Review Article

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Is Renal Denervation Effective in Treating Resistant Hypertension?

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Resistant hypertension is diagnosed in patients whose blood pressure target is unmet despite the use of three or more antihypertensive medications. Systemic sympathetic hyperactivation is associated with the development of resistant hypertension. As the kidney is largely pervasive of the sympathetic nervous system renal denervation procedure was developed to control blood pressure by attenuating the renal and systemic sympathetic hyperactivity. Renal denervation is a minimally invasive procedure that uses radiofrequency or ultrasound energy waves to reduce the activity of the renal artery nerves. Previous clinical trials have shown conflicting results regarding the efficacy of the procedure. Symplicity HTN-1 and -2 trials showed effective blood pressure lowering results in the renal denervation group with a good safety profile. However, the Symplicity HTN-3 trial showed no difference in blood pressure lowering effect between the renal denervation and control Sham procedure groups. Notwithstanding, some recent clinical trials with Sham control and meta-analysis showed clinical benefits of renal denervation. Other clinical benefits of renal denervation include glucose control, cardiovascular protective effect, reduction of obstructive sleep apnea, and neuralgia control. A subset of patients with satisfactory blood pressure control response to the procedure may experience improved glucose control due to the overall reduced sympathetic activity and insulin resistance. Sympathetic activity control after renal denervation has cardioprotective effects, especially for those with arrhythmia and left ventricular hypertrophy. Also, renal denervation could be helpful in renal-origin pain control. Renal denervation is an effective, safe, non-invasive procedure with many clinical benefits beyond blood pressure control. Further development in the procedure technique and selection of target patients are needed for wider clinical use of renal denervation in resistant hypertension.

Key Words: Hypertension, Renal denervation, Cardiovascular disease, Glucose control

INTRODUCTION

Resistant hypertension is a condition in which the patient's blood pressure target is unmet despite the use of three or more antihypertensive medications including diuretics. It is estimated to affect approximately 8% of hypertensive patients. The prevalence of resistant hypertension has nearly doubled between 2005 and 2008 compared to 1998 and 2004[1)]. In the case of resistant hypertension, it is necessary to check the patient's antihypertensive medication compliance. According to a clinical study that measured the urine antihypertensive drug concentration level to objectively check the patient’s medication compliance, 28.8% of the patients had poor compliance with antihypertensive medication.

Also, 23.5% of patients who were considered for renal denervation due to uncontrolled hypertension had poor compliance with antihypertensive medications[2]. In situations where it is difficult to accurately assess medication compliance the prevalence of resistant hypertension can increase up to 30%. Therefore, even though the options for antihypertensive medication have increased resistant hypertension remains a serious challenge for nephrologists.

The first surgery to remove the autonomic nerve from the human blood vessel was performed by Jaboulay in the late 19th century and surgery to remove the sympathetic nerve from the kidney for treatment of severe pain due to hydronephrosis has been attempted since the 1920s[3]. Since the 1930s, renal denervation surgery has been performed on young females with malignant hypertension which was uncontrolled with medication and a decrease in blood pressure has been confirmed[4]. However, surgical nerve block has not been widely performed due to the side effects of autonomic nerve ablation which include irreversible impotence, urinary incontinence, and orthostatic hypertension.

The association between systemic sympathetic activation to the progression of resistant hypertension is the theoretical background of renal denervation[5,6]. The kidney is an organ largely pervasive of the sympathetic nervous system and is connected to the central nervous system, which activates the systemic sympathetic nervous system when the effective circulating plasma volume is insufficient. In cases of hypotensive bleeding, hypoxia, hypercapnia, cardiac tamponade, and carotid baroreceptor unloading the kidneys suppress natriuresis by various stimuli without affecting the glomerular filtration rate. Conversely, in situations of atrial stretching, vascular volume overload, and stellate ganglion stimulation situations natriuresis is increased. All of these sympathetic responses can be blunted or eliminated by neural denervation[5].

The use of renal denervation procedures in clinical practice began in the late 2000s when catheter procedures were developed[7]. It mainly uses radiofrequency energy or ultrasound waves, but neurotoxin injection is also performed. A catheter is usually injected through the femoral artery to the renal artery, placed in the area with a diameter of 3 to 8 mm, and radiofrequency energy is given targeting to reach the adventitia. This procedure is commonly repeated 4 to 6 times by an experienced physician for effective renal denervation[8].

Clinical results of renal denervation for resistant hypertension

Symplicity HTN-1, 2, 3 studies

The 'Renal Denervation in Patients with Uncontrolled Hypertension (Symplicity HTN)' study is a multicenter, randomized trial that evaluated the efficacy of renal denervation in patients with resistant hypertension. In the 'Symplicity HTN-1' trial, 153 patients with systolic blood pressure ≥ 160 mmHg and resistant to three or more antihypertensive drugs including diuretics received renal denervation. After 24 months reduction in 32 mmHg of systolic blood pressure and 14 mmHg of diastolic blood pressure was observed[9]. Additional reductions in systolic blood pressure of 32.0 mmHg and diastolic blood pressure of 14.4 mmHg were observed after 3 years of follow-up[10]. Although this study showed that renal denervation effectively reduced both systolic and diastolic blood pressures and had few complications, the limitation of the study was that there was no control group. Therefore, researchers from Austria, Europe, and the United States conducted a similar study titled the 'Symplicity HTN-2' trial which included a control group[11]. A total of 106 resistant hypertension patients were randomized into a 1:1 ratio and 52 patients underwent renal denervation while 54 patients in the control group were treated with medication. After 6 months, the renal denervation group showed a 33 mmHg decrease in systolic blood pressure while that in the control group was 11 mmHg. The renal denervation procedure had almost no complications. In 2014 the 'Symplicity HTN-3' trial, centered in the United States, included 535 patients and compared the efficacy of the renal denervation procedure to the Sham procedure[12]. Unlike previous trials there was no difference in the reduction of both office systolic blood pressure (-14 mmHg in the renal denervation group vs. -12 mmHg in the control group, p=0.26) and ambulatory blood pressure monitoring (-6.75 mmHg in the renal denervation group vs. -4.79 mmHg in the control group, p=0.98) between the two treatment groups. This study was more reliable than previous studies due to the larger number of enrolled patients, randomization of patients into procedure and control groups, and inclusion of 24-hour blood pressure measurements.

Other studies

A meta-analysis of 15 randomized controlled trials found no significant clinical benefits of renal denervation on resistant hypertension. There was no significant difference in both systolic blood pressure and ambulatory blood pressure monitoring between the renal denervation and control groups[13)]. However, Ahmad et al. analyzed 7 larger trials totaling 1,328 patients including the Symplicity HTN-3 trial, and found that the renal denervation group showed significantly higher blood pressure lowering effect including office systolic blood pressure of -5.86 mmHg, diastolic blood pressure of -3.63 mmHg and ambulatory blood pressure monitoring of -1.85 mmHg, respectively ($p<0.001$)[14)].

A Japanese study that compared 67 patients in the renal denervation group and 65 patients in the Sham treatment control group showed no significant difference in systolic blood pressure between the two groups after 3 months (-8.7 mmHg vs. -6.9 mmHg, $p=0.488$)[15)]. However, the Global Symplicity Registry, which included a total of 102 resistant hypertensive patients including Korean patients, showed that the renal denervation group had a reduction in systolic blood pressure of 32.5 mmHg without significant difference between the diabetic and non-diabetic patients[16)]. Also, Mahfoud et al. analyzed 80 patients with resistant hypertension over 36 months of which 38 patients in the treatment group received radiofrequency renal denervation and 42 patients in the control group received Sham treatment. After 36 months even though the number of antihypertensive medications in use was the same between the two groups, there was a significant reduction in the systolic blood pressure confirmed by ambulatory blood pressure monitoring (-18.7 mmHg vs. -8.6 mmHg, $p=0.0039$). In particular, significant reductions in both morning systolic (-11.0 mmHg) and diastolic (-11.8 mmHg) blood pressures were found. The authors suspect this would be an important factor in reducing cardiovascular complications[17)]. Although this study enrolled only a small number of patients and had a short observation period, it provides evidence that renal denervation may be effective in resistant hypertension.

Benefits of renal denervation beyond refractory hypertension

Diabetes mellitus control effect of renal denervation

It is generally known that sympathetic nerve activity is increased in diabetes mellitus (DM) and hypertensive DM patients have significantly higher sympathetic nerve activity[18)]. Inflammatory changes, oxidative stress, and inhibition of vascular smooth muscle cell apoptosis due to sympathetic hyperactivity are associated with insulin resistance and cardiovascular complications in diabetic patients. Therefore, inhibition of sympathetic nerve activation by renal denervation can reduce insulin resistance, prevent DM, and have a cardiovascular protective effect. According to the study by Mahfoud et al., in patients who received renal denervation, there was a significant decrease in both insulin (20.8 to 9.3 IU/mL, $p=0.006$) and C-peptide (5.3 to 3.0 ng/mL, $p=0.002$) levels respectively. After 3 months, homeostasis model assessment–insulin resistance decreased from 6.00.9 to 2.40.8 ($p=0.001$). Also, the post-prandial 2-hour glucose level was significantly reduced by 27 mg/dL ($p=0.012$)[19)]. Another study by Witkowski et al. showed a reduction in glycated hemoglobin A1C level from 6.1% to 5.6% ($p<0.05$) in renal denervation patients[20)]. However, as the degree of sympathetic hyperactivity or insulin resistance varies from patient to patient renal denervation may not be effective in blood sugar control in all patients. It may be helpful in a subset of patients who show good results in blood pressure control after renal denervation.

Reduction in obstructive sleep apnea after renal denervation

Obstructive sleep apnea (OSA) is associated with hypertension and is also known to cause resistant hypertension due to sympathetic hyperactivity. Therefore, it is recommended to check for the presence of OSA before treatment of resistant hypertension[21)]. OSA is a risk factor for many cardiovascular diseases such as arrhythmia and left ventricular hypertrophy, which can cause vascular endothelial dysfunction and progression of arteriosclerosis due to inflammatory reactions. Witkowski et al. performed renal denervation in 10 patients with OSA and at 6 months both systolic and diastolic blood pressure significantly decreased by 34 mmHg and 13 mmHg (p<0.01)[20]. The apnea-hypopnea index decreased significantly from 16.3 to 4.5 (p=0.059) and although there was no statistical significance sleep apnea symptoms improved along with the blood pressure reduction effect. As OSA causes excessive sympathetic hyperactivation during the day resulting in hypoactivation of sympathetic nervous response during the night even when there is hypoxia, renal denervation may be effective in improving OSA and cardiovascular complications associated with OSA.

Cardiovascular effects of renal denervation

When blood pressure and heart rate increase due to sympathetic activation left ventricular hypertrophy commonly occurs and is closely related to cardiovascular mortality. If hypertension persists, left ventricular hypertrophy occurs and left ventricular hypertrophy aggravates hypertension in a vicious cycle resulting in resistant hypertension[22]. Therefore, treatment of resistant hypertension is important to prevent cardiovascular complications.

A few studies analyzed the effect of blood pressure control with renal denervation on left ventricular hypertrophy suppression in resistant hypertension patients. Pisano et al. reviewed 15 studies and found that there was low-certainty evidence that renal denervation had little or no effect on the risk of myocardial infarction, ischemic stroke, unstable angina, or hospitalization. However, there was moderate-certain evidence that renal denervation may improve 24-hour ambulatory blood pressure monitoring and office diastolic blood pressure[23]. A study by Brandt et al. compared 46 bilateral renal denervation patients with 18 control patients and found that the renal denervation group had a reduction in both systolic and diastolic blood pressures by 27.8 mmHg and 8.8 mmHg after 6 months, respectively. Also, there was a significant decrease in the left ventricle mass from 47.0 m^2 to 44.7 m^2 (p<0.001)[24]. Another study by Tsioufis et al. evaluated left ventricle mass after renal denervation in 11 patients with resistant hypertension and the study results show that 70.6% of patients had a decrease in left ventricular size by at least one stage after 24 months[25]. Also, in the animal model of resistant hypertension there was more significant suppression in the ventricular fibrosis after sympathectomy compared to the control group where antihypertensive agents were used for blood pressure control[26].

Studies evaluating the cardiac function of congestive heart failure patients after renal denervation are rare, but Hopper et al. performed renal denervation on 39 patients with left ventricular ejection fraction <40% and followed up on cardiac function for 12 months. After 12 months, the N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) significantly decreased from 1,530 ng/mL to 1,428 ng/mL (p=0.006), and the 120-minute glucose tolerance test also decreased from 201.6 mg/dL to 178.2 mg/dL (p=0.026). However, there was no difference in glomerular filtration rate and left ventricular contractility measured using the ejection fraction (28 vs. 29%, p=0.536)[27]. There is a possibility that heart failure may worsen after 12 months, so maintenance of heart function itself may confirm the effect of renal denervation on heart function preservation. Yet, observational studies with longer follow-up duration are necessary.

Effects on kidney function and blood pressure control in advanced CKD

It is difficult to find evidence that renal denervation preserves or improves the glomerular filtration rate. However, many studies show that there is no worsening of renal function and increased risk of chronic kidney disease after the procedure[28-30].

Although there is a lack of data on large patient populations there are studies that confirmed a decrease in blood pressure after renal denervation in moderate to severe chronic kidney disease patients. According to the study by Hering et al., when renal denervation was performed on 15 patients with an average estimated glomerular filtration rate of 31.2 mL/min the systolic blood pressure decreased by 25 mmHg and 32 mmHg after 3 and 6 months (p<0.01). Also, there was no impairment in kidney auto-regulation and electrolyte levels. However, hemoglobin levels tended to gradually increase (p=0.08)[29]. Ott et al. confirmed the effectiveness of renal denervation in treating hypertension in 6 hemodialysis patients. After 6 months, the systolic blood pressure decreased by 20 mmHg (p=0.043) and diastolic blood pressure decreased by 11 mmHg (p=0.043)[30]. Therefore, renal denervation can be considered in cases of refractory hypertension unresponsive to medications, even in moderate to severe chronic kidney disease patients.

Renal denervation for neuralgia

Attempts to reduce pain through removal of sympathetic nerves have been made since the early 1920s. Recently renal denervation has been performed in an attempt to reduce pain in patients with hematuria-loin pain syndrome and polycystic kidney disease and has shown satisfactory results[31-33]. Currently, renal denervation is not recommended as the first line for pain control, however may be attempted to control renal-origin pain such as polycystic kidney disease by reducing the sympathetic nerve activity of the kidney.

Future perspectives of renal denervation

Renal denervation has shown some satisfactory clinical outcomes, but data regarding its long-term effects are still insufficient for clinical application. In 2022, the Thailand Society of Nephrology established a guideline for renal denervation for the treatment of hypertension[34]. The guideline recommends considering renal denervation in cases of refractory hypertension unresponsive to conventional antihypertensive treatments and may be beneficial for a subset of resistant hypertension patients with cardiovascular complications. However, based on the results of previous clinical trials including Symplicity HTN-3, the 2022 Korean Society of Hypertension guideline suggests that although renal denervation is a relatively safe procedure there is still a lack of evidence for the clinical benefits in blood pressure control and therefore is not currently recommended in clinical practice[35].

According to the results of Symplicity HTN-3, blood pressure was significantly reduced even in patients who received Sham procedure. Therefore, the overall sympathetic nerve activity of the patient as well as that of renal arteries have an important role in controlling resistant hypervascularization. Sardar et al. conducted a meta-analysis of 6 clinical studies with the Sham procedure control group. Blood pressure was statistically significantly reduced in the renal denervation group and the effect was greater in second-generation studies compared to the first-generation studies[36]. Additionally, in resistant hypertension, blood pressure is effectively decreased after sympathetic nerve blockade, but rebounds over time. This is believed to be due to incomplete blockade or the subsequent increase in the activity of the remaining sympathetic nerves leading to the overall increase in blood pressure. If the sympathetic nerves around the tunica adventitia are blocked with higher radiofrequency or ultrasound energy to increase the effectiveness of sympathetic nerve blockade a more sustained antihypertensive effect may be expected. However, there may be an increase in the side effect rates. In addition, as suggested by Hart et al., if a more specific standard for measuring human sympathetic nerve activity is established, the safety of renal denervation is expected to be highly improved[37].

The next thing to consider is how to predict which patients will have an effective response to renal nerve denervation. The degree of sympathetic nerve activity varies among patients with resistant hypertension and the response to renal nerve denervation may vary depending on previous beta-blocker or renin-angiotensin blockade use[38]. A previous study by Zuern et al. showed that cardiac baroreceptor sensitivity was highly associated with response to renal denervation[39]. Therefore, it is predicted that patients who have higher sympathetic activity and sensitivity will respond better to renal denervation.

CONCLUSIONS

Although renal denervation is not yet the current standard treatment for resistant hypertension the benefits of the procedure including effective blood pressure control and cardioprotective effects via sympathetic blockade are warranted with relatively good safety profile. With further development of technical devices and treatment protocols we can expect promising results of renal denervation with increased use in the real world clinical practice. Furthermore, by selecting patients who are expected to have effective responses to the procedure and establishing optimal treatment program renal denervation may become one of the standard treatments for resistant hypertension in the future.

Conflict of Interest

The authors have no conflicts of interest to declare.

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