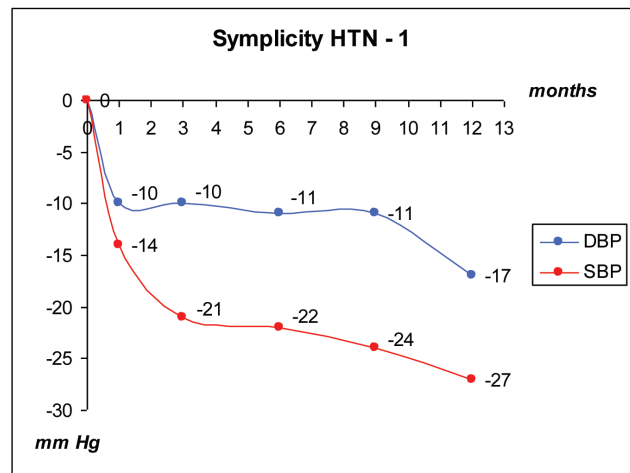


FIGURE 9. Blood pressure results from Symplicity HTN-1 Study. DBP = diastolic blood pressure; SBP = systolic blood pressure.

antihypertensive medications. Blood pressure control (defined as systolic BP < 140 mmHg) was achieved in 39% of patients in the RSD group and in 3% in the control group.

However, it is also important to note that there is a substantial variability with regards to the BP effects, and that the procedure fails to reduce BP in about 10% of treated patients. A total of 84% of RSD patients had a reduction of systolic BP > 10 mmHg. The reduction of BP is observed at rest and during exercise, with preservation of BP adaptation, and no signs of chronotropic incompetence or a negative influence on ventilator parameters. The glucose metabolism is favorably influenced by RSD with reductions in glucose and insulin con-

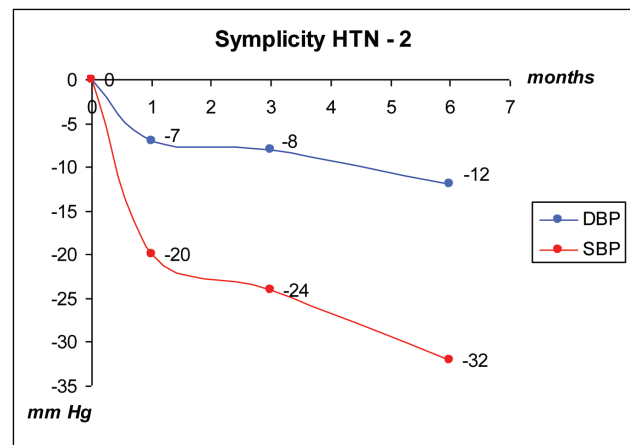


FIGURE 10. Six months after renal denervation mean blood pressure in the treatment group had decreased significantly by 32/12 mmHg; DBP = diastolic blood pressure; SBP = systolic blood pressure.

centration and improvement in insulin sensitivity as is shown in another study of 50 patients.³³

SAFETY AND CONTRAINDICATIONS

The procedure was without immediate serious complications in 201 (98%) of the 206 patients. Minor periprocedural events included 1 pseudoaneurysm of the femoral artery treated conservatively. In one patient the procedure led to renal artery dissection, unconnected with RF ablation and treated with a stent. Another patient showed worsening of a pre-existing renal artery stenosis after 6 months, also managed by stenting. Other minor complications after renal denervation, each found in one patient, comprised short-term back pain (necessitating the administration of analgesic and sedatives which ceased immediately on termination of the ablation), a post-procedural decrease in blood pressure, urinary tract infection, and prolongation of hospital stay due to paresthesias. Seven patients presented with transient bradycardia during the procedure, and were treated with atropine. In two patients RSD was followed by a decrease in eGFR >25%. During follow-up, serious adverse events occurred in 4 denervation patients (1 with nausea and edema possibly related to underlying hypertension, 1 with a hypertensive crisis after abruptly stopping clonidine, 1 transient ischemic attack, and 1 patient who received a coronary stent for angina) and 2 controls (1 transient ischemic attack, 1 coronary stent for angina). Contraindications for RSD include unfavorable anatomy of the renal artery (diameter <4 mm; length <20 mm), fibromuscular dysplasia, significant renal artery stenosis, other abnormalities of the renal arteries, and GFR <45 ml/min/1.73 mm².^{28,34}

CONCERNS

Concerns with the present study include the relatively small sample size and short duration of follow up, use of only a handful of experienced operators, and a study design that did not require the placebo group to undergo a sham procedure, which would have made the study double blind. Additionally, patients with secondary and white coat HTN were not excluded. The extent of ablation induced on afferent RSD is not currently known and the cost effectiveness needs to be carefully examined (the cost is high, around \$12,000).

In conclusion, the procedure is not technically difficult, appears to be safe, takes about 40 minutes to perform, and only requires periprocedural analgesia. Its long-term efficacy and cost-effectiveness remain to be determined.

THE FUTURE OF RENAL SYMPATHETIC DENERVATION

Renal sympathetic denervation (RSD) should be conducted in more patients, with more operators, and longer follow up (>2 years) in different registries necessary to evaluate the long term effects and the safety of the procedure. Also RSD should be conducted in other conditions, such as older

age, obesity, diabetes, sleep apnea, essential hypertension, left ventricular hypertrophy (LVH), congestive heart failure, chronic or end-stage kidney disease, conditions characterized by hyperactive sympathetic nervous system drive. At present time, although attractive, RSD is difficult to be accepted at the early stages or in milder forms of hypertension. Current recommendations suggest that it should be reserved for patients in whom drug therapy fails. However, in the future, RSD can possibly be used as initial therapy in younger patients obtaining greater benefit. Although not yet approved by the FDA for commercial distribution in the US, the system has been commercially available in Australia and Europe since April 2010. According to the company, the Symplicity system has been used since 2007 to treat more than 2,000 patients with treatment-resistant hypertension worldwide. In August 2011, the FDA granted Medtronic approval to conduct SYMPLICITY-HTN-3, a US clinical trial of the system in patients with treatment-resistant hypertension. SYMPLICITY HTN-3 is a single-blind, randomized controlled trial designed to evaluate the safety and effectiveness of renal denervation with the company's Symplicity catheter system in patients with resistant hypertension. The study will enroll approximately 500 patients at 60 medical centers in the United States. The patients will be randomized to receive either renal denervation and treatment with antihypertensive medications or treatment with antihypertensive medications alone. The primary endpoints of the study are the change in blood pressure from baseline to 6 months after randomization and incidence of major adverse events at 1 month after randomization. Another objective is to better identify specific or ethnic populations who will respond best to this procedure.

Another study, the SYMPLICITY-HF clinical trial, will examine whether regulating sympathetic activity through renal denervation may also provide benefit in patients with both heart failure and renal insufficiency, two other conditions characterized by hyperactive sympathetic nervous system drive. The multicenter, prospective, open-label Global SYMPLICITY Patient Registry will evaluate the long-term impact of renal denervation in more than 5,000 patients. The registry will facilitate the collection of real-world data on the safety, efficacy and outcomes of the Symplicity renal denervation system in patients with a number of conditions associated with hyperactive sympathetic nervous system drive, including treatment-resistant hypertension, heart failure, insulin resistance, chronic kidney disease and sleep apnea. To this end, the German Renal Denervation (GREAT) registry has been established to enable systematic follow-up of patients treated with renal denervation.

REFERENCES

1. Löwel H, Meisinger C, Heier M, Hymer H, Alte D, Völzke H. [Epidemiology of hypertension in Germany. Selected results of population-representative cross-sectional studies]. *Dtsch Med*

INTERVENTIONS IN RESISTANT HYPERTENSION

- Wochenschr* 2006; 131:2586-2591.
2. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; 25:1105-1087.
 3. Mahfoud F, Himmel F, Ukena C, Schunkert H, Böhm M, Weil J. Treatment strategies for resistant arterial hypertension. *Dtsch Arztebl Int* 2011; 108:725-731.
 4. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117:e510-526.
 5. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol* 2008; 52:1749-1757.
 6. Experimental and Computational Neurobiology Laboratory. USA. Arterial Baroreceptor reflex
 7. Chappleau M. Arterial Baroreflexes. *Hypertension Primer: The Essentials of High Blood Pressure*. 2nd ed. London: Lippincott Williams & Wilkins; 1999. p83.
 8. Bristow JD, John Honour A, Pickering GW, et al. Diminished baroreflex sensitivity in high blood pressure. *Circulation* 1969; 39:48.
 9. Lohmeier TE, Lohmeier JR, Warren S, May PJ, Cunningham JT. Sustained activation of the central baroreceptor pathway in angiotensin hypertension. *Hypertension* 2002; 39(2 Pt 2):550-556.
 10. Papademetriou V, Doumas M, Tsioufis K. Renal sympathetic denervation for the treatment of difficult-to-control or resistant hypertension. *Intern J Hypertens* 2011; 2011:196518. Epub 2011 Mar 30.
 11. Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension: results in 1,266 cases. *JAMA* 1953; 152:1501-1504.
 12. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension* 2004;43:306-311.
 13. Georgakopoulos D, Wagner D, Cates AW, Irwin E, Lovett EG. Effects of electrical stimulation of the carotid sinus baroreflex using the Rheos(R) device on ventricular-vascular coupling and myocardial efficiency assessed by pressure-volume relations in non-vagotomized anesthetized dogs. *Conf Proc IEEE Eng Med Biol Soc* 2009; 1:2025-2029.
 14. Filippone JD, Bisognano JD. Baroreflex stimulation in the treatment of hypertension. *Curr Opin Nephrol Hypertens* 2007; 16:403-408.
 15. Mohaupt MG, Schmidli J, Luft FC, et al. Management of uncontrollable hypertension with a carotid sinus stimulation device. *Hypertension* 2007; 50:825-828.
 16. Group Health Clinical Review Criteria 2010
 17. Illig KA, Levy M, Sanchez L, et al. An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg* 2006; 44:61213-1218.
 18. Scheffers IJ, Kroon, AA, Schmidli J, et al. Novel baroreflex activation therapy in resistant hypertension: results of a European multicenter feasibility study. *J Am Coll Cardiol* 2010;56:1254-1258.
 19. Bisognano JD, Bach D, Lovett E, de Leeuw P. Improved cardiac structure and function with chronic treatment using an implantable device in resistant hypertension: Results from European and United States trials of the Rheos system. *J Am Coll Cardiol* 2011; 57:1787-1788. Letter to the Editor.
 20. Lovett EG, Schafer J, Kaufman CL. Chronic baroreflex activation by the Rheos((R)) system: An overview of results from European and North American feasibility studies. *Conf Proc IEEE Eng Med Biol Soc* 2009; 1:4626-4630.
 21. Wustmann K, Kucera JP, Scheffers I, et al. Effects of chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension. *Hypertension* 2009; 54:530-536.
 22. Lohmeier TE, Irwin ED, Rossing MA, Serdar DJ, Kieval RS. Prolonged activation of the baroreflex produces sustained hypotension. *Hypertension* 2004; 43:306-311.
 23. Heusser K, Tank J, Engeli S, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension* 2010; 55:619-626.
 24. Jürg Schmidli, MD, on behalf of the DEBuT-HT Investigators. 4-Year Results Of The RHEOS® Trial for control of intractable hypertension by carotid sinus baroreceptor stimulation. Presented at the 38th Annual Vascular and Endovascular Issues, Techniques and Horizons (VEITHsymposium), November 16-20, 2011, New York City.
 25. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos pivotal trial. *J Am Coll Cardiol* 2011; 58:765-773.
 26. Smithwick RH. Hypertensive vascular disease. Results of and indications for splanchnicectomy. *J Chronic Dis* 1955; 1(5):477-496.
 27. Schlaich M, Krum H, Sobotka P. Renal sympathetic nerve ablation: the new frontier in the treatment of hypertension. *Curr Hypertens Rep* 2010; 12:39-46.
 28. Krum H, Schlaich M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-principle cohort study. *Lancet* 2009;373:1275-1281.
 29. Symplicity HTN-1 Investigators: Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57:911-917.
 30. Doumas M, Douma S. Interventional management of resistant hypertension. *Lancet* 2009; 373(9671):1228-1230.
 31. Doumas M, Faselis C, Papadimitriou V. Renal sympathetic denervation and systemic hypertension. *Am J Cardiol* 2010; 105:570-576.
 32. Symplicity HTN-2 Investigators. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903-1909.
 33. Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; 123:1940-6. Epub 2011 Apr 25.
 34. Mahfoud F, Bohm M. [Interventional renal sympathetic denervation - a new approach for patients with resistant hypertension]. *Dtsch Med Wochenschr* 2010;135:2422-2425.