Review

Drug Resistant Hypertension – No SIMPLE Way Out

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Key Words

Hypertension • Renal denervation • Blood pressure • Heart failure • Chronic kidney disease • Sleep apnea syndrome • Metabolic syndrome

Abstract

Hypertension poses growing challenge for health policy-makers and doctors worldwide. Recently published results of Symplicity-III trial (HTN-3), the first blinded, randomized, multicenter study on the efficacy of renal denervation for the treatment of resistant hypertension did not show a significant reduction of BP in patients with resistant hypertension 6 months after renal-artery denervation, as compared with controls. In this paper we review clinical and experimental studies on renal denervation. In order to identify causes of inconsistent results in renal denervation studies we look at basic science support for renal denervation and at designs of clinical trials.

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History of antihypertensive treatment

Hypertension poses growing challenge for health policy-makers and doctors worldwide. It has been estimated that 26% of the population was hypertensive in 2000 and this percentage is bound to increase to almost 30% by 2025 [1]. The history of hypertension is relatively short. In 1905, Korotkoff described a non-invasive, auscultatory method of determining systolic and diastolic blood pressure (BP) [2]. The discovery that high BP is correlated with an increased mortality dates back to the beginning of the 20th century. First assumptions were made in 1906, but clear epidemiological data was presented in 1939 by the Actuarial Society of America. While insurance companies quickly adopted this epidemiological data in their risk assessment protocols, it took some more time until it was widely accepted by the physicians [3, 4].

The early methods of antihypertensive treatment included a surgical sympathectomy, an invasive procedure based on the removal of thoracic, abdominal or pelvic sympathetic

ganglia. Results were not satisfactory and hypotensive effect was found only in 50% of the treated patients. Furthermore, the sympathectomy was associated with many adverse effects, including periprocedural death. Therefore, as soon as antihypertensive drugs were developed, the sympathectomy was abandoned [5-10]. First antihypertensives were hexamethonium and pentolinium. They were shown to significantly reduce arterial BP by inhibiting the sympathetic activity. However, again, due to multiple side effects, they have not become widely used [5, 10]. The road to safe and effective antihypertensive drugs has been long, paved with numerous moderately successful compounds, such as methyldopa or clonidine [11, 12]. The introduction of thiazide diuretics (1958), beta blockers (1973), calcium channel blockers (1981), angiotensin converting enzyme inhibitors (1982), and angiotensin receptor blockers (1995) marks big milestones in the search of efficient antihypertensive treatment [13].

Although many effective drugs have been developed, it is estimated that about 10% of patients do not respond with a sufficient reduction in BP [14]. Apart from that, some people do not adhere to the treatment regimen due to drugs' side effects, mental disability or medication phobia.

Renal denervation in drug-resistant hypertension

Drug resistant hypertension is defined as BP of over 140/90, despite the treatment with three different antihypertensive drugs, including diuretic in maximal tolerable doses. The precise number of patients diagnosed with drug resistant hypertension remains unknown, however, some studies estimate that it may reach about 10% [14]. It triggers the search for new, non-pharmacological therapies, such as stimulations of baroreceptors and renal denervation [15-18].

As early as in 1935, Page and Heurle described renal denervation. They found no significant effect of bilateral renal denervation in a 25-year old hypertensive woman suffering from severe essential hypertension and concluded that the results gave no ground for expecting that denervation in cases of essential hypertension was of therapeutic value [19].

The first study showing that percutaneous renal denervation is effective and safe in the treatment of drug resistant hypertension was published in 2009 in Lancet [20]. Since then, the efficacy of this method has been evaluated in various clinical settings, such as heart failure, chronic kidney disease and obstructive sleep apnea [21-24].

Early studies

Early studies presented encouraging results. First, HTN-1 (Symplicity -I), a non-blinded, non-randomized observational study showed that mean arterial pressure was significantly lower at 1, 3, 6, 9 and 12 months in patients who underwent the renal denervation in comparison to controls. The final report of a 3-year follow-up also confirmed the efficacy of the treatment [20, 25]. In that study, 45 patients diagnosed with drug resistant hypertension underwent the renal denervation, while five patients who were excluded from the denervation due to anatomical criteria served as a control group. It was followed by optimistic results of HTN-2 (Symplicity - II), which was a non-blinded, randomized study. It enrolled patients with office systolic BP of over 160 mmHg (or 150 mmHg and diabetes), despite antihypertensive therapy with three or more drugs. From the group of 106 enrolled patients, 52 were assigned to renal denervation and 54 were included in a control group. Six- and twelve-month follow-up showed that patients with renal denervation had significantly greater decrease in office arterial BP than controls [26, 27]. Further evidence for the efficacy of renal denervation in the treatment of hypertension came from other small studies. Namely, Mahfoud et al. showed that renal denervation may be beneficial for patients with moderate resistant hypertension defined as a systolic BP between 140 mmHg and 160 mmHg [28]. Besides, Lenski and collaborators found an increase in the quality of life three months after the renal denervation in patients with resistant hypertension [29].

However, the designs of HTN-1 and HTN-2 studies have raised many concerns. The lack of blinding and the lack of sham group have been highlighted as major limitations [30]. Furthermore, inclusion criteria were based on office blood pressures while it has been shown previously that in resistant hypertensive patients higher ambulatory blood pressure predicts cardiovascular morbidity and mortality, whereas office blood pressure has no prognostic value [31]. Moreover, it has been claimed that the criteria of resistant hypertension adopted in the HTN-1 and HTN-2 studies were not strict enough, and that the lack of a biochemical testing for compliance led to false diagnoses and enrollments [32]. In this context, Elmula and collaborators found that from the group of 18 patients who meet HTN-1 criteria of resistant hypertension and were referred by physicians for renal denervation, 12 patients did not fulfill the criteria of truly resistant hypertension and were excluded from the study because of undiagnosed primary aldosteronism, renal artery abnormalities and drug non-adherence. Furthermore, only 2 out of 6 patients who qualified for renal denervation showed a consistent decrease in BP [33]. All these objections were supposed to be addressed in the rigorously designed HTN-3 trial.

HTN-3 trial

Symplcity-III (HTN-3), a controlled, blinded, randomized study enrolled 535 patients treated in 87 US medical centers. It is currently the largest trial on renal denervation and it is the only study that includes sham-operated control group [34, 35]. At the enrollment, patients had office systolic BP of 160 mmHg or more, despite having been treated with maximal tolerable doses of 3 different hypotensive drugs, including a diuretic. Major exclusion criteria included inappropriate renal artery anatomy, renal failure and secondary hypertension [35]. Symplcity-III (HTN-3) showed that there was no significant difference in office systolic BP and 24h ambulatory BP between the controls and the renal denervation group at 6 months of a follow-up. For many, the results of HTN-3 trial came as a disappointment. The results made the experts verify highly optimistic statements and guidelines on the role of renal denervation in hypertension treatment. Scientists responsible for evaluation of Symplcity III results concluded: "a significant effect on systolic BP was not observed. Further evaluation in rigorously designed clinical trials will be necessary (...) to confirm previously reported benefits of renal denervation in patients with resistant hypertension" [34].

However, it is worth noting, that a subgroup analysis showed several non-significant differences between the denervation group and the sham procedure group, which could become significant with a longer follow-up and larger number of study participants. For example, there was a trend towards a better response in the subgroup of patients treated with aldosterone antagonists. Besides, HTN-3 subgroup analysis revealed differences between the races. There were 140 Afro-Americans(AA) and 394 non-Afro-Americans(non-AA) enrolled and randomized in the study. Researchers observed significant response to renal denervation only among non-AA. On the other hand, sham procedure induced greater reduction in SBP among AA than non-AA. Such data may suggest that the effects of renal denervation may depend on additional factors which should be considered when selecting patients for the procedure. Finally, the results of the HTN-3 study might be affected by technical issues, such as different level of experience of operators from 87 study centers or selection of a renal denervation device. These issues are especially important as no marker to confirm efficacy of renal denervation is available [36].

Renal denervation in other cardiovascular diseases

Heart failure

Heart failure results in renal hypoperfusion, which triggers the activation of the sympathetic nervous system, and leads to deterioration of the heart's pumping ability [37, 38]. Therefore, it was suggested that lesion of the neural connection between kidneys and central nervous system may be beneficial in heart failure [39].

As the results from animal studies were optimistic, [40] and HTN-1 and HTN-2 trials confirmed safety of the renal denervation, two small clinical trials, Symplicity – HF (Renal denervation in Patients with Chronic Heart Failure and Renal Impairment Clinical Trial) and REACH (Renal Artery Denervation in Chronic Heart Failure) have been launched. Early results from REACH study are promising. All patients (n=7) who underwent renal denervation showed improvement in terms of symptoms and six minute walk distance. Loop diuretic was reduced or stopped in 4 patients due to reduction in peripheral edema and there were no periprocedural complications [41].

Chronic Kidney Disease

Increased renal sympathetic activity is well-documented in chronic kidney disease [42]. Observational study performed in 15 patients with chronic kidney disease showed a significant decrease in mean BP and non-significant decrease in proteinuria, glycosylated hemoglobin and brain natriuretic peptide (BNP) levels. Furthermore, no deterioration in renal function was found, which suggests that lowered GFR should not exclude patients from renal denervation [23].

Sleep apnea syndrome

It has been suggested that renal denervation may be beneficial in patients with sleep apnea syndrome and hypertension. For example, Witkowski and collaborators found that 8 out of 10 patients undergoing renal denervation showed reduced severity of obstructive sleep apnea [21].

Metabolic syndrome

It has been shown that SNS plays a pivotal role in pathophysiology of metabolic syndrome [43]. Renal denervation gave a potential tool for restoring balance in sympathetic activity, glucose metabolism and BP [44]. Efficacy of renal denervation in the treatment of metabolic syndrome has been found in animal models [45] and in one study in humans. Namely, Mahfoud et al showed that renal denervation in hypertensive patients with metabolic syndrome improves BP values as well as glucose tolerance [46, 47].

Basic science support for renal denervation

Nervous system in BP control and etiology of hypertension

The significance of the nervous system in the regulation of the arterial BP was shown in the middle of nineteenth century by Bernard and Shiff [48, 49]. In the early 1970s, Guyton proposed a model in which arterial pressure in the long-term was determined by the kidneys regulating blood volume, according to the renal function curve describing the relationship between the renal perfusion and excretion of sodium and water. In this model, the role of the nervous system was limited to short-term control of BP [50-52]. Since then, the notion that the nervous system plays a role in the short-term regulation of BP has been widely accepted, in part due to the great popularity of magnificent physiology textbook for medical students by Guyton. However, recent clinical and experimental studies [20, 53-55] suggest that the role of the nervous system in the long-term regulation of the arterial BP and the development of hypertension may have been underappreciated [56-58]. Namely, it has been shown that chronic mechanic [59] and electric stimulation of baroreflex causes long-term lowering of arterial BP [53, 60-62]. Furthermore, a growing number of experimental studies reveal multiple alterations in the brain signalling systems in animal models of hypertension [63, 64]. Finally, the ablation of renal nerves has been found to lower arterial BP in both experimental [65] and clinical settings [20].

An increased activity of the sympathetic nervous system has been well-documented in many cardiovascular and metabolic diseases, including essential hypertension, obesity,

Fig. 1. Hypertensive effect of renal sympathetic nerves. Renal sympathetic nerves increase arterial blood pressure via peripheral (1) and neurogenic (2) mechanisms. 1. Renal sympathetic nerves stimulates the activity of the renin-angiotensin-aldosterone system. This promotes water and sodium reabsorption in the kidneys and increases total peripheral resistance. 2. Higher concentration of blood borne angiotensin II and sodium increases sympathetic activity via neurogenic mechanisms. ERSN - efferent renal sympathetic nerves; ARSN - afferent renal sensory nerves; Ang II - angiotensin II; CVOs - the circumventricular organs, CVOs neurons sense changes in the concentration of blood borne hormones and ions as they lack the blood-brain barrier; RVLM - rostral ventrolateral medulla, comprised of presympathetic neurons; NTS - nucleus of the solitary tract; IML - spinal cord intermediolateral nucleus; DH - spinal cord dorsal horn.

obstructive sleep apnea, heart failure, polycystic ovary syndrome, atrial fibrillation [66-73]. Although the increased activity of the sympathetic nervous system may be primary as well as secondary, the pharmacological inhibition of the sympathetic system has been proven to reduce cardiovascular mortality [74].

Renal nerves

Kidneys are innervated by efferent renal sympathetic nerves (ERSN) and afferent renal sensory nerves (ARSN) [75]. ERSN terminate in renal arterial vessels, renal tubules and cells of juxtaglomerular apparatus [76]. The sympathetic stimulation of juxtaglomerular cells leads to the activation of the renin-angiotensin-system and a subsequent increase in BP via multiple mechanism [76, 77] Furthermore, Ang II interacts with the circumventricular organs in the brain and the sympathetic ganglia, which further increases the sympathetic activity [76, 78-82], (Figure 1).

ARSN originate in kidney vasculature and have their synapses in the NTS in the medulla oblongata. It has been found that ischemia and kidney damage increase ARSN activity, which leads to the stimulation of the sympathetic nervous system and the increase in BP [82-89]. However, the role of ARSN in human hypertension is not clear as there is no method of selective and complete ARSN lesion.

Renal denervation

The mechanisms behind the therapeutic effect of renal denervation are not clear. A likely mechanism involves a decrease in renal sympathetic activity, which reduces the stimulation of β 1-adrenoreceptors on juxtaglomerular cells and α 1- adrenoreceptors on renal

tubules. This attenuates the secretion of renin and the tubular absorption of sodium, respectively [77, 90, 91]. In addition, renal denervation increases renal blood flow, mainly due to the interruption of sympathetic stimulation of renal arterial resistance vessels [92, 93]. In this context, the inhibition of ERSN overactivity has been found to prevent from an increase in fluid and sodium retention, a pathological sequence which often leads to hypertension and congestive heart failure [94].

Furthermore, several studies have shown that renal denervation reduces an overall sympathetic activity, i.e. diminishes the total body norepinephrine spillover and the activity of muscle sympathetic nervous system [68, 95, 96]. These may explain potential effects of renal denervation not only in hypertension, but also in wide spectrum of cardiovascular and metabolic diseases.

Renal denervation – experimental studies

The role of renal nerves and renal denervation in hypertension, heart failure and chronic kidney disease has been widely studied in many species, including rats, mice, miniature swine, sheep and dogs [44, 65, 97-103]. The experiments utilize several methodological approaches to renal denervation. The most common is surgical exposure of renal arteries and chemical coagulation of renal nerves with solution of phenol in absolute ethanol [101, 103]. Intrarenal delivery of guanethidine or 6-hydroxydopamine [104, 105], and electrical denervation has also been used [106]. Some conclusions on hemodynamic effects of renal denervation have also been drawn from experiments on kidney-transplanted animals [107].

It has been found that renal denervation lowers BP and delays the onset of hypertension in spontaneously hypertensive rats (SHR), Borderline hypertensive rat, New Zealand SHR, Stroke prone SHR [65, 68]. Furthermore, it has been shown that ablation of afferent sensory renal nerves prevents from the development of hypertension in animal model of CKD [108, 109]. In contrast, studies in hypertensive model of DOCA-salt sensitive rats and 1-clip Golblatt hypertension provided inconsistent results [68]. Animal studies suggest that the hypotensive effect of renal denervation is mostly due to an increased natriuresis [106, 110, 111]. Besides, Nozawa et al. showed that renal denervation in rats with myocardial infarction improved left ventricular ejection fraction, decreased level of BNP and increased urine output [40].

Conclusion

Recently published results of HTN-3 trial, the first blinded, randomized, multicenter study on the efficacy of renal denervation for the treatment of resistant hypertension did not show a significant reduction of BP in patients with resistant hypertension 6 months after renal-artery denervation, as compared with the control. Certainly, a lesson learned from renal denervation studies should encourage the inclusion of a sham-operated group as controls in interventional cardiology trials.

It is worth noting, however, that while Symplicity III study showed that renal denervation does not lower BP in hypertensive patients receiving maximal tolerable doses of 3 different hypotensive drugs, the study did not negate the hypotensive effect of renal denervation. Additionally, HTN-3 trial proved that renal denervation is not associated with significant side effects. Currently, there is no reason to recommend the use of renal denervation as a routine procedure in drug resistant hypertension. Further, better designed studies than HTN-3 are needed to establish the role of renal denervation as a treatment option in selected groups of hypertensive patients [17,112].

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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