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REVIEW

Are We on the Path to Solve the Enigma of Resistant Hypertension: Renal Sympathetic Denervation

Vjekoslav Gerc, Marko Buksa
Clinic for Heart Disease, Clinical Center of University of Sarajevo, Sarajevo, Bosna and Herzegovina

Renal sympathetic denervation (RSD) opens new perspectives and possibilities not only in the treatment of resistant hypertension but also of other cardiometabolic diseases. In patients with hypertension, it has been demonstrated that activity of the sympathetic nervous system correlates with grade of hypertension. Decreasing sympathetic activity using RSD significantly reduces blood pressure in resistant hypertension. It is too early to say a definite opinion about appropriateness of this method in the treatment of resistant hypertension, because there are not great studies with huge number of the patients. After we get and evaluate these results through a longer span of time, only than we shall know what is the role of RSD in the treatment of resistant hypertension and other cardiometabolic conditions related to increased function of the sympathetic nervous system, such as heart failure, diabetes mellitus, obstructive sleep apnea, renal disease with microalbuminuria and macroalbuminuria. Key words: resistant hypertension, sympathetic denervation.

Corresponding author: prof. Vjekoslav Gerc, MD, PhD. E-mail: orinoko@bih.net.ba

1. INTRODUCTION

Unlike the other risk factors of cardiovascular diseases, arterial hypertension has got a special position. Today it's known that arterial hypertension is one of the most important health problems, maybe the most important one which implicates early disease, disability and mortality in adult population. According to its characteristics, essential hypertension has assumed the features of the biggest non infectious epidemic of the 21st century. According to great *Global Burden of Disease Study* in 2010, 9.4 million of people in the world died because of hypertension (1).

Hypertension treatment was effective during a few last decades thanks to very impressive palette of antihypertensive medicaments. However, although when a few drugs are administered, the target values of blood pressure are not reached in some patients. In these cases we talk about resistant hypertension. In the latest guidelines for the management of hypertension issued by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC), resistant hypertension is defined as failure to achieve a blood pressure (BP) goal of <140/90 mm Hg, despite treatment with ≥3 different antihypertensive medication classes at a maximally tolerated dose and, including a diuretic (2). Nowadays it is considered that prevalence of resistant hypertension is 5 to 30% (3, 4, 5, 6). Resistant hypertension is associated with an increased risk of cardiovascular events, including myocardial infarction, stroke, congestive heart failure, and chronic kidney disease (7, 8, 9). Besides, there is often decreased stress tolerance in the patients with resistance hypertension, and at the same time they suffer from anxiety and depression. Quality of life of those patients is decreased significantly as well as their quality of sleep. Also, with the time, cognitive dysfunctions develop. Resistant hypertension has a substantial impact on many areas of everyday life, including attitudes, functional abilities, and interpersonal relationships (10). In these patients, one should consider new therapeutic options, because their arterial blood pressure can't be normalized by already used drugs.

2. CENTRAL ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOPHYSIOLOGY OF RESISTANT HYPERTENSION

Man is exposed to a fast way of living and, at the same time, to the chronic hyperactivity of the sympathetic nervous system with more or less stress, which results in serious consequences. Sympathetic overactivity is during long period associated with arterial hypertension, reduced renal function, left ventricular hypertrophy, heart insufficiency, arrhythmia, obstructive sleep apnea syndrome (OSA), insulin resistance and diabetes mellitus. Relationship between increased activity of the sympathetic nervous system and arterial hypertension is of a particular importance (11).

Activity of the sympathetic nervous system in patients with hypertension is proved to correlates with the degree of hypertension. The sympathetic nervous system overactivity involves the kidney and increases progressively and parallel with hypertension severity stages (12).

In other words, the higher value of arterial hypertension is measured, the more activity of the sympathetic nervous system is found. The kidneys have a very important role in long term regulation of blood pressure. The kidney is an organ where efferent sympathetic impulses are active, but the activity of the sympathetic nervous system is also mediated by the afferent nervous fibers.

Efferent impulses of sympathetic nervous system make a greater resistance in kidneys, reducing of blood flow in kidneys, increasing of reabsorption of sodium and water, and at the same time they stimulate production of renin.

It leads to increasing of blood pressure and creates a vicious circle: development of renal ischemia activates renin-angiotensin system (RAS) and, through the oxidative stress, it activates the afferent sympathetic renal fibers which go from kidneys to central nervous system, and continue to activate sympathetic nervous system (13, 14).

Pathophysiological concept that high blood pressure can be lowered if overactivity of the sympathetic nervous system is reduced is not recent information. In the first half of the 20th century when there were no antihypertensive drugs available, surgical sympathectomy was used as a last resort.

But this procedure was not used in everyday practice because of high peri- and postoperative mortality, as well as because of other adverse events such as postural hypotension, functional disorder of the bladder and intestines, anhidrosis, perioperative death, stroke, myocardial infarction, paraplegia and spinal cord injury.

At the same time, the intervention was unpleasant for patient and the success of the intervention could not be estimate. In the 50s of the past century, the interest for this procedure declined when reserpine was discovered. The discovery of diuretic chlorothiazide in 1957 and its use in the therapy of hypertension caused the surgical sympathectomy to become definitely obsolete.

3. RENAL SYMPATHETIC DENERVATION

Nowadays there is an alternative access to drug treatment in resolving of resistant hypertension using new access and method. Percutaneous transluminal radiofrequency sympathetic denervation (RSD) of the renal artery for resistant hypertension aims to disrupt neurogenic reflexes involved in blood pressure control. Intervention is performed under local anesthesia. The patient will receive an adequate premedication in term of analgesics (e.g. morphine 5-10 mg), as well as sedation (e.g. midazolam 1-3mg). Unfractionated heparin is given intravenously at a dose aimed at reaching an activated clotting time (ACT) of > 250 seconds. Besides, dosed 100 μg nitroglycerine must be introduced through the guiding catheter before the procedure to avoid vasospasm (15). Device consists of a catheter with tip connected to the radiofrequency generator (50 Hz, 5–8 W). Catheter-based renal denervation is a minimally-invasive procedure in which doctors use a catheter, inserted through the femoral artery in the groin, to send radio waves that burn away nerve tissue around the kidney arteries. The catheter is connected to a generator which delivers low-power radiofrequency energy in 2-minute applications to each renal artery at 4–6 points along its length, in a spiral pattern. The catheter tip requires multiple rotations and application of further radiofrequency energy in a spiral pattern to ensure all nerves are evenly exposed. Continuous temperature monitoring assures that the power unit detects any overheating of the arterial wall and the application of energy interrupted immediately. Then it should be repeated on the contralateral kidney. The intervention lasts about 45 min. Next day, the patient will be discharged. In Symplicity HTN-1 as well as in Symplicity HTN- 2 studies, Medtronic Symplicity catheter system is used. Currently, more than 50 companies are developing renal denervation systems. Techniques beyond radiofrequency include: ultrasound, “external ultrasound”, direct drug delivery/pharmacological injection system, microwave. Single electrode based system is now considered “first generation”. Use of multielectrode devices appear to improve outcomes and increased safety.

4. INDICATIONS AND CONTRAINDICATIONS FOR RENAL SYMPATHETIC DENERVATION

In the meantime, International Society of Hypertension and European Society of Cardiology have published guidelines for patient selection and also the intervention itself (16, 17). Indications for renal denervation in patients with resistant hypertension are: a) on at least 3-4 antihypertensive drugs; and b) blood pressure under treatment >140/90 mmHg. Anatomically favorable factors are following: one renal artery supplying each kidney length of main renal artery >20 mm and renal artery diameter more than 4 mm (15).

Contraindications for renal sympathetic denervation are the following: previous renal artery intervention (balloon angioplasty or stenting), evidence of renal artery atherosclerosis (defined as a renal artery stenosis >50%), presence of multiple main renal arteries in either kidneys or main renal arteries of less than 4 mm in diameter or less than 20 mm in length and estimated glomerular filtration rate <45 ml/min per 1.73m (16).

5. CLINICAL STUDIES

Clinical studies of this therapeutic option, show that systolic pressure decreases significantly and in average by 25 to 30 mmHg and diastolic by 10 to 15 mmHg and that antihypertensive effect is lasting at least for two years. Symplicity HTN-1 was the first great study where the procedure of renal sympathetic denervation was used (18). In this study 153 patients (mean age 58+_9 years) with severe resistant hypertension (office systolic blood pressure _>160mmHg with at least three or more antihypertensive medications, including a diuretic) were included. Baseline office systolic blood pressure/diastolic blood pressure values were 177/101 mmHg with 5.1 antihypertensive drugs on average. RSD was achieved using a radiofrequency ablation catheter inserted through the femoral artery. After RSD was performed and controls were made after 1, 3, 6, 9, 12, 18 and 24 months, blood pressure values were lower by 20/10, 24/11, 25/11, 23/11, 26/14 and 32/14 respectively. Renal noradrenaline spillover was found to be reduced by 47% thereby demonstrating the effectiveness of sympathetic renal fibers ablation. Noradrenaline spillover is a marker of sympathetic overactivity. Measurements of noradrenaline spillover may help with estimating the activity of the efferent renal sympathetic nerve (19, 20, 21). Besides, it's important that the effects of denervation persist at least until 24 months. The intervention was free of complications in 97% of patients (149 of 153). Neither reported adverse effects associated with hemodynamics, electrolytic abnormalities, or reducing of the renal function. Together with the decreasing of blood pressure, improvement in health-related quality of life was observed (22).

The Symplicity HTN-2 trial is an international, multi-center, prospective, randomized, controlled study of the safety and effectiveness of renal denervation in patients with treatment-resistant hypertension. Patients with baseline systolic blood pressure of 160 mmHg or more were randomly assigned to renal denervation with previous treatment or to maintaining previous treatment alone (control group). A group of 106 patients were randomized to renal denervation (52) or control (54) groups. Office based blood pressure measurement in the renal denervation group decreased by 32/12 mmHg, whereas they did not differ from baseline in the control group. Between group differences in blood pressure at 6 months were 33/11 mmHg. At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mmHg or more, compared with 18(35%) of 51 controls (23).

6. "NON DIPPING" AND "REVERSE DIPPING"

It's important to emphasize that in context of Symplicity HTN-1, Symplicity HTN-2 trial and RSD, activity of the sympathetic nervous system is significantly decreased in both non dipping and reverse dipping patients. Today it is known that, during the night, blood pressure doesn't decrease in patients so called *non dippers*, and the risk of cardiovascular death increases by 2,5 in relation to *dippers*, what is demonstrated with help of ambulatory blood pressure measurement (ABPM). The risk is still higher *in reverse dippers*, in patients who suffer from increasing of blood pressure during the night. In these patients risk of lethal cardiovascular event is four times higher in relation to *dippers* (24). RSD decreases activity of the sympathetic nervous system, as mentioned above. Because of that it's expected that renal denervation will be effective in *non dippers*.

Consequently, RSD is safe and effective in reducing office blood pressure, home blood pressure, and 24 h blood pressure in patients with drug resistant hypertension. The positive effect persisted during the period of 36 months. However, blood pressure did not decrease immediately after the RSD. That means that RSD changes neurohumoral control of excretion of water and salt and blood pressure, accordingly. RSD did not cause any damage of the vessel wall. No serious adverse events related to the procedure were reported either in Symplicity HTN-1 or in Symplicity HTN-2 trial.

7. SYMPLICITY HTN-3 TRIAL

Symplicity HTN-1 and HTN-2 have shown sustained blood pressure reduction at 24 months. It is not a long period when considered essential hypertension to be a chronic disease with permanent medical treatment. And after all, the crucial question whether that effect of decreasing blood pressure will continue and how long. Maybe Symplicity HTN-3 trial will solve the dilemmas. This trial is a multicentre, prospective, single-blind, randomized, and controlled study. In this study, 530 patients aged 18 to 80, with average systolic blood pressure ->160 mmHg will participate. The patients will be on stable medication regimen of full tolerated doses of -> 3 antihypertensive medications, with one being a diuretic (25).

8. ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN RENAL DENERVATION IN CONGESTIVE HEART FAILURE

Today it is well known that disturbed neurohumoral system has a key role in the process of chronic heart failure. In patients with heart failure several neurohumoral systems are activated, especially the sympathetic nervous system and renin-angiotensin system (RAS). The mentioned systems contribute to deterioration of heart failure. The long-term activation of neurohormonal systems has a toxic effect upon heart failure. Catecholamines and angiotensin II have negative effect upon heart failure **in**. Activation of RAS can produce peripheral edemas and increased retention of sodium and water. At the same time, the activation of RAS contributes to hemodynamic abnormalities, leading to constriction of peripheral arteries and veins. The longer the period of heart failure, the higher is the level of noradrenalin. The patients with the highest values of noradrenalin have the worst perspective (26). Noradrenalin can cause dysfunction and death of cardiac myocytes. Increasing of cyclic AMP, noradrenalin can rise concentration of intracellular calcium which, if prolonged, causes the state of calcium overload and cell necrosis (27). Following prolonged activation of the sympathetic nervous system, the cellular pathways that respond to and mediate the effects of catecholamines are altered in heart failure. Activation of the sympathetic nervous system increases heart rate, which negatively influences upon further development of chronic heart failure. Further effects of the intensified secretion of angiotensin and aldosterone together with simultaneous increasing of already mentioned heart rate, have negative effects on the heart. The increased renal afferent sympathetic activity contributes, on its part, to worsening of the pathophysiology mechanism, so making RSD to be one of therapeutic options in management of heart failure. A study which enrolled patients with resistant hypertension who were treated using RSD recorded not only significant decreasing of systolic and diastolic blood pressure, but also significant regression of the left ventricular hypertrophy (28). Results of this study have very important prognostic implications in high risk patients with resistant hypertension. In another study involving patients with resistant hypertension, RSD led to significant decrease of systolic and diastolic blood pressure. At the same time, the number of premature ventricular contractions was significantly decreased. The total number of premature supraventricular contractions was also significantly decreased after RSD (29). Symplicity HF Study (Renal Denervation in Patients With Chronic Heart Failure) will answer the question how effective RSD is in patients with heart failure. The study will enroll approximately 40 adult subjects with chronic heart failure (NYHA II-III) and renal impairment and ejection fraction less than 40% with optimal medical therapy.

9. INFLUENCE OF RENAL DENERVATION OF THE SYMPATHETIC NERVOUS SYSTEM ON REGULATION OF GLUCOSE AND DIABETES

It's not rare that hypertension is associated with damaged glucose tolerance, type 2 diabetes, obesity or increased values of cholesterol. In patients with both hypertension and type 2 diabetes increased activity of the symphatetic nervous system is observed (30). Studies show that people with sympathetic reactivity are inclined to develop insulin resistance with increased glucose values (31). Just because of that, resistant hypertension is discovered in great number of patients with diabetes (32). Obesity, hypertension and insulin resistance have common pathophysiology mechanism. Insulin resistance is found in both thin and fat people suffering from hypertension which means that insulin resistance is related to the basic determinants of blood pressure. Consequently, adrenergic nervous system plays a crucial role in glucose and insulin metabolism regulation, and insulin resistance may represent an important determinant of the adrenergic activation detectable in cardiometabolic disease (33). As mentioned above, obviously decreasing of sympathetic activity with RSD can improve insulin sensitiveness and glucose metabolism. Two studies have observed changes in insulin resistance following renal denervation for the treatment of resistant hypertension (34, 35). Another meta-analysis shows that ablation of efferent and afferent sympathetic renal nerves improves glucose metabolism, reducing the incidence of glucose intolerance, fasting hyperglycemia and diabetic state in resistant hypertensive patients (33).

The effect of RSD was assessed in a sub-study of the Symplicity HTN-2 trial in 37 patients and 13 controls. Three months after the procedure, the authors observed a significant decrease in fasting glucose, insulin, and C-peptide levels. Oral glucose tolerance and the sensitivity to insulin measured by the HOMA-IR (homeostasis model assessment-insulin resistance) were both significantly improved compared to the control group where no significant changes were observed (36). Also, it was demonstrated that the level of glycosylated hemoglobin (HbA1c) decreased after RSD was performed.

In another sub-study of the Symplicity HTN-2 trial, where ten patients with resistant hypertension, obstructive sleep apnea, and metabolic syndrome were included, evident significant decreasing of the office blood pressure by 34/13 mmHg, together with improvement of the glucose homeostasis, as well as reduction in severity of the obstructive sleep apnea were demonstrated after 6 months 37. Useful effects of RSD effects upon metabolic syndrome can be explained in the following way: inhibition of central sympathetic tonus, reduced noradrenalin release, better perfusion of skeletal muscles, which is achieved reducing alpha adrenergic tonus that gives rise to enlarged glucose uptake. Other mechanisms such as inhibitor effect on renin-angiotensin system, reduced glucogenesis and reduced secretion of glucagon are included.

The role of renal denervation in improving of insulin resistance will be topic of DREAMS (Denervation of the Renal Artery in Metabolic Syndrome) study. This study is an observational study, with the aim to investigate the effect of renal denervation on changes in insulin resistance and blood pressure in patients with obesity related hypertension.

10. EFFECT OF RENAL DENERVATION UPON OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea, often considered a cause of resistance in patients with essential hypertension, may also be a consequence of increased central sympathetic tone (38, 39). Obstructive sleep apnea syndrome is associated to increasing incidence of sudden cardiac death, heart failure and ischemic heart disease (40, 41). In these patients with dream disturbance, during the night, very strong activity of the sympathetic nervous system is present, which could be a cause of arterial hypertension. Because of that, influence of renal denervation on development and clinical features of obstructive sleep apnea syndrome has been studied. Witkowski studies series of patients with sleep apnea and pre and post renal denervation for resistant hypertension suggesting that denervation and/or blood pressure reduction alone reduces the frequency of apneic–hypopneic episodes. Apnea/hypopnea index was reduced from an average of 16.9 to 4.5 episodes per hour, with a concomitant decrease in oxygen desaturation index (37).

11. CONCLUSION

RSD is a new method in treatment of resistant hypertension. This procedure opens new perspectives and possibilities in management of resistant hypertension. Perhaps one day it will be used for treatment of grade 1 and grade 2 hypertension, which would be important not only from medical aspect, but from economical one, also. However, it is too early to define final attitude towards appropriateness of this method in treatment of resistant hypertension, because we still do not have results of huge studies with great number of patients. After we get and evaluate these results through a longer span of time, only than we shall know what is the role of RSD in the treatment of resistant hypertension and other cardiometabolic conditions related to increased function of the sympathetic nervous system, such as heart failure, renal disease with microalbuminuria and macroalbuminuria, diabetes mellitus, obstructive sleep apnea or intolerance to drugs. Current studies should answer a few questions, such as what are long-term consequences upon kidney function after RSD, and others. Also, evaluation of eGFR (glomerular filtration rate) should be done in significantly greater number of patients than before. We should get the answer concerning effect of RDS on cardiovascular morbidity and mortality through longer period. Another important question is whether re-innervation develops, in other words, whether regeneration of afferent and efferent fibers arise. The problem why 23% of patients did not respond to RSD treatment expects the answer. Finally, there is an important question if RSD can be repeated in the patients with whom we did not succeed on the first time to burn the afferent and efferent fibers. Resistant hypertension is still actual and complicated problem, despite of great number of antihypertensive drugs which block the sympathetic nervous or renin-angiotensin system on a few levels, but without significant effects. However, it must be emphasized that the studies with RSD involving relatively small number of patients and sometimes without a control group, speak in favor that renal denervation, may solve the problem of resistant hypertension.

CONFLICT OF INTEREST: NONE DECLARED.

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