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Chapter 9

Treatment of Resistant Hypertension: An Update in Device Therapy

Ghazal Quinn, Phillip John Gary, Christopher Damiano and Geoffrey Teehan

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Abstract

Hypertension is the most prevalent cardiac risk factor. In the United some estimates show 60% of 60-year-olds, 70% of 70-year-olds, an 80% of 80-year-olds being hypertensive. Often, blood pressure becomes resistant or refractory. Device therapy represents a new approach to treating this disease. The best studied of these nonpharmacologic approaches to resistant/refractory hypertension include renal denervation, carotid sinus stimulators, and central arteriovenous fistula placement. This chapter will focus on novel device therapy and literature review of its use in clinical trials.

Keywords: resistant hypertension, renal denervation, central arteriovenous anastomosis, carotid sinus baroreceptor electrical stimulators

1. Introduction: Resistant hypertension and renal denervation

Resistant hypertension, defined as blood pressure greater than 140/90 despite the use of optimal doses of three blood pressure-lowering medications, including a diuretic, is a growing epidemic. Today, approximately 86 million Americans and 1.4 billion people worldwide suffer from hypertension, and of these, 8–12% are estimated to have resistant hypertension [1, 2]. The sequelae of resistant hypertension include significant cardiovascular morbidity and mortality as well as significant healthcare costs. Medication non-adherence is among the foremost important factors in the propagation of hypertension, and may affect up to 50% of patients, obscuring the true prevalence of resistant hypertension [3]. Nevertheless, as the problem of hypertension grows, so do the various modalities of its treatment. Here, we review the efficacy and future of device based therapy in the treatment of resistant hypertension.

Surgical intervention in the management of hypertension originated over 60 years ago, when significant decreases in blood pressure were noted following surgical lumbar sympathectomy [4]. Significant adverse effects including orthostatic hypotension, impotence and bowel and bladder dysfunction were common, thus when oral blood pressure-lowering agents became available just a few years later, such surgical techniques essentially ceased. Over the last decade, there has, once again been a resurgence of device-based therapies for the treatment of resistant hypertension, part due to the first proof-of-principle trial, the SYMPLICITY-HTN-1 trial. Renal denervation in particular has been the most-studied device-based therapy and continues to garner much attention with an ever-growing body of evidence, both critical of, and in support of its use. Other modalities such carotid sinus baroreceptor electrical stimulators and central arteriovenous anastamoses have shown some promise but neither therapy has found a niche and remained unapproved by the Food and Drug Administration in the United States. Because of their novel approach to hypertension, this chapter will review these modalities and their associated clinical trials data.

2. The theory behind renal denervation

Increased sympathetic nervous system (SNS) activity may partially underlie both high blood pressure and hypertension maintenance [5, 6]. Although the SNS innervates the entire human body, hypertensive patients do not experience increased SNS activity in all organs. By detecting SNS activity through measurements of norepinephrine release, SNS over-activity is detected in renal, cerebral and cardiac circulations but not in the pulmonary or splanchnic systems [7]. Within the kidneys, outflow from the efferent sympathetic nerves stimulates renin release and increased tubular sodium reabsorption and as a result, increases blood pressure [8]. The afferent sympathetic outflow from kidneys can contribute to neurogenic hypertension via increased total peripheral resistance, including increased sympathetic nerve activity to the heart and kidneys, all of which work to increase blood pressure [8]. The specific targeting of organs, such as the kidneys, is therefore a logical approach in mitigating SNS hyperactivity.

Renal denervation involves accessing the renal arteries via the femoral artery and delivery of either radiofrequency or ultrasound energy, resulting in frictional heating of the arterial wall (see **Figure 1**) [9]. The aim of this is to destroy a significant portion of the renal sympathetic nerves, which are believed to lie closely to the renal artery, usually within the adventitia [10]. In rat models of renal denervation, renal norepinephrine levels were measured following denervation and were found to be significantly decreased, which correlated with significant delays in onset of hypertension in spontaneously hypertensive rats [11]. Swine studies later performed also demonstrated that consistent reduction in norepinephrine could be achieved and that targeted treatment of the renal artery branches, distal segment of the main renal artery or a combination of the two resulted in the most dramatic reductions in blood pressure [12]. Various methods have been used to assess the efficacy of renal denervation in humans. The most common method, the renal norepinephrine spillover method, measures the release of norepinephrine from the renal sympathetic nerves bilaterally via isotope dilution [13, 14]. Decreased norepinephrine spillover would indicate successful renal denervation. The amount by which norepinephrine should decrease per renal nerve denervation is, however, unknown.

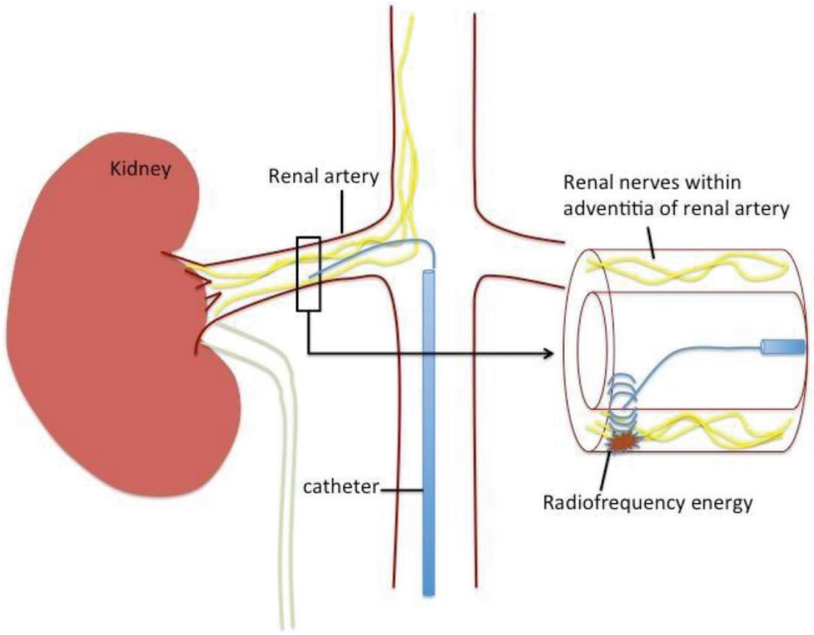


Figure 1. Schematic of renal nerve denervation.

3. Current evidence behind renal denervation

The Symplicity-HTN-1 trial thrust renal denervation into the spotlight. The patient population in this study had resistant hypertension, defined as systolic in-office blood pressure >160 mm Hg despite the use of three antihypertensive agents including one diuretic. In this open-label trial, the patient population was subject to renal denervation via a percutaneous radiofrequency catheter. The study investigators achieved the primary endpoint of sustained decrease in systolic and diastolic blood pressures at 1, 3, 6, 9 months and 12 months out from renal denervation, in contrast to the untreated control group (n = 5), who showed no significant change in blood pressure [15]. The investigators measured the renal norepinephrine spillover in a subset of patients (n = 10) and saw a modest but significant reduction of 47%. This study showed that renal denervation was safe and tolerated well among patients and was further backed up by a 3-year follow up study by the same group showing persistent reduction in blood pressure as well as continued safety following renal denervation in the Symplicity-HTN-1 trial [16].

Following up this success, the same study investigators constructed an open-label randomized trial, Symplicity-HTN-2, which randomized 106 patients to receive renal denervation via a percutaneous radiofrequency catheter or to continue their previous treatment regimen. Again, the investigators showed they achieved the primary endpoint, a significant decrease in office-based blood pressure at 6-month follow-up versus no significant change in blood pressure in the control group at 6-month follow-up [17]. A 36 month follow-up study conducted by the same investigators again showed sustained reduction in blood pressure and good safety profile in patients who had undergone renal denervation in the Symplicity-HTN-2 trial [18].

The major criticism of the Symplicity-HTN-2 trial and other major renal denervation trials was a lack of blinding and appropriate powering, thus the Symplicity-HTN-3 trial was designed as a randomized, single-blind, sham-controlled trial. Following randomization of 535 patients, investigators assessed the primary outcome of in-office blood pressure and secondary outcome of 24-hour ambulatory blood pressure. This trial however, failed to show a significant difference in blood pressure at the 6-month follow-up in the experimental group compared with the sham-procedure group [19]. Prior to completion of this trial, renal denervation had gained enough momentum to be on track for approval by the Unites States Food and Drug Administration and was to be used in an even larger international trial, the Symplicty-HTN-4 trial. However, following the negative results of the Symplicity-HTN-3 trial, the Symplicity-HTN-4 trial as well as FDA approval, were put on hold.

There are many possible explanations for why the Symplicity-HTN-3 trial did not reach its primary outcome. Patel et al., highlight several important factors distinguishing Symplicity-HTN-3 from earlier trials. First, the original trials lacked ambulatory blood pressure monitoring and may have misidentified white-coat-hypertension as resistant hypertension. The experience of the probe operators was brought into question and that there was uncertainty regarding whether the procedures were technically successful, as there was no objective measurements made (i.e., norepinephrine spillover measurement) following renal denervation. Finally, the sham-control group in Symplicity-HTN-3 had a larger drop in blood pressure than the control group and that had it not been for this, the trial would have actually met its primary outcome. They note the important finding that placebo effects do wear off over time, and that it may have been telling to monitor blood pressure beyond 6 months following the renal denervation procedure [20]. Renal denervation has not been abandoned but continues to undergo fine tuning.

4. Central arteriovenous fistula formation

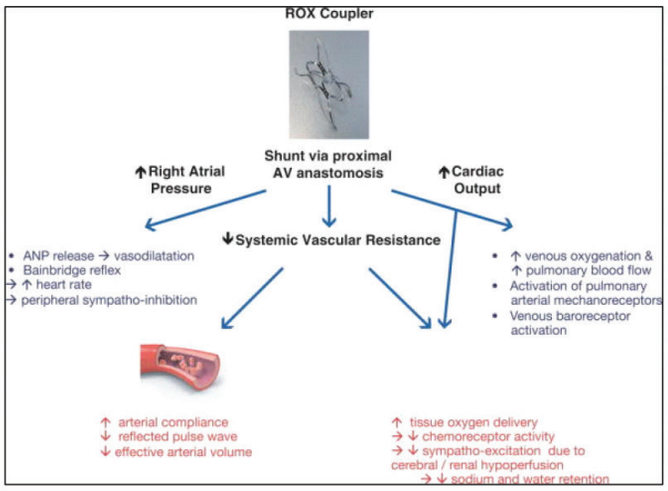
Several physiologic mechanisms have been suggested to allow blood pressure reduction in patients with arterial hypertension who undergo arteriovenous fistula formation. Burchell et al. outlined these potential mechanisms in great detail. The primary mechanisms are likely a reduction in total systemic vascular resistance and a reduction of effective arterial volume [21, 22]. The reduction in systemic vascular resistance (SVR) likely occurs given the creation of two parallel circuits leading to the total resistance being less than the value of the lowest resistance circuit. Furthermore, by allowing arterial blood to flow preferentially through the low resistance anastomosis, arterial blood volume and thus afterload are reduced leading to decreased cardiac work with an associated increased cardiac output [21]. Multiple studies evaluating the resultant effects of arteriovenous fistula (AVF) formation support a reduction in SVR and arterial volume with an increase in cardiac output [23]. The resulting cardiopulmonary response to AVF formation is unclear, however, multiple mechanisms may play a role. Some of these responses even represent conflicting physiologic mechanisms. Cardiac reflexes may include increased right atrial pressure and subsequent atrial natriuretic peptide release leading to vasodilation and increased renal blood flow, the Bainbridge reflex leading to diuresis

and tachycardia, activation of vagal mechanoreceptors leading to bradycardia and inhibition of sympathetic activity, and coronary baroreceptors leading to decreased SVR. Pulmonary reflexes may include increased pulmonary arterial oxygen content leading to pulmonary arterial vasodilation, and activation of pulmonary arterial baroreceptors triggering sympathetic activity leading to tachycardia and increased peripheral arterial pressure [21].

Renal chemoreceptors may also play a role in reducing sympathetic activity due to increased afferent arterial oxygen delivery. This mechanism can be likened to those affected by renal artery denervation and are described elsewhere [21].

Due to the coexistence of multiple pathways, studies are unclear as to the effect of AVF formation on arterial oxygen content and delivery. It has been suggested that increased arterial oxygen content would at least partially offset or in some ways suppress already active or secondarily activated peripheral and central pathways of sympathoexcitation. Suggested pathways include the renin-angiotensin-aldosterone pathway, the Cushing response, and other less specific peripheral chemoreceptors [21].

Initially developed for treatment of patients with chronic obstructive pulmonary disease (COPD) , the ROX coupler system is a nitinol device that is placed forming a 4 mm diameter anastomosis between the external iliac vein and artery. Early prospective data suggested improvement in office and 24-hour arterial blood pressures after AVF creation in patients with both COPD and



Arteriovenous Anastomosis: Is This the Way to Control Hypertension?.
Burchell, Amy; Lobo, Melvin; Sulke, Neil; Sobotka, Paul; Paton, Julian

Hypertension. 64(1):6-12, July 2014.
DOI: 10.1161/HYPERTENSIONAHA.114.02925

Figure 2. Schematic of the ROX Coupler.

hypertension [22, 24]. In 2015, the ROX CONTROL HTN study, a multi-center randomized controlled trial compared current treatment to ROX coupler placement plus current treatment via intention-to-treat analysis. Eighty-three subjects with resistant hypertension were randomized. Those in the ROX coupler group experienced a statistically significant decrease in both mean systolic blood pressure and mean systolic 24 hour ambulatory blood pressure over 6 months. ROX coupler patients were given graduated surgical compression stockings on the treated limb for at least 2 weeks post-placement. The most common adverse effect was symptomatic venous stenosis occurring in 12 (29%) of the 42 patients treated with coupler placement. All 12 patients were subsequently managed with self-inflating venous stents with resolution of symptoms. No patients in the coupler arm were admitted for hypertensive crisis while 3 (8%) of the 39 in the control arm were [25]. As of 2017, multiple randomized trials involving the ROX COUPLER are either recruiting or are underway. **Figure 2** illustrates the Rox-Coupler system [21].

5. Carotid sinus baroreceptor electrical stimulators

Recognizing that as hypertension progresses, changes in the Sympathetic Nervous System occur and can contribute to congestive heart failure and blood pressure. Reduced parasympathetic and elevated sympathetic tone lead to increased peripheral vascular resistance, lower renal blood flow, salt retention, and vascular remodeling. In 2011 the Rheos Pivotal Trial addressed the use of Baroflex Activation Therapy (BAT). This surgically implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota) was created to administer BAT via electrical stimulation of the carotid baroreceptors. The device, placed subcutaneously, consists of a pulse stimulation generator on the anterior chest wall with bilateral electrodes tunneled to each carotid sinus. It delivers an exogenous source of energy to the carotid baroreceptors, interpreted in the central medulla as a rise in BP. The brain then sends sympathoinhibitory signals to the blood vessels, heart, and kidneys resulting in a reduction of BP [26]. **Figure 3** illustrates the BAT system [26].

The 2011 Rheos Pivotal trial enrolled 265 subjects. Each had the device surgically implanted but only half had it activated at first. After 6 months all subjects had the device activated. While the trial did show a significant change in subjects whose blood pressure fell below 140/90 mm Hg, it failed to show a significant drop in systolic blood pressure. Furthermore, several safety issues arose and temper enthusiasm for this device moving forward. The device remains unapproved by the Food and Drug Administration [27].

Recognizing that both BAT and Renal Denervation modulate sympathetic signals, Wallbach et al. identified 28 subjects who had previously undergone renal denervation and enrolled them in a clinical trial to evaluate their collective response to BAT. Enrolled patients still had resistant hypertension at the time of BAT deployment with a mean systolic blood pressure (SBP) >180 mm Hg. 68% of subjects had >10 mm Hg fall in SBP after BAT. SBP dropped from 182 down to 163 mm Hg. Both findings were statistically significant. Although renal function did not differ, interestingly, albuminuria fell significantly as well. This suggests that those who “fail” one form of device therapy may benefit from a different approach [28].

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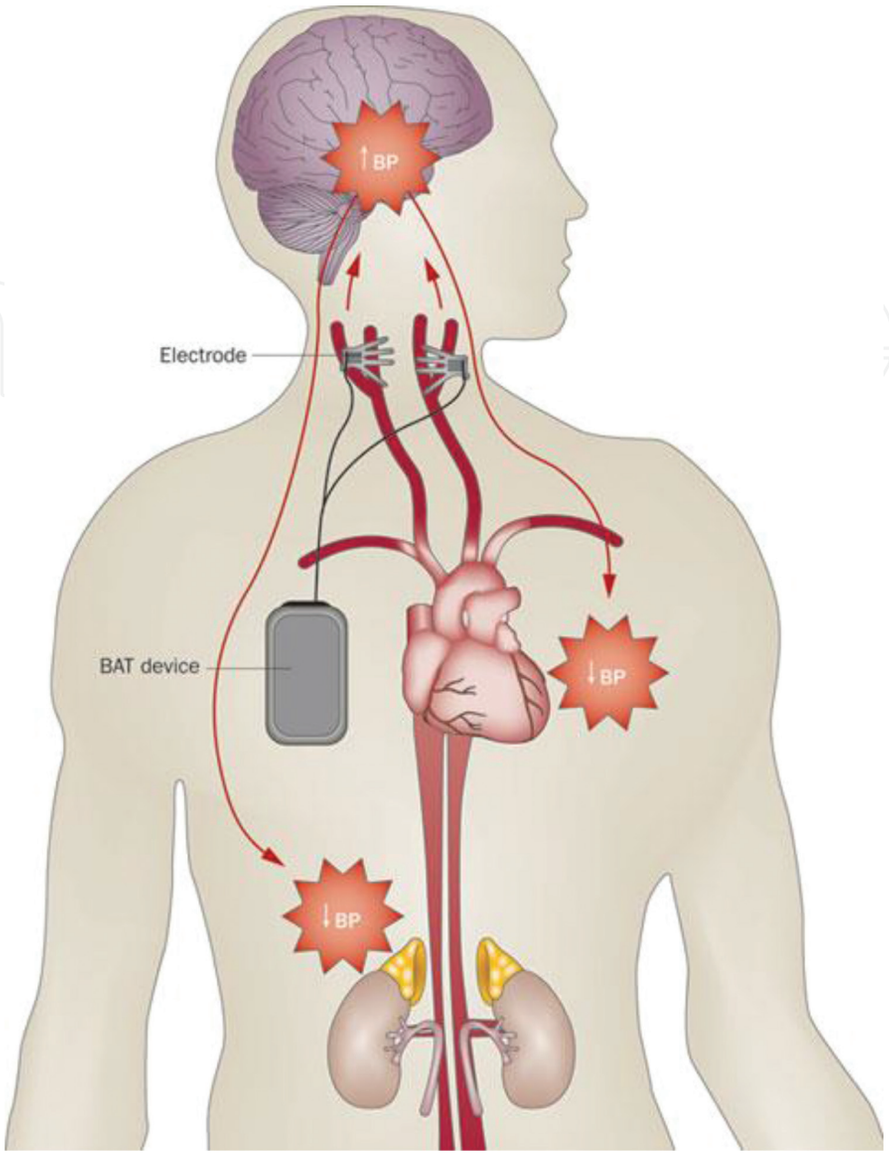

Figure 3. Schematic of carotid sinus baroreceptor electrical stimulators.

In 2016 Wallbach et al. prospectively evaluated subjects who had undergone BAT placement and performed 24 hour ambulatory blood pressure monitoring (ABPM) before device implantation and 6 months after it. His group was able to show a statistically significant drop in systolic and diastolic pressures (8 and 5 mm Hg) as well as a drop in blood pressure medications (6.5–6) follow device deployment [29].

6. Optimal modality for blood pressure monitoring

The decision to look at 24 hour ABPM is interesting given the debate regarding best practices in terms of obtaining the most accurate and reliable blood pressure readings. Bakris et al.

commented on this. Most cardiovascular outcome trials, to date, have used either auscultatory or automatic oscillometric methods of seated BP measurement performed shortly after the patient's arrival for a visit, with similar methods currently used in most clinical practices [30].

Giorgini et al. point out that in many hypertension clinical trials there is tremendous variability in the methodology from one trial to the next. For example, the actual practitioner measuring the blood pressure, the temporal relationship to the last medication dosage, the number of readings taken to provide a documented blood pressure, resting time between readings, and the device used. It is this lack of uniform procedures in such outcome studies that continue to make evidence-based guidelines difficult to determine a single best practice for blood pressure measurement that improves the ability to compare one trial to the next [31]. For now it would appear that so long as the method chosen is sound and reproducible in multiple centers, that may suffice.

7. Conclusions

Resistant and refractory hypertension often lead practitioners to consider device therapy. Thus far, the results from major trials in device therapy have been disappointing. While there was much hope following the initial SYMPLICTY trials, when this procedure/device therapy was applied to a larger cohort, the results were no different statistically. There is some debate however that the denervating instrument in earlier trials was not sophisticated enough to complete the process of denervation. Newer probes are now available renewing optimism in this procedure. The ROX Coupler caused significant venous stenosis, lacks longer-term follow-up data, and BAT while effective to some extent, was also fraught with significant side effects limiting applicability. Those with resistant hypertension who fail one form of device therapy may be considered for an alternative provided it is available. We believe there may be some hope for device therapy, particularly in the field of renal denervation, and studies are underway to address this.

Author details

Ghazal Quinn, Phillip John Gary, Christopher Damiano and Geoffrey Teehan*

*Address all correspondence to: gteehan@nephrodocs.com

Lankenau Medical Center, Wynnewood, PA, USA

References

[1] Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: Mechanisms and treatment. Current Hypertension Reports. 2017 Jul;**19**(7):56. DOI: 10.1007/s11906-0170754-x

[2] Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension—Its identification and epidemiology. Nature Reviews. Nephrology. 2013 Jan;**9**(1):51-58. DOI: 10.1038/nrneph.2012.260. Epub 2012 Nov 20

[3] Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. Journal of Hypertension. 2013 Apr;**31**(4):766-774. DOI: 10.1097/HJH.0b013e32835e2286

[4] Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. Journal of the American Medical Association. 1953;**152**(16):1501-1504

[5] de Champlain J, Karas M, Toal C, Nadeau R, Larochelle P. Effects of antihypertensive therapies on the sympathetic nervous system. The Canadian Journal of Cardiology. 1999 Mar;**15**(Suppl A):8A-14A

[6] Mancia G, Grassi G. The autonomic nervous system and hypertension. Circulation Research. 2014 May 23;**114**(1):1804-1814

[7] Esler M, Jennings G, Korner P, Blombery P, Burke F, Willett I, Leonard P. Total, and organ-specific, noradrenaline plasma kinetics in essential hypertension. Clinical and Experimental Hypertension. Part A. 1984;**6**(1-2):507-521

[8] DiBona GF. Sympathetic nervous system and hypertension. Hypertension. 2013 Mar;**61**(3):556-560. DOI: 10.1161/HYPERTENSIONAHA.111.00633

[9] Patel H, Dhillon P, Mahfoud F, et al. The biophysics of renal sympathetic denervation using radiofrequency energy. Clinical Research in Cardiology. 2014;**103**(5):337-344

[10] Patel HC, Hayward C, Vassiliou V, Patel K, Howard JP, Di Mario C. Renal denervation for the management of resistant hypertension. Integrated Blood Pressure Control. 2015 Dec 3;**8**:57-69. DOI: 10.2147/IBPC.S65632. eCollection 2015

[11] Kline RL, Stuart PJ, Mercer PF. Effect of renal denervation on arterial pressure and renal norepinephrine concentration in Wistar-Kyoto and spontaneously hypertensive rats. Canadian Journal of Physiology and Pharmacology. 1980 Nov;**58**(11):1384-1388

[12] Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, Linz D, Davies J, Kandzari DE, Whitbourn R, Böhm M, Melder RJ. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. Journal of the American College of Cardiology. 2015 Oct 20;**66**(16):1766-1775. DOI: 10.1016/j.jacc.2015.08.018

[13] Esler M, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. Hypertension. 1988;**11**:3-20

[14] Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. Circulation Research. 2015 Mar 13;**116**(6):976-990. DOI: 10.1161/CIRCRESAHA.116.303604

[15] Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: A multicentre safety and proof-of-principle cohort study. The Lancet. 2009;**373**:1275-1281

[16] Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: Final 3-year report of the Symplicity HTN-1 study. Lancet. 2014 Feb 15;**383**(9917):622-629. DOI: 10.1016/S0140-6736(13)62192-3

[17] Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A randomised controlled trial. Lancet. 2010;**376**(9756):1903-1909

[18] Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, Mahfoud F, Schlaich MP. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. European Heart Journal. 2014 Jul;**35**(26):1752-1759. DOI: 10.1093/eurheartj/ehu209

[19] Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. The New England Journal of Medicine. 2014 Apr 10; **370**(15):1393401. DOI: 10.1056/NEJMoa1402670

[20] Patel HC, Hayward C, Di Mario C. SYMPLICITY HTN 3: The death knell for renal denervation in hypertension? Global Cardiology Science & Practice. 2014;**2014**(1):94-98. DOI: 10.5339/gcsp.2014.15

[21] Burchell AE, Lobo MD, Sulke N, Sobotka PA, Paton JF. Arteriovenous anastomosis: Is this the way to control hypertension? Hypertension. 2014;**64**:6-12

[22] Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circulation Research. 2014;**116**:1074-1095

[23] Guyton AC, Sagawa K. Compensations of cardiac output and other circulatory functions in areflex dogs with large A-V stulas. The American Journal of Physiology. 1961;**200**: 1157-1163

[24] Faul J, Schoors D, Brouwers S, Scott B, Jerrentrup A, Galvin J, Luitjens S, Dolan E. Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension. Journal of Vascular Surgery. 2014;**59**:1078-1083

[25] Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, André Ng G, Ott C, Schmieder RE. Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): A randomised controlled trial. Lancet. 2015;**385**:1634-1641

[26] Bloch M, Basile J. The Rheos Pivotol trial evaluating baroreflex activation therapy fails to meet efficacy and safety end points in resistant hypertension: Back to the drawing board. Journal of Clinical Hypertension. 2012;**14**(3):184-186

[27] Bisognano JD et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled Rheos Pivotal Trial. Journal of the American College of Cardiology. 2011 Aug 9;**58**(7):765-773

[28] Wallbach M et al. Baroreflex activation therapy in patients with prior renal denervation. Journal of Hypertension. 2016 Aug;**34**(8):1630-1638

[29] Wallach M et al. Effects of baroreceptor activation therapy on ambulatory blood pressure in patients with resistant hypertension. Hypertension. 2016 Apr;**67**(4):701-709

[30] Bakris G. The implications of blood pressure measurement methods on treatment targets for blood pressure. Circulation. 2017 Oct;**136**:16

[31] Giorgini P et al. A review of blood pressure measurement protocols among hypertension trials: Implications for "evidence-based" clinical practice. Journal of the American Society of Hypertension. 2014 Sep;**8**(9):670-676

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