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Renal Sympathetic Denervation: An Effective Non-Pharmacological Treatment Strategy for Sympathetic Over-Activation Related Diseases

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Abstract

The renal sympathetic nerve is a main target in cardiovascular diseases, because of the special relationship between the heart and kidney. Therefore, many drugs that inhibit the neuroendocrine system, such as angiotensin converting enzyme inhibitors/angiotensin receptor blocker (ACEI/ARB), beta blockers, and aldosterone inhibitors, have emerged to treat cardiovascular diseases. Renal sympathetic denervation (RDN) is the most influential non-pharmacological treatment method and was first reported by the Lancet in 2009. Although the negative conclusions of the Symplicity HTN-3 trial have hindered the application of RDN in resistant hypertension, there is increasing interest in RDN for the treatment of diseases other than hypertension because of its ability to inhibit sympathetic nerve over-activity. Therefore, we reviewed current studies about RDN with a focus on sympathetic nerve over-activation related diseases, such as, ventricular tachycardia, atrial fibrillation, myocardial remodeling, endothelium dysfunction, insulin resistance, obstructive sleep apnea, and so on.

Keywords: Renal sympathetic denervation; Hypertension; Atherosclerosis; Atrial fibrillation; Insulin resistance

Introduction

In 1943, Smithwick reported that lumbar dorsal sympathectomy decreased blood pressure and reduced long-term mortality, but clinical application of this procedure was prevented because of its side effects [1]. The renal sympathetic nervous system plays a major role in regulating the entire body and local organ function and includes an efferent and afferent nerve. The activated afferent nerve of the kidney activates the central sympathetic nerve and pathological changes in the structures and functions of organs emerge due to the excessive activity of the central sympathetic nerve. In addition, when the efferent nerve is activated, it changes renal blood flow, affects the reabsorption of sodium and water in the renal tubular, and causes the release of renin and renal prostaglandin. Eventually, chronic activation of the sympathetic system causes the development of cardiovascular diseases through a vicious neuroendocrine cycle. Therefore, the renal sympathetic nerve influences cardiovascular diseases.

In 2009, Krum [2], an Australian researcher, was first to report that they successful control of resistant hypertension by percutaneous radiofrequency ablation of the renal sympathetic nerve in the Lancet, and the efficiency and safety of that procedure were also was proven in that trial. However, the findings of the Symplicity HTN-3 and a follow-up clinic trial [3,4], have hindered the application of RDN. Although those trials denied the efficiency of RDN for the treatment of resistant hypertension, RDN is safe and inhibits over-activation of the sympathetic nerve. Our group found that RDN effectively decreased the blood pressure of spontaneous hypertensive rats and, especially, inhibited the progression of left ventricular hypertrophy in a hypertensive beagle model [5].

Some researchers showed that RDN has a vital influence on diseases with over-activation of the sympathetic nerve, such as ventricular hypertrophy, ventricular arrhythmia, atrial fibrillation, insulin resistance, endothelium dysfunction, chronic kidney diseases, obstructive sleep apnea and so on. Therefore, many clinical trials have been performed, and a great deal of exciting research results will emerge in upcoming years.

RDN and hypertension

Although the efficiency of RDN for hypertension has been doubted by some researchers, RDN is a milestone in the progression of hypertension treatment, and other investigators are still investigating how to resolve the issues with the process of RDN. Renal sympathetic nerve activity plays a crucial role in the pathogenesis of hypertension. In addition to regulating sympathetic nervous system activity, it also regulates the renin-angiotensin-aldosterone system (RAAS). Because of these unique features, inhibiting the renal sympathetic nerve is likely an effective intervention for controlling hypertension [6].

Inhibition of the renal sympathetic nerve results in complex physiological changes and affected by multiple factors. Therefore, the functional mechanism of RDN is still unclear. Many investigators are trying to determine the mechanism of RDN. During the development of RDN, researchers mainly focused on how RDN affected the SNS; however, many paradoxical results were obtained. Yoshida [7] and reported that blocking renal sympathetic nerve does not change the concentrations of circulating catecholamines. Holmer [8] showed that renin, angiotensin II and aldosterone levels significantly declined after renal nerve radiofrequency ablation; however, Voskuil [9] found that plasma renin activity did not change after RDN.

In summary, although RDN had been applied to control resistant hypertension, the functional mechanism of RDN is unclear; therefore, we cannot fully deny the value of RDN and discontinue its use based on the findings of Symplicity HTN-3. More accurate and effective targets should be explored to illuminate the mechanism of RDN. Additionally, an increasing numbers of multicenter randomized clinical studies with large sample sizes are being carrying out to determine the efficiency of RDN.

RDN and arrhythmia (ventricular tachycardia (VT), atrial fibrillation)

Sympathetic over-activation directly increases catecholamine levels, and catecholamine disturbs the autorhythmicity of myocardial cells and induces trigger action or reentry in local ventricle, eventually causing arrhythmia. In addition, catecholamine aggravates ventricular repolarization by disturbing Ca^{2+} and Ca^{2+} transporter levels, which ultimately induces ventricular arrhythmia [10-12]. Ventricular arrhythmia is closely related to increased density of the sympathetic nerves. Cao [13] studied 53 native hearts of transplant recipients and found that abnormally increased post-injury sympathetic nerve density may be partially responsible for the occurrence of ventricular arrhythmia and sudden cardiac death in these patients. Therefore, inhibiting sympathetic activity can reduce the occurrence of cardiac arrhythmias. After RDN was developed, researchers found that it reduced SNS activity and proved that renal sympathetic denervation affects heart rate and atrioventricular conduction [14]. Subsequently, other researchers found that RDN can treat arrhythmia. Huang [15] reported that RDN reduced the occurrence of long QT syndrome by inhibiting SNS activity. Remo [16] used RDN as an adjunctive therapy for refractory VT in 4 patients with cardiomyopathy and found that the number of VT episodes was decreased from 11.0 ± 4.2 (5.0-14.0) during the month before ablation to 0.3 ± 0.1 (0.2-0.4) per month after ablation. Ukena [17] reported that RDN reduced the incidence of ventricular tachyarrhythmias in 2 patients with chronic heart failure (NYHA III) and electrical storm. RDN also reduced the incidence of secondary ventricular arrhythmia. RDN effectively and safely reduced the occurrence of VT and VF in that patients, therefore, the researchers proposed that RDN may be a new adjunctive interventional bailout treatment for such highly challenging patients.

Atrial fibrillation is the most common arrhythmia clinically and is associated with significant morbidity and mortality. The sympathetic nerve is directly involved in atrial fibrillation as indicted by its excessive activation during it [18]. Pulmonary vein isolation (PVI) through radiofrequency ablation or cryoablation is the most widely used and most effective clinical treatment for atrial fibrillation [19]. However, atrial fibrillation had not completely been controlled by this method of local electrical isolation; 10 -20% patients experience a recurrence of atrial fibrillation after PVI. With the development of RDN in recent years, performing RDN in conjunction with PVI can effectively improve the success rate of PVI and reduce the risk of recurrence [20]. Pokushalov designed a randomized study to compare PVI with and without concomitant RDN and enrolled 27 patients with atrial fibrillation and hypertension in 2012. They found that the atrial fibrillation free rate in the PVI with RDN group was higher than that in the PVI only group at the 12-month post-ablation follow-up (69% *vs* 29%, p=0.033) [21]. Another doctor, Vollmann, reported one case of use of RDN instead of PVI in a 58-year-old female, the patient showed marked improvement in symptoms and exercise capacity after RDN.

Several potential antiarrhythmic strategies involving modulation of the autonomic nervous system, such as baroreflex stimulation, ganglion ablation, thoracic epidural anesthesia, low-level vagal nerve stimulation and RDN, have been explored. RDN had been showed to have a special effect on arrhythmia. We believe that RDN may be an effective treatment or adjuvant therapy for atrial fibrillation or other arrhythmias.

RDN and myocardial remodeling

Neurohumoral activation, for which enhanced activity of the sympathetic nervous system is a key component, plays a pivotal role in heart failure. Myocardial remodeling is the key pathological process of heart failure, and involves changes to cardiac structure and function in patients with left ventricular hypertrophy or cardiomyopathy. Renal sympathetic nerve activity directly or indirectly impacts the structure and function of the heart. Renal sympathetic afferent nerve activation activates systemic sympathetic nervous system activity, and activation of the renal sympathetic efferent nerve stimulates the release of rennin and increases water sodium retention and renal vascular resistance. Therefore, inhibiting the renal sympathetic nerve is also another strategy with significant value for the treatment of heart failure. Davies et al. [22] designed a pilot study that evaluated the safety of RDN for the treatment of heart failure, they researched 7 patients (mean age 69 years) with chronic systolic heart failure and found improvements in both symptoms and exercise capacity following RDN over 6 months of intensive follow-up. The six minute walk distance was significantly increased at six months (Δ=27.1 ± 9.7 m, p=0.03). Furthermore, Nozawa [23] reported that RDN reduces LV filling pressure and improves LV function after myocardial infraction. Therefore, decreased renal sympathetic nerve activity may help inhibit the progression of heart failure after myocardial infraction. Sympathetic activation has been suggested to contribute to ventricular

hypertrophy. McLellan [24] researched the effects of lowered blood pressure after RDN on structural remodeling in 14 patients, and they found significant reductions in left ventricular mass (from139 ± 37 g to 120 ± 29 g, P<0.01) and diffuse ventricular fibrosis (T1 partition coefficient reduced from 0.39 ± 0.07 to 0.31 ± 0.09, P=0.01) on cardiac magnetic resonance imaging.

The currently available research findings have proven that RDN has a significant influence on cardiac structure and function; however, these findings were obtained by trials with small sample sizes. Many randomized studies are being performed to confirm the safety and effectiveness of RDN in patients with heart failure; maybe more satisfying results will emerge from those studies.

RDN and endothelium dysfunction (atherosclerosis, inflammation)

Endothelial dysfunction is the onset of cardiovascular diseases and is also a predictor of the pathological changes and the progression of cardiovascular diseases. Excessive sympathetic activation has a negative influence on the endothelium. Therefore, it is theoretically possible to inhibit or delay endothelial damage by reducing sympathetic nerve excitability. RDN can obviously inhibit SNS and consequently reduce inflammation. Dörr et al. [25] studied 60 patients (age 67.9 ± 9.6 years) who underwent RDN. They reported that the serum levels of high-sensitive C-reactive protein (hsCRP) (p<0.001) and the pro-inflammatory cytokine interleukin-6 (IL-6) (p<0.001) were significantly lower and the levels of matrix metalloproteinases-9 (MMP-9) (p=0.024) and MMP-2 (p<0.01) were significantly higher after RDN compared to the baseline values. Wang et al. [26] studied apolipoprotein E-deficient mice undergoing RDN and found that serum levels of aldosterone, monocyte chemoattractant protein-1, and 8-isoprostane were lower in mice that received RDN compared to sham-operated mice (aldosterone; RDN: 206.8 ± 33.2 *versus* SO: 405.5 ± 59.4 pg/mL, P<0.05; monocyte chemoattractant protein-1; RDN: 51.7 ± 7.9 versus SO: 91.71 ± 4.6 pg/mL, P<0.05; 8-isoprostane; RDN: 331.9 ± 38.2 *versus* SO: 468.5 ± 42.0 pg/mL, P<0.05). Our research group found that catheter-based radiofrequency RDN inhibits the renin-angiotensin system and the oxidative stress response and improved vascular endothelial function in hypertensive dogs [27]. These trials confirmed that RDN inhibits excessive activation of the sympathetic nerve and helps repair endothelial damage. Therefore, RDN should be examined as a possible new strategy for improving endothelial function.

RDN and insulin resistance

Chronic over-activity of the sympathetic nerve plays a vital role in diabetes and insulin resistance is the common feature of diabetes mellitus (DM) and metabolic syndrome. Insulin resistance and sympathetic activity have positive feedback systems. Attenuation of sympathetic nervous system activity improves insulin sensitivity and we believe that the development of DM or metabolic syndrome can be slowed down by reducing sympathetic nervous system activity. Mahfoud et al. [28] enrolled 50 patients undergoing RDN and found that fasting glucose was reduced from 118 ± 3.4 to 108 ± 3.8 mg/dL (P=0.039), insulin levels were reduced from 20.8 ± 3.0 to 9.3 ± 2.5 μIU/mL (P=0.006), and C-peptide levels were reduced from 5.3 ± 0.6 to 3.0 ± 0.9 ng/mL (P=0.002) after RDN. In a homeostasis model assessment, insulin resistance decreased from 6.0 ± 0.9 to 2.4 ± 0.8 (P=0.001) at 3 months after RDN 118. Witkowski [29] reported that plasma glucose concentration at 2 hours after glucose administration (median: 7.0 *versus* 6.4 mmol/L; P=0.05) and hemoglobin A1C level (median: 6.1% *versus* 5.6%; P<0.05) were obviously decreased 6 months after RDN in patients with resistant hypertension and sleep apnea.

The currently available research results have proven that RDN effectively improves insulin resistance and decreases plasma glucose concentration in patients with DM or metabolic syndrome. However, additional large-scale, double-blind, multicenter, randomized controlled studies are needed to further explore the possible relationship between RDN and insulin resistance.

RDN and chronic kidney dysfunction (CKD)

The sympathetic nerve has a significant influence on kidney function. Multiple clinical studies have confirmed that patients with end-stage renal disease exhibit excessive activation of the SNS and that sympathetic nerve activity is associated with the progression of renal insufficiency. RDN significantly decreased the release of neurotransmitters in patients with hypertension and CKD. Thus, RDN is a potential treatment strategy in patients with excessive activation of the sympathetic nerve. Many scholars are concerned about the safety of RDN; there are some doubts regarding whether the internal membrane of the renal artery is damaged by RDN and whether thrombosis at the local ablation point or renal dysfunction can occur after RDN. However, many investigators have reported that RDN does not aggravate functional or structural renal damage; rather, RDN may improve renal function by decreasing SNS over-activation. Liang Xiao [30] recently performed a study in an angiotensin II-induced hypertension model and reported that RDN reduced renal inflammation by decreasing the accumulation of total leukocytes, T cells and both CD4+ and CD8+ T cells in the kidney, which were associated with a marked reduction in renal fibrosis, albuminuria and nephrinuria. Mahfoud [31] enrolled 100 consecutive patients with resistant hypertension, and 88 underwent RDN. After 6 months follow-up, they reported that RDN reduced the renal resistive index and the incidence of albuminuria without adversely affecting glomerular filtration rate or renal artery structure. Because of the special relationship between the sympathetic nervous system and kidney, we also believe that RDN has more beneficial effects on patients with CKD.

RDN and obstructive sleep apnea (OSA)

OSA is a highly prevalent disorder of breathing rhythm and frequency during sleep. Increasing evidence suggests that OSA is independently associated with an increased risk of

cardiovascular disease. We created the following figure (**Figure 1**) to demonstrate the relationship between sympathetic nerve activation and OSA.

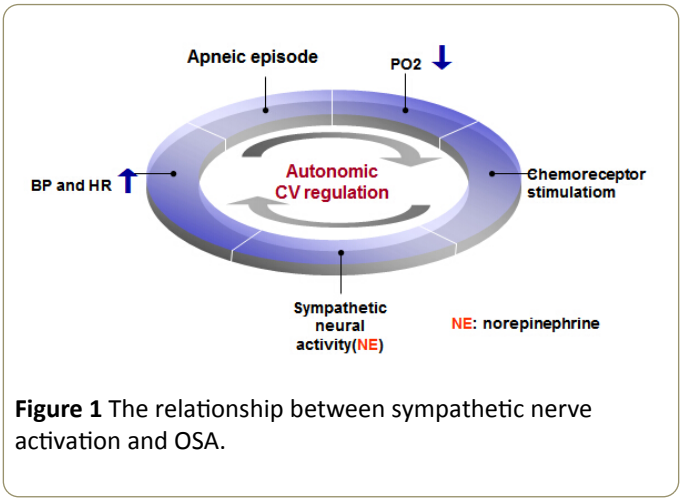

Figure 1 The relationship between sympathetic nerve activation and OSA.

Early recognition and nasal CPAP treatment can improve cardiovascular function [32]. Witkowski [29] reported that RDN decreased the apnea-hypopnea index at 6 months after the operation (median: 16.3 *versus* 4.5 events per hour; P=0.059), which indicates that RDN might serve as an adjuvant therapy for OSA. There is not sufficient evidence to prove that RDN can serve as the main treatment for OSA, but RDN might be an important auxiliary treatment. More clinical research is necessary to confirm this.

RDN and other diseases (polycystic kidney, polycystic ovarian syndrome)

The sympathetic nervous system effectively regulates body functions and plays a pivotal role in the neuroendocrine system. RDN decreases the activity of the SNS and significantly influences hypertension, heart failure, diabetes, atherosclerosis and other sympathetic over-activation diseases. There are also some reports that RDN may be useful in the treatment of non-cardiovascular diseases.

Chronic pain is a common concern in patients with polycystic kidney disease. Casteleijn [33] reported a case of a 43-year-old woman with polycystic kidney disease whose chronic pain could not be controlled by pain medication or splanchnic nerve blockade but was successfully managed by catheter-based RDN.

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disturbance disease clinically. It is associated with long-term health risks, including type 2 diabetes and vascular dysfunction. Lansdown [34] summarized the animal and human studies of PCOS and found that RDN reduced sympathetic nerve activity, which is increased in PCOS due to increased production of noradrenaline, and improved insulin sensitivity.

Conclusion

RDN, a novel non-pharmacological treatment strategy, reduces sympathetic nervous activity. The results of numerous studies have demonstrated the capability of RDN to inhibit the excessive activation of SNS and to protect against sympathetic over-activation related diseases. The exact mechanism through which RDN decreases blood pressure, improves insulin resistance and cardiac function, inhibits endothelium inflammation, and so on is still unclear. Although the Symplicity HTN-3 trial reported a negative findings regarding the use of RDN in resistant hypertension in 2014, there is not sufficient evidence to fully deny the application of RDN in diseases other than resistant hypertension. To some extent, RDN is a potential strategy, or novel therapeutic method, for the prevention and/or treatment of sympathetic over-activation related diseases.

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