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Back to Life Treatment of Resistant Hypertension- An Update

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ABSTRACT

Resistant hypertension is characterized by severe and persistent high blood pressure that is not normalized even after administering two or more anti-hypertensive medications, of which one is a diuretic. Although resistant hypertension is commonly encountered in clinics, the prognosis is largely unclear. Mounting evidence indicate that resistant hypertension is a multifactorial pathology of diverse etiology. A wide variety of predisposed factors including age, ethnicity, obesity, obstructive sleep apnea, primary aldosteronism, chronic kidney disease, excessive sympathetic activation and baroreflex dysfunction may be implicated. Although a cocktail of three or four major classes of antihypertensive drugs are recommended for treatment, the benefits of pharmacological interventions is limited in many patients, so surgical denervation of the renal artery is widely practiced to improving patient outcome. Thus, surgical interventions include (i) renal sympathetic denervation, (ii) renal sympathetic innervation, and (iii) device-based carotid baroreceptor electric stimulation may be considered back-to-life options to treat resistant hypertension. Moreover, over the years, these surgical procedures have been refined and fine-tuned to optimize benefits, while minimizing adverse effects. Thus, the current surgical practice has been greatly improved from the time of inception. Therefore, this review will focus on the role of surgical interventions in the treatment and management of resistant hypertension. With the global escalation of hypertension in epidemic proportions and the huge socio-economic burden posed to patients, their families and healthcare systems, it is of utmost importance to improve treatment strategies for all forms of hypertension including resistant hypertension.

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Introduction

Resistant hypertension (RH) is a multifactorial pathology of diverse etiology, and is generally characterized by severe and persistent high blood pressure that even after the administering at the maximal tolerated doses, two or more anti-hypertensive medications, of which one is a diuretic, the goal of blood pressure <140/90 mmHg (or <130/80 mmHg in patients with diabetes or chronic kidney disease) is not attained [1-3]. Epidemiological data indicate RH is fairly common, although the exact prevalence is still a highly contested issue [1,4-11]. Although resistant hypertension is commonly encountered in clinics, the prognosis is largely unclear. A wide variety of predisposed factors including age, ethnicity, obesity, sleep apnea, primary aldosteronism, chronic kidney disease, excessive sympathetic activation and baroreflex dysfunction are implicated [1, 4-30].

Older patients are more likely to have hypertension that is resistant to treatment [31]. Hypertension in the elderly is associated with increased rates of sodium sensitivity, isolated systolic hypertension, and "white coat effect". As well, arterial stiffness and endothelial dysfunction also increase by age [32]. All these factors are more prominent in elderly if compared with young-aged hypertensive patients that may further increase the chance of developing a difficult-to-treat hypertension state. In order for achieving the goal of confirming a state of resistant hypertension in the elderly, the agents that most commonly cause an elevation in blood pressure such as NSAIDs, some immune suppressants (tacrolimus, cyclosporine) as well as corticosteroids should be ruled out [32].

In ALLHAT, it has been stated that African American participants had more treatment resistance, as did women, such that black women had the lowest control rate (59%) and non-black men the highest (70%) [33,34]. A Few studies in sub-Saharan Africa were aiming to determine the frequency of resistant hypertension in hypertensive black African population. The number of 692 patients with 14.6% of resistant hypertension were included in the studies with an average age of patients was 54.8 ± 11.1 years in the general population, 56.5 ± 11.8 years in the subgroup of non-resistant hypertension and 64.2 ± 5.4 years in the subgroup of resistant hypertension consecutively. Dyslipidemia, diabetes and obesity/overweight were significantly more frequent in the subgroup of resistant hypertension. The global cardiovascular risk was high in 24.9% of cases in the general population, 22.5% in the subgroup of non-resistant hypertension and 38.6% in the subgroup of resistant hypertension. This study concluded that resistant hypertension is common in black Africans. It is mostly subjecting of the sixth decade, with limited economic income and living in rural areas [35].

The evaluation of RH in Chronic kidney disease (CKD) patients is highly relevant for the fact that RH is common in CKD patients, and its prevalence increases with worsening of kidney damage [36]. As well, RH represents an independent risk factor for renal,

and cardiovascular outcomes in CKD patient [36, 37].

The pathogenesis of hypertension in CKD comprises a combination of factors including sodium retention, increased activity of the renin-angiotensin system, and enhanced activity of the sympathetic nervous system [38].

From a prognostic perspective, studies have shown that presence of mild-to-moderate GFR reduction and/or microalbuminuria amplifies the cardiovascular risk correlated to RH in the general hypertensive population [39,40]. Persistence of hypertension despite optimal antihypertensive treatment specifically identifies patients with more severe vascular damage [41]. Diabetes, left ventricular hypertrophy, higher proteinuria, and high salt intake are found to be independently associated with true resistance and all associated with endothelial dysfunction and arterial stiffness [42-45]. In particular, CKD has shown that proteinuria, rather than GFR, relates to the severity of hypertension [46]. Indeed, although low GFR is recognized as a CV risk factor [47]. Proteinuria in CKD patients is considered a better marker of the presence of vascular disease [48, 49].

Excessive sympathetic activation is associated with several illnesses, among them are coronary heart disease, end-stage renal disease and essential hypertension [50]. In patients with essential hypertension, sympathetic activation is in perhaps 50% of patients [51]. Recent evidence with endovascular radiofrequency ablation of the renal sympathetic nerves in patients with drug-resistant hypertension suggests that the activation of the sympathetic nervous system sustains the blood pressure elevation [51]. Taken this, the sympathetic nervous system stimulation produced by some antihypertensive drugs (diuretics and dihydropyridine calcium channel blockers being examples might be harmful, as renin release is expected to elevate in chronic diuretics users and 50-100% increase in plasma catecholamine is expected with dihydropyridine calcium channel blockers [52, 53].

The carotid baroreflex originates from mechanoreceptors located in the walls of the internal, external, and common carotid arteries, aorta, and kidney [54]. The nucleus tractus solitarius in the medulla oblongata recognizes changes in the firing rate of action potentials from the baroreceptors [54]. Carotid baroreflex buffers acute changes in blood pressure through the modulation of both parasympathetic and sympathetic nervous systems [54]. Stimulation of baroreflex afferent nerves is sensed by the brainstem cardiovascular centers as a blood pressure elevation [55-57]. The baroreceptor stimulator physiologically activates the reflex to obtain neuro-humoral mediated decreases in BP, reducing sympathetic activity and increasing parasympathetic outflow [54]. Studies performed in animals with Ang II-induced acute and chronic hypertension indicated that prolonged activation of the carotid baroreceptors elicited a decrease in renal sympathetic activation in animals with an intact baroreflex but not in those with previous sino aortic denervation [58- 60]. These data suggest that the baroreflex is crucial in chronic hypertension and that renal sympathoinhibition, with a resultant increase in natriuresis, may be the mechanism by which the baroreflex participates in long-term blood pressure control [61]. More details in this regard will be discussed further in this review.

Pseudo-Resistance

In order to confirm a proper diagnosis of RH, pseudo-resistance is to be ruled out. The term "pseudo-resistance" refers to lack of BP control with appropriate treatment in a patient who does not have resistant hypertension [62]. Several factors contribute to elevated BP readings and produce the perception of resistant hypertension [63-68]. Such factors include the following: 1) suboptimal BP measurement technique; 2) the white-coat effect; and 3) poor adherence to prescribed therapy and other causes described in the following text [13,14]. A careful evaluation to exclude these factors before labeling someone as having resistant hypertension should be performed.

Subjects with increased body mass index (BMI) are more likely to suffer from hypertension and exhibit RH compared to non-obese controls [69-72]. Hypertension and diabetes screening and awareness (HYDRA) cross-sectional study of 45,125 primary care patients, showed that those with a BMI $\geq$ 40 kg/m^2 had a higher prevalence of hypertension, as well as a 5.3- and 3.2-fold higher probability of requiring 4 or 3 anti-hypertensive drugs, respectively, to achieve BP control compared with patients with normal weight (BMI, $\leq$ 25 kg/m^2) [71, 73]. Increased free leptin and elevated plasma insulin are associated with increased SNS activity in experimental animal models and in human subjects. Obesity is frequently observed in obstructive sleep apnea (OSA) patients in whom sympathetic activation is fired [74-78]. However, sympathetic overactivity *per se* is accompanied by BP and heart rate (HR) increases, as well as by enhanced sodium retention [69]. The relationship between OSA and BP has been studied in several epidemiological, longitudinal, and cross-sectional studies, as well as in studies from specialized clinics [79-83]. It has been shown that OSA in normotensive subjects predicts future development of hypertension [79]. A Swedish study of 16 patients with RH reported a 56 % prevalence of OSA in these patients compared to 19 % in patients with controlled hypertension [84]. In a study of 41 consecutive resistant hypertensive, 83 % prevalence of unsuspected OSA was found; OSA was defined as an apnea/hypopnea index (AHI) of $\geq$10 events/h [85]. Other study of 71 patients with RH revealed an 85 % prevalence of OSA (AHI $\geq$ 5 events/h) [86]. A study from Spain in 62 resistant hypertensive patients reported a 90% prevalence of OSA (AHI $\geq$ 5 events/h) [87].

A cross-sectional evaluation of 1190 consecutive patients referred for evaluation of possible sleep-disordered breathing demonstrated a positive linear association between the respiratory disturbance index and BP suggesting that OSA is related to hypertension [88]. A dose-response association between sleep-disordered breathing at baseline and the presence of hypertension 4 years later was reported in the Wisconsin Sleep Cohort Study conducted on 709 participants [82]. It was concluded that OSA is a strong and independent risk factor for the presence and future development of hypertension [82, 83, 88, 89].

Primary aldosteronism (PA) is now recognized as one of the most common causes of resistant hypertension. In patients referred to hypertension specialty clinics, as many as 20% demonstrate PA [71,72]. PA is characterized by the overproduction of the mineralocorticoid hormone aldosterone by the adrenal gland [90,91]. The syndrome can be the result of bilateral or unilateral adrenal hyperplasia, aldosterone producing adrenal adenoma [90,91]. Therefore, testing for PA should be considered in patients with resistant hypertension [68]. The best initial test is a morning plasma aldosterone-to-renin ratio. A ratio below 20 (when plasma aldosterone is reported in ng/dL and plasma renin activity is in ng/mL/hr) effectively rules out PA. A ratio of $\geq$ 20 with a serum aldosterone >15 ng/dL suggests PA, but the diagnosis must be confirmed by a salt suppression test [68]. The evaluation of patients with RH was based on a suppressed plasma renin activity (PRA; <1.0 ng/mL per hour) and a high 24-hour urinary aldosterone

excretion (>12 μg/d) in the course of a high dietary sodium intake (>200 mEq/d) [92]. The elevated circulating aldosterone levels lead to hypokalemia, hypernatremia, metabolic alkalosis, and hypertension [90,91].

Surgical Intervention as a Possible Remedy of Resistant Hypertension

Although a cocktail of three or four major classes of antihypertensive drugs are recommended for treatment, the benefits of pharmacological interventions is marginal in many patients [1-3]. So that, the surgical denervation of the renal artery with or without antihypertensive drugs is widely practiced to better improve patient outcome.

Thus, surgical interventions that include (i) renal sympathetic denervation, (ii) renal sympathetic innervation, and (iii) device-based carotid baroreceptor electric stimulation may be considered back-to-life options to treat resistant hypertension.

Different Methods of Surgical Treatment

Despite the availability of multiple conventional medications, control rates of hypertension are still very low worldwide, about 50% in the USA and even much lower in the rest of the world [93]. The beneficial effects of pharmacologic therapy shown first by the Veteran Administration study group [94,95], and later confirmed by many other trials made pharmacologic therapy the preferred and only option for the treatment of hypertension [93].

A) Renal Sympathetic Denervation (RSDN)

Is (RSDN) Back to Life?

Radical sympathectomy was known on the time of 40s and 50s when therapeutic options for hypertension were limited and has been forgotten for decades [93]. Recently, radical sympathectomy has been recalled when the prevalence of RH exceeds 17% of the hypertensive populations. However, total sympathectomy was poorly tolerated by most patients [93] as it had to include the abdominal organs in order to be effective, and it was thus termed splanchnicectomy [93]. Partial sympathectomy was conducted more than 40 years ago in patients with malignant hypertension [96]. Sympathectomy was mainly applied in patients with severe or malignant hypertension [97-98]. After the introduction of anti-hypertensive drugs, sympathectomy was reserved for patients who failed to respond to anti-hypertensive therapy or could not tolerate it [93]. Sympathectomy was performed either in one or two stages, required a prolonged hospital stay (2–4 weeks) and a long recovery period (1-2 months) and more importantly a skilled surgeon to perform it [99]. Pioneers with significant contribution in this field include Page, Craig, Peet, Isberg, Smithwick, Allen, and Adson [93]. In general, sympathectomy proved to be effective in reducing BP immediately postoperatively and was associated with improved survival in the long run [93]. In a large observational study of more than 2,000 patients (1,506 splanchnicectomy), survival rates were more than doubled in patients undergoing sympathectomy, and the benefits were evident in all stages of hypertension [100]. A satisfactory BP response was observed in about half of the patients that underwent splanchnicectomy [93].

The antihypertensive effects of splanchnicectomy and sympathectomy in these pioneering studies, led to the inception of other surgical interventions like renal denervation to counteract hypertension in experimental animal models and subsequently in humans. Accordingly, several experiments of renal denervation were done in animal species (rodents, swine, dogs, sheep) with diverse pathological conditions including hypertension, heart failure and kidney disease in attempt to improve the health status [101]. Interestingly, bilateral renal denervation prevented or reduced the development of hypertension in the animal models of experimental hypertension [101,102]. These observations were consistent with other studies in which renal denervation reduced sodium retention and BP in a model of obesity-related hypertension associated with sodium retention and increased sympathetic activity [103]. Similarly, in the 5/6 nephrectomy rat model of chronic renal failure and hypertension, dorsal rhizotomy prevented the elevation of BP [104]. Furthermore, in another related model characterized by excessive sympathetic activity and sodium retention, renal denervation prevented the rise of BP [105]. Based on these findings, it was clear that the renal denervation is effective against BP elevation in experimental animals, and thus was explored as a tool against resistant hypertension patients.

Several clinical studies have been done to validate the effect of renal denervation on sympathetic tone and BP. Although the procedure of renal denervation was pioneered by Sobotka and Krum, the proof-of-principle trial was done by Papademetriou and co-workers, who reported that renal sympathetic denervation evokes a sustained reduction of blood pressure for 12 months [106, 93]. Interestingly, similar observations were reported in the SYMPLICITY HTN-1 study [106] in which renal sympathetic denervation ablated the elevation of blood pressure [106]. In these studies, renal sympathetic ablation was achieved using a radiofrequency ablation catheter inserted through the femoral artery and selectively engaging the renal artery bilaterally [93, 106,107].

Ablation Modalities Used in RSDN

Radiofrequency Ablation

Radiofrequency is the most commonly used energy source for RAD [108]. Radiofrequency lesion size is an important determinant for successful denervation that could be affected by several factors including ablation power, electrode surface area, ablation duration and catheter contact force [109].

Ultrasound (US)

Both intraluminal and extracorporeal high intensity focused US (HIFU) have been studied and applied in RSD [108,110]. Significant nerve injury and reduction in kidney NE level was achieved with at least two energy applications per artery [111]. The preliminary first-in-man REDUCE study demonstrated significant office and home BP reduction at 3 months [108]. Minimal complications were reported, including lower abdominal and back pain, as well as a single case of guide related RA dissection requiring stenting [112].

Chemical Denervation

Chemical denervation uses neurotoxins like vincristine and alcohol, infused into the renal perivascular tissue resulting in neurolysis [113]. Vincristine is an anti-neoplastic agent that produces giant axonal swelling and ultimately leads to peripheral nerve demyelination [108]. In a swine model, RSD using vincristine delivered through a modified angioplasty catheter significantly decreased the number of renal nerves [113]. In alcohol renal denervation, a dedicated three-needles Peregrine catheter (Peregrine System, Ablative Solutions, Inc., Kalamazoo, MI, USA) was used to deliver alcohol into the perivascular space [114]. Studies in a swine model demonstrated significant reduction in renal NE content (up to 88% using 0.6 ml dose) at 3 months compared to saline control, without associated intimal and vascular wall injury on histology and angiography. Furthermore,

no nephrotoxic effect was observed after direct alcohol injection into renal artery (114) AND [115]. In a first-in-man study (n = 18) assessing the feasibility and safety of alcohol denervation (0.3 ml), significant office BP change from baseline (-24/-12 mmHg) was observed at 6 months without procedural related adverse event [116].

Symplicity HTN-1

Renal artery angiography was performed before the procedure to access anatomic eligibility for the procedure and to confirm the absence of significant renal artery stenosis [117]. Renal angiography was also conducted immediately and 14-30 days after procedure, and magnetic resonance angiogram 6 months after the procedure in some patients [93]. After renal artery angiography, anticoagulation and administration of opioid analgesics for control of diffuse abdominal pain that invariably occurs during this procedure, via 8-F femoral artery access [107]. The treatment catheter is introduced into the renal artery and positioned in the distal part of the artery. The proximal end of the catheter is connected to a radiofrequency (RF) generator to apply a discrete RF ablation lasting 2 min [117]. Up to six ablations are conducted in each artery, separated both longitudinally and rotationally to achieve circumferential coverage of the renal artery [117]. To better monitor changes in office blood pressure, it was measured at 1, 3, 6, 9, and 12 months after the procedure [93].

Outcome of the Study

Surgical renal denervation has been shown to be an effective means of reducing sympathetic outflow to the kidneys (confirmed by a significant reduction in renal norepinephrine spillover), augmenting natriuresis and diuresis, and reducing renin release, without adversely affecting other functions of the kidney such as glomerular filtration rate (GFR) and renal blood flow (RBF) to end up with reducing blood pressure in a safe way with long acting results [99,107,117]. Also the proof-of-principle trial has indicated that RSD resulted in impressive BP reductions that were maintained during the 12-month follow-up period [93]. In addition, the cardiac muscle mass assessed by cardiac magnetic resonance imaging decreased by 15 g [118].

Limitations of the Study

Regardless the impressive outcomes of this study, some concerns were raised. Radiofrequency-induced renal sympathetic nerve ablation was the potential for development of suitable substrate for renal artery stenosis due to intimal injury [93]. As well, tissue damage and fibrosis have been observed with radiofrequency ablation in other areas of the body [93]. Also this study was not randomized or placebo controlled [93].

Symplicity HTN-2

More recently, a randomized study has been conducted [Symplicity HTN-2] (Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension) [107, 119]. The study included 106 patients with RH that were randomly assigned to undergo RSD while continuing prior therapy (52 patients) or to continue prior medical therapy alone (54 patients) [119,120]. Office BP showed a dramatic reduction of 32/12 mmHg at 6 months in patients who underwent renal denervation, although there was no significant reduction in the control group (1 mmHg) [119,120]. Home BP fell by 20/12 mmHg and ambulatory blood pressure by 11/7 mmHg at 6 months in the renal denervation group vs. no change in the control group [119,120]. This substantial difference in office and ambulatory blood pressure reduction raised concerns [121]. The difference could be attributed to the small number of ambulatory BP assessments (only 20 patients) and the well-known lower reduction of ambulatory, compared with office BP [122]. Another disturbing finding is the lack of response to renal denervation in a small subgroup of patients [120]. It can be assumed that either renal sympathetic denervation was incomplete due to technical limitations or renal sympathetic denervation is not efficient in some patients with RH [120].

Limitation of the Study

Significant limitations of the study include the absence of a sham-operation in the control group, inadequate exclusion of white-coat or secondary hypertension, and the relatively short follow-up period (6 months) that provides no reassurance for the long-term efficacy of renal sympathetic denervation [123]. In addition, although the study was randomized, the investigators were not blinded [107].

To further confirm the safety and the efficacy of RSD in individuals with RH through existing literature, Gosain, reported nineteen studies (n=683 persons) were included with a follow-up duration ranged from 1 to 24 months. All studies reported significant reductions in systolic (18 mmHg to 36 mmHg and diastolic (9 mmHg to 15 mmHg) pressures [124]. They also reported that sustained benefit of BP reduction at 12 months was observed in 5 studies. However, no worsening of renal function was reported and there were few procedure-related adverse events such as pseudo-aneurysm formation, hypotension, and bradycardia [124].

The beneficial effects of RSD extend to also include the protection against metabolic syndrome and impaired glucose metabolism. In a study, conducted by Mahfoud, they enrolled 50 patients RH. Thirty-seven patients underwent bilateral RSD, and 13 patients were assigned to a control group [125]. In addition to the dramatic improvement in systolic and diastolic blood pressures, fasting glucose, insulin, C peptide, hemoglobin A1c, calculated insulin sensitivity (HOMA–IR), and glucose levels during oral glucose tolerance test dramatically improved when measured 3 months after RSD when compared against controls. The only parameter that was not changed after RSD was BMI [124]. They demonstrated for the first time that selective denervation of the renal sympathetic nerves has the potential to improve glucose metabolism and blood pressure control concurrently in patients with HR in the absence of significant changes in body weight and alterations in lifestyle or anti-hypertensive medication [125].

Collectively, The Symplicity HTN-1 (2009) and HTN-2 (2010) studies re-introduced an old treatment approach for RH and showed that catheter-based RDN was feasible and resulted in substantial blood pressure (BP) reductions [126] . However, they also raised questions of durability of BP reduction, correct patient selection, anatomical and physiological effects of RDN as well as possible beneficial effects on other diseases with increased sympathetic activity [126] .

Symplicity HTN-3

The Symplicity HTN-3 trial is the first blinded, randomized, sham-procedure controlled trial of RDN for the treatment of RH [127]. The Symplicity HTN-3 trial included 535 eligible RH patients out of assessed 1440 from 88 medical centres in the USA with a systolic BP (SBP) $\geq$ 160 mm Hg [128]. Two weeks after initial screening, a confirmatory screening visit was conducted at which SBP $\geq$ 160 mm Hg was confirmed, adherence to the therapy according to the patient's diary was documented and ambulatory BP monitoring was performed to confirm the hypertension resistance (daytime

SBP average ≥ 135 mm Hg) [128]. Patients included in the study were randomly assigned in a 2:1 ratio to renal nerve ablation using the Symplicity Flex Catheter (Medtronic, MN, USA) or to renal angiography only (sham control) with no change in the antihypertensive regimen during the 6 months follow up unless otherwise was necessary [128]. The primary efficacy endpoint and secondary efficacy endpoint were the change in office SBP at 6 months the change in mean 24-hour ambulatory SBP respectively [128]. Disappointingly, RDN did not reach the primary efficacy endpoint of reduction in office SBP, or the secondary efficacy endpoint of decrease in 24-hour ambulatory BP levels ($p = 0.26$ and 0.98) respectively [128]. These findings contradict the published clinical data regarding renal denervation, which showed larger reductions in blood pressure 6 months after denervation and, in the unblinded SYMPLICITY HTN-2 trial, no reduction of systolic blood pressure in control patients [127, 129-131].

Adverse Effects of RSD

Adverse events are common and included orthostatic hypotension, tachycardia, palpitation, breathlessness, anhydrosis, cold hands, intestinal disturbances, loss of ejaculation, sexual dissatisfaction, thoracic duct injuries and atelectasis [117].

B) Renal Sympathetic Innervation:

The contribution of renal sympathetic efferent and afferent nerve activity towards the development and progression of hypertension has been convincingly demonstrated in both preclinical and human studies involving models of hypertension, MI, heart failure, CKD, and diabetic nephropathy [102].

- **Efferent Sympathetic Innervations**

The kidney achieves the own sympathetic innervation through a dense network of postganglionic neurons [132,133]. Additionally, alongside the renal artery, renal pre-ganglionic nerves run entering the hilus of the kidney [93]. Renal sympathetic nerve activation enhances nor-epinephrine (NE) production for nerve endings and NE spillover [134-136] and also enhances renin secretion and release through β1 adrenergic receptors [93,99]. However, α1 receptor activation results in increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow [93,99]

- **Afferent Renal Sympathetic Innervation**

Afferent renal sympathetic nerves originate mostly from the renal pelvic wall [137-139]. Mechanoreceptor and chemoreceptors respond to stretch and detect renal ischemia respectively [102,140]. Overall afferent sympathetic fibers may have important contribution in regulation of systemic vascular resistance and BP control [93].

C) Carotid baroreceptor electric stimulation:

- **History**

The Control of blood pressure by an arterial reflex has been known since ancient times [30]. The observation in Ancient Rome that pressing on the arteries of the neck in animals produced sedation might have been the first observation of this homeostatic mechanism [141]. A Syrian doctor used carotid compression for curing headache during the ninth century [142].

- **Physiology**

Carotid baroreceptors physiologically modulate autonomic tone by inhibiting sympathetic cardiovascular drive and stimulating vagal influences on the heart [117]. This homeostatic function is impaired in hypertension leading to vasoconstriction and tachycardia [121]. With increases in arterial pressure, the brain interprets increased signals as a rise in BP and attempts to counteract the perceived rise in BP by transmitting signals to various end organs [143,144]. This effect will result in a decreased sympathetic outflow and an increased parasympathetic outflow [145]. The net effect is a decrease in heart rate (HR), contractility and vascular tone, natriuresis, and a decrease in arterial pressure [143].

- **Preclinical Studies**

Lohmeier, conducted a study on conscious dogs by chronically implanting electrodes around both carotid sinuses and using an external adjustable pulse generator to electrically activate the carotid baroreflex in a period of 7 days followed by subsequent 7-day recovery period [146]. They noticed an immediate activation of the baroreflex with a reduction in BP [146]. The hypotensive response was observed throughout the entire week of activation associated with reduced mean arterial pressure (MAP) and HR as well as 35% reduction in plasma NE levels. No significant changes in plasma epinephrine, plasma renin activity (PRA), plasma aldosterone, or cortisol were observed during the 7 days of activation [147]. They concluded that a drop in MAP was expected to trigger a compensatory increase in renin release; therefore, the absence of an increase in PRA suggests that baroreflex activation exerts an inhibitory effect on renin release [147]. In a different study, Lohmeier, chose to investigate the effects of carotid sinus stimulation on arterial hypertension induced by feeding dogs a high-fat diet [147]. After 4 weeks of a high-fat diet, there were increases in body weight, MAP, HR and plasma NE concentrations [147]. Following a weeklong period of baroreflex activation, MAP immediately decreased, while the drop in HR delayed until day 7 [147]. After termination of the weeklong period of carotid sinus stimulation, MAP returned to obesity-induced hypertensive levels within a week [147]. After the first day of baroreflex activation, only plasma NE levels decreased [147]. Lohmeier and others thought that SNS activation contributes to the pathogenesis of obesity-related hypertension [148-150]. The hyperinsulinemia and hyperglycemia induced by the high-fat diet were not affected by baroreflex activation [151].

- **Clinical studies**

From a surgical perspective in human studies, Illig, Tordoir and Lovett described the short-term outcomes following Rheos device implantation from European and US Feasibility Trials [152,153,107]. Dose related decreases in SBP, DBP, and HR were seen with intra-operative stimulation, and the same trend for BP to be reduced was seen in the same patients after awakening from the surgery with a voltage range of 0–6 V [152]. The relationship between voltage and hemodynamic response was strongly linear [152]. Prior to discharge from the hospital, dose response testing showed an average decrease in SBP of 41 mm Hg, an average decrease in DBP of 19 mm Hg, and an average decrease in HR of 9 beats/min [147]. However, Tordoir concluded from their short-term studies that the Rheos device at reasonably low voltages can produce significant and sustained reductions in BP in a safe manner and that implantation can be performed with "reasonable safety" [154].

1) Rheos System Human Studies

a) BRASS and DEBuT-HT

The first human proof-of-principle trial with the Rheos system, the Baroreflex Activation System Study (BRASS), was performed in 2003 [155]. The study was conducted on 11 normotensive patients undergoing an elective endarterectomy, which averaged 18 mmHg for systolic BP and 8 mmHg for diastolic BP [156]. Acute voltage-dependent BP drop was observed [156].

b) Phase II, multicenter, nonrandomized Device-Based Therapy of Hypertension Trial (DEBuT-HT)

This study was conducted on 45 participants [157]. The participants showed a mean BP reduction of 33/22mmHg after 2 years of follow-up with an acceptable safety profile [157]. Bisognano et al [158]. demonstrated in a prospective sub study of the DEBuT-HT and the original US Feasibility Trials utilizing the Rheos device that therapy was shown to not only lower BP but also effectively reverse cardiac remodeling in early-stage HF patients with drug-resistant hypertension.

c) Pivotal Trial

The Rheos Pivotal Trial is the first large-scale randomized double-blinded placebo-controlled trial to evaluate baroreflex activation therapy [159,160]. The Rheos Pivotal Trial (NCT00442286) is an FDA-approved randomized, double-blind, parallel-design phase III trial with 267 enrolled patients who meet the systolic criteria for stage 2 drug-resistant hypertension (office cuff SBP ≥160 mm Hg and DBP≥80 mm Hg despite maximally tolerated doses of at least 3 antihypertensive medications, one of which is a diuretic), enrolled from about 50 sites in the United States and Europe [122]. The goal of the Pivotal Trial was to demonstrate the efficacy and safety of device: clinically significant SBP reduction (10 mmHg) as measured by an office cuff after 6 months and 1 year of device activation, and both acute and long-term safety of the device during implantation and activation periods [161]. The Rheos system provides the ability to optimize and individualize the programming of the device for each patient [155]. Subjects with unilateral BAT showed a systolic BP reduction of 32 ± 3 mmHg and 31 ± 4 mmHg for right- and left-sided programming, respectively, after 6 months of BAT [155]. This was comparable to patients who had bilateral BAT (21 ± 4 mmHg decrease in BP) [155]. These results minimize the necessity to activate carotid baroreflex pathways to achieve maximum decrease in BPs [115]. Also, there is no preference for a side over the other side as reported by Furlan et.al, who showed no functional asymmetry in sympathetic discharge in response to unilateral neck suction in 12 healthy subjects [161]. This is contradicted by a previous study which has been conducted by Williamson et. al, who indicated left-sided dominance for MSNA by direct measurements from right peroneal nerve during unilateral sustained neck pressure by a neck collar device in 10 healthy volunteers [162,163].

- **Procedure of Rheos Hypertension System**

i. Device Components

The Rheos Hypertension System is comprised of following 3 components, Rheos Implantable Pulse Generator (IPG), bilateral Rheos Carotid Sinus Leads (CSL), and Rheos Programmer System [122, 164,165]. The IPG is comprised of a battery and circuit system that delivers between 1 and 7.5 V of activation energy in a pattern that varies temporally via the CSL [122]. The Rheos Programmer System is a computer-based programming system that allows noninvasive communication with and control of the IPG via radiofrequency coupling, much like the system used for programming cardiac pacemakers [122]. The IPG dimensions are height of 90 mm, width of 48 mm, thickness of 12 mm, and weight of 95 g [122]. The IPG is directly connected to the CSLs, which measure 50 cm in length [122]. The CSLs are available in 2 different-sized models, with the smaller model capable of covering the free wall of the carotid sinus and the larger models recommended for use in bigger arteries or larger anatomic variants of the carotid sinus [122].

ii. Surgical Implantation

The surgical implantation technique was described by Illig et. al, [122, 152]. Carotids are exposed under narcotic anesthesia to preserve the reflex [122, 152]. Once the carotid bifurcation is identified, the electrode is centered on the carotid sinus and the lead is connected to the IPG [122, 152]. Stimulating the carotid sinus at a low voltage and observing a BP-lowering effect is generally obtainable within 30 seconds [122, 152]. Once that area is identified, the electrode is sutured in place [122, 152]. The IPG is implanted in a pocket created infraclavicularly, usually on the right side to avoid confusion with pacemakers that are typically implanted on the left side [122, 152]. Subcutaneous tunnels connecting the CSLs, and pocket are created allowing the leads to be connected to the IPG [122, 152].

iii. Adverse Effects of Baroreflex Activation Therapy (BAT) by Using Rheos device

According to Sakellaris et al [117], The adverse events were 1) Procedure-related: transient (4.4 %) or permanent (4.8 %) nerve injury at the time of im¬plant, general surgical complication, respiratory complaint or a wound complication (2.6 %); 2) BAT-related: hypertensive crisis; as well as 3) Device-related: hypertension-related stroke (2.3%). The authors explained that nerve injury was the main contributor to the adverse events, and that per¬forming a unilateral implant may reduce the complexity and duration of the procedure [117].

2) Barostim neo-Human Studies

a. XR-1 Verification Study

This study is the first human trial with the second generation of carotid baroreflex activators [155]. It is a nonrandomized, open-label trial at up to 15 clinical sites in Europe and Canada [155]. The purpose of the trial is to assess the safety and efficacy of the Barostim neo™ system in patients with drug-resistant hypertension [155]. Forty subjects were implanted with Barostim neo™ and BAT initiation was started 2 weeks after implantation of the device [155, 166]. Patients with secondary hypertension, known or suspected baroreflex failure or autonomic neuropathy, and myocardial infarction, unstable angina, syncope, or cerebral vascular accident within 3 months before implant were excluded from the study [166]. The study targeted 2 objectives: 1) Primary efficacy objective which was to describe the reductions of office cuff systolic BP after 6 months of BAT initiation compared to baseline BP. 2) The primary safety objective was to describe all system- and procedure-related complications through the study 6-month visit [166].

i. Methods

The new generation device is comprised of a pulse generator and a lead similar to a contemporary pacemaker system and controlled with a laptop computer-based programming system via radiofrequency telemetry [166]. The pulse generator is implanted unilaterally in the pectoral region ipsilateral to the stimulated carotid sinus. In order to expose the carotid sinus, a small incision (2.5-5 cm) is required to be done to insert the lead [166]. Once the device is implanted in, the lead is sutured to carotid sinus [166].

ii. Outcome

The second-generation, minimally invasive system for BAT, Barostim neo™, led to substantial systolic BP reductions, averaging 26 mm Hg at 6 months, that are comparable to the 21 mmHg and 26 mmHg reductions in the DEBuT trial at 3 months and Rheos Pivotal Trial at 6 months respectively [160,167]. Furthermore, 43 % of the resistant hypertensive patients achieved systolic

BPs <140 mm Hg by 6 months of therapy [117]. Additionally, Comparing with Rheos system, preliminary data reported by Hasenfuss et.al, at the European Society of Cardiology meeting (ESC 2011) showed that systolic BP decreased by 28.7 mmHg in 12 patients after 3 months of continuous unilateral right-sided BAT with a better safety profile [168,155].

Based on the preliminary data from the new generation system, it provided a better safety profile and a similar efficacy profile when compared with the Rheos system [157]. The implantation of the second-generation device is less invasive and might be more likely to convince physicians and patients for the implantation. As in pacemakers, the development of rechargeable batteries is desirable for the future [169]. Even patients who have undergone RDS with no success in BP reduction, they showed a better efficacy when BAT was provided [157]. In this regard, according to a preclinical study has been conducted by Lohmeier et.al, [146], they suggested a chronic influence of baroreflexes on renal sympathetic nerve activity resulting in an effect on renal excretory function which accounts for sustained reductions in BP.

Adverse Effects

Only post-procedural three complications occurred (pocket hematoma, self-inflicted wound complication, and device repositioning due to IPG discomfort) [166]. One system-related complication was reported, consisting of pain near the IPG [119]. One of the limitations of this study is lack of ambulatory BP measurement [166].

Conclusions

Successful treatment of hypertension is rendered critical nowadays. The burden of unsuccessful treatment of hypertension is not only health problem but also economic one. CKD is one of the most important fates of uncontrolled hypertension that will lead dramatically to End-Stage renal Disease (ESRD). From health perspective, the success in controlling hypertension before emerging chronic renal problems is more optimistic than putting the patient on the renal replacement therapy option. However, from an economic perspective, having the blood pressure of a patient been controlled even by using surgical treatment is still more reasonable than having the patient for years on renal replacement therapy. Our view matches well with the view of Geisler et.al, [170]. They indicated that RSD cost is $ 12,500 (one-time material and procedure cost; $ 8,000 to $ 15,000). They also reported that ESRD costs are $ 76,851 for diabetic patients; all others $ 66,844 (both per year; $ 53,935 to $ 89,882 and $ 45,159 to $ 79,350). Even the pharmacological treatment of hypertension costs about $868 (annually, $ 203 to $ 1,355) [170]. According to Geisler et.al, renal denervation reduced cardiovascular mortality by 30 % and all-cause mortality by 15 % compared with standard therapy over 10 years while increasing median survival from 17.07 to 18.37 years and quality-adjusted life expectancy from 12.07 to 13.17 quality-adjusted life-years [170].

We thought that surgical treatment of resistant hypertension, if approved in clinical setting, will eradicate this health problem and will open the door wide for other options to treat mild hypertension such as immunization against RAAS components.

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