International Heart and Vascular Disease Journal
Volume 3, Number 6, June 2015

Journal of the Cardioprogress Foundation

Experience of using renal denervation in clinical practice

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Abstract

In this article we present an overview and analysis of the results of various trials (including randomized – Simplicity I, II, III), studying clinical effectiveness of the method in the treatment of various pathologies of the cardiovascular system: hypertension, circulatory insufficiency, heart rhythm disorders, etc.

Keywords

Hypertension, renal denervation, Simplicity

Abnormal activation of the sympathetic nervous system because of chronic stress on a modern person is one of the main triggering factors of hypertension. The development of hypertensive disease includes three main components: an increase in cardiac output, increase in peripheral resistance due to vasoconstriction, and an increase in circulating blood volume [1].

Modern pharmacotherapy of hypertension is represented by different agents of central and peripheral action that block the links of the pathological chain of development of hypertension at different levels. Nevertheless, it is well known that a certain class of drugs act primarily on one of the mechanisms of hypertension, and that is why monotherapy of hyperten-

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sion is rarely effective in current clinical practice. In real life, in order to achieve a reliable and persistent hypotensive effect, a cardiologist has to treat with combination therapy, where the amount of antihypertensive drugs and their dosage depends on a variety of clinical factors.

Nonpharmacologic impact on the sympathetic nerves as a type of treatment was seen before the advent of modern antihypertensive pharmacotherapy. Radical surgical techniques for thoracic, abdominal, and pelvic sympathetic denervation were relatively successfully used to lower blood pressure (BP) in patients with so-called malignant hypertension. However, these operations were associated with a high risk of complications happening immediately after the intervention and delayed, including disorders of the gastrointestinal tract and pelvic disorders [2]. In this regard, the interests of researchers have been focused on the development and introduction of minimally invasive methods of sympathetic denervation, the most studied and promising of which is by far selective catheter-based renal sympathetic nerve ablation.

The technique consists of the selective destruction of the sympathetic nerves along the renal artery by radiofrequency ablation (RFA). After a series of experimental and first clinical studies [3,4,5,6], indicating the stable hypotensive effect of renal denervation, in late 2011, the results of two multicenter studies confirming the safety of this technique and its long-term clinical efficacy were presented.

The Symplicity HTN-1 cohort study was not randomized, and its task was to assess safety of the procedure and a comparative analysis of BP before and after denervation of the renal arteries in patients with drug-resistant hypertension [7]. The study included 153 patients from five centres in Europe and Australia. There were the following inclusion criteria: age of 18 years and older; systolic BP >160 mmHg (>150 mmHg in patients with type 2 diabetes); glomerular filtration rate (GFR) using the modification of diet in renal disease (MDRD) formula >45 mL/min/1.73 m^2; therapy using three or more antihypertensive drugs (including one diuretic); absence of secondary hypertension. The end points were the magnitude of BP reduction and safety of denervation of the renal arteries; evaluation of these indicators was conducted before the intervention and 1, 3, 6, 9, and 12 months after the procedure.

All patients underwent bilateral denervation via the femoral access. The duration of the procedure was approximately 40 minutes. Of 153 patients, 149 (97%) of them had the surgery without any complications. In one case, 1 renal artery dissection developed during the catheter insertion before supplying the power of radio waves into the artery. This violation was successfully eliminated by stenting. 3 cases had local complications in the femoral access (hematoma, pseudoaneurysm) which were treated with antibiotics and analgesics. After the ablation of the renal sympathetic nerves, BP decreased by -19/-9, -21/-10, -22/-10, -26/-13, -26/-12, -33/-15, -33/-14, and -33/-19 mmHg after 1, 3, 6, 12, 18, 24, 30 and 36 months, respectively (Figure 1). No long-term adverse effects were observed after the intervention, namely, there were no cases of aneurysms or stenosis of the renal artery confirmed by multiple tests including renal angiography 14–30 days after the intervention and magnetic resonance angiography (MRA) after 6 months.

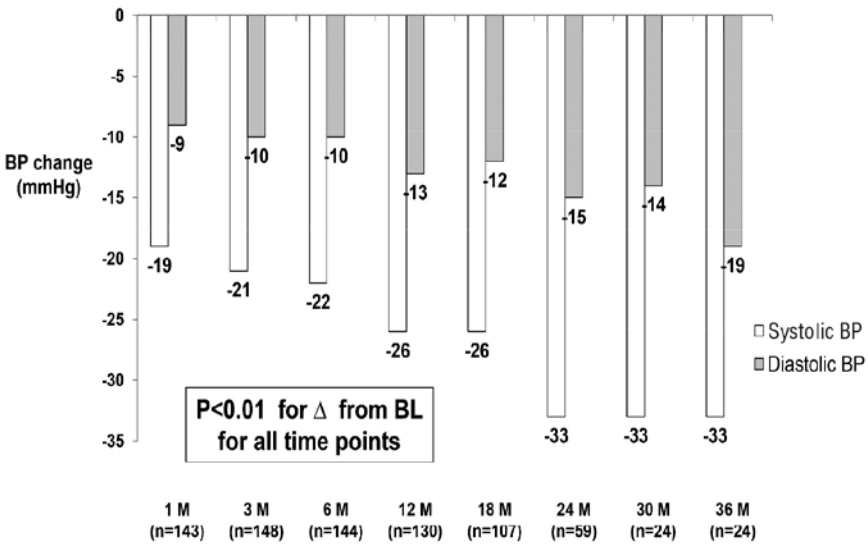

Figure 1. Results of the Symplicity HTN-1 study

Positive results were also obtained in the Symplicity HTN-2 multicentre study, which was, unlike Symplicity HTN-1, randomized [8]. The study involved 24 centres in Europe, Australia and New Zealand. Inclusion and exclusion criteria were similar to those in the Symplicity HTN-1 study.

106 patients were randomized into 2 groups: patients in group 1 (main group, n = 52) were performed ablation of the renal nerves and patients in group 2 (control, n = 54) received only medication.

The primary endpoint was the dynamics of office systolic BP at 6 months (the average of three BP readings at the doctor's office). The secondary endpoints were immediate perioperative safety; incidence of delayed complications (decreased GFR >25% from baseline or the occurrence of renal artery stenosis >60%, confirmed by angiography at 6 months); combined cardiovascular endpoint (myocardial infarction, stroke, sudden cardiac death, etc.); and change in 24 hour ambulatory blood pressure. The study was completed by 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 patients from the control group. In the study group, there was noted an average decrease in systolic BP of 32/12 mmHg with average baseline BP of 178/96 mmHg. In the control group, there were no changes in BP compared to average baseline BP (Figure 2). The results revealed that the total amount of antihypertensive drugs consumed by patients after renal denervation significantly decreased (Figure 3). Of different groups of drugs, the consumption of angiotensin-converting enzyme inhibitors and central sympatholytic drugs significantly decreased. Drugs of the latter group have inhibitory effect on the central nervous system (especially in the elderly), and therefore they are usually prescribed when modern and commonly used drugs with peripheral effects (ß-blockers, calcium antagonists, angiotensin-converting-enzyme (ACE) inhibitors and diuretics) are not effective.

The results of the pilot Symplicity HTN-1 and randomized Symplicity HTN-2 studies largely determined wide dissemination of renal denervation, mainly in developed countries of Europe. The Symplicity HTN-3 study differed from previous ones in the place where it was conducted and in design [9]. Eighty-eight US medical centres took part in the Symplicity HTN-3 study with the total number of randomized patients was 535. The principle of randomization was 2:1, where 364 patients underwent renal denervation and 171 patients underwent sham procedure, which was only an imitation of invasive treatment, namely the installation of a diagnostic catheter and angiography. The results in the study and control groups were evaluated on two criteria: clinical efficacy and safety. The primary efficacy endpoint was the reduction in office systolic BP at 6 months, the secondary efficacy endpoint was the reduction in systolic BP at 6 months according to 24-hour BP monitoring. The safety endpoint was the incidence of clinical or morphological complications in the groups studied during the 6-month follow-up period (mortality, development or progression of renal failure, development of crisis hypertension, renal artery stenosis, and renal artery intervention).

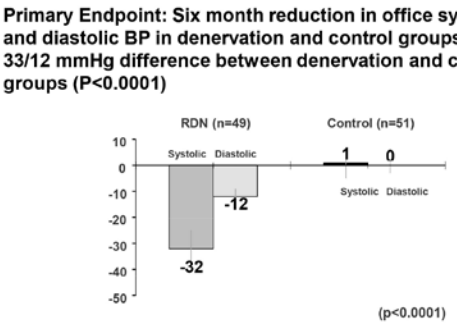

Figure 2. Results of the Symplicity HTN-2 study

Results of the Symplicity HTN-2 study

6 months

	Control	Denervation	*P*
Amount of medication (Mean±SD)	5.1 ± 1.5	4.6 ± 1.6	0.023
ACE inhibitors	47.5%	35.0%	0.025
Central sympatholytic drugs	57.5%	32.5%	0.002

Figure 3. Drug therapy before and after denervation

After 6 months, there was a significant decrease in the office systolic BP (primary efficacy endpoint) in the group of renal denervation: the difference before and after treatment was 14.1±23.9, $P<0.001$. However, the analysis of the six-month clinical results of the sham procedure group revealed that its patients had a significant decrease in BP after the procedure (11.7±25.9, $P<0.001$, Figure 4). At the same time, there were no significant differences in the BP reduction between the groups. Similar results were obtained in relation to the BP recorded with ABPM. In the group of renal denervation, the treatment resulted in a statistically significant reduction in the mean ambulatory systolic BP, the difference before and after the treatment was 6.8±15.1, $P<0.001$; in the sham procedure group, BP also significantly decreased – 4.8±17.3, $P<0.001$ (there were no significant differences between the groups, too).

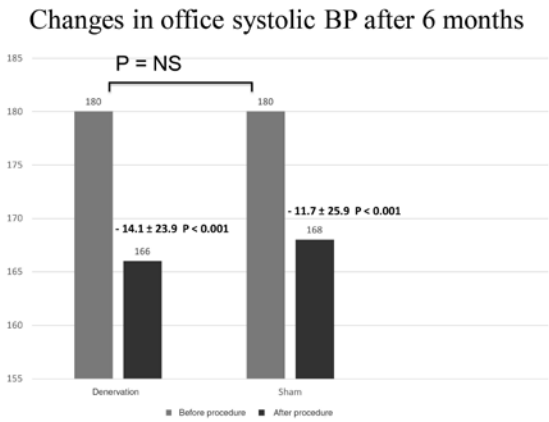

Figure 4. Results of the Symplicity HTN-3 study

In our opinion, one of the most important research findings is that not all patients with resistant hypertension should be treated with sympathetic denervation. Although pathological activation of the sympathetic nervous system is the most important mechanism for development of hypertension, it is not the only one. A subgroup analysis of the results of these two groups, depending on their initial clinical and demographic characteristics, can serve as confirmation. Thus, in assessing the impact of renal denervation in different age groups, it was revealed that a significant positive impact of this procedure on BP numbers was observed in patients under 65 years old and white Americans. Accordingly, in patients over 65 years old and Afro-Americans, there were no significant differences between the groups of renal denervation and sham-procedure. The differences in the age subgroups can be explained by a higher activity of the sympathetic nervous system in young patients and its involutional changes with old age, but the lack of effect of denervation in Afro-Americans requires further study. Apparently, most of the black patients included in Symplicity HTN-3 could significantly affect the results of the study. This feature of the Symplicity HTN-3 study was an important distinction from the Symplicity HTN-2 study, which was conducted in Europe and the percentage of black patients undergoing randomization was insignificant.

It should be noted that a variety of pathophysiological processes, triggered by hyperactivation of the sympathetic nervous system, are not limited to hypertension. The results of large clinical studies suggest that denervation of the renal arteries has positive effects not only in reducing BP, but also in other pathologies caused by chronic sympathetic hyperactivity.

Witkowski et al. [10] have studied clinical effects of renal denervation in 10 patients with a combination of resistant hypertension, impaired glucose tolerance, and respiratory apnoea. There were studied the following clinical parameters: BP dynamics after the treatment, glucose tolerance test, glycated haemoglobin, and apnoea-hypopnoea index. Six months after the treatment, the mean reduction in systolic and diastolic BP was -34/-13 mmHg. Significant changes in the results of the glucose tolerance and glycated haemoglobin tests were observed: average glucose level after a load was 7.0 mmol/L before the renal ablation and 6.4 mmol/L after 6 months (P=0.05), glycated haemoglobin value decreased from 6.1 % to 5.6 % (P<0.05). The apnoea-hypopnoea index had also undergone significant changes after 6 months: 16.3 events per hour before the treatment to 4.5 events per hour after it; P=0.059).

Another promising field of using renal denervation is treatment of heart rhythm disorders. Despite a small number of clinical observations, the first results of research in this area look promising. One of the most common adverse effects of the structural changes of the heart in the presence of hypertension is left ventricular (LV) hypertrophy. It is well known that LV hypertrophy leads to diastolic dysfunction, expansion of the left atrium, which in turn, is a major trigger for atrial fibrillation. It is logical to suppose that a decrease in myocardial hypertrophy and diastolic dysfunction after renal denervation may be accompanied by a decrease in the incidence of atrial fibrillation. Confirmation of this clinical effect can already be found in clinical studies. The scientists at Columbia University in New York conducted radiofrequency ablation of the mouths of the pulmonary veins in 27 patients with resistant hypertension and chronic atrial fibrillation [11]. Thirteen of these patients had a radiofrequency isolation in conjunction with radiofrequency renal ablation. During 1-year follow-up, there were no cases of recurrence of atrial fibrillation in 29 % of patients in the group of radiofrequency ablation of the mouths of the pulmonary veins and in 69 % of patients in the group of the combined intervention (radiofrequency ablation + renal denervation), P=0.033. Pokushalov EA *et al*. studied the results of combined radiofrequency exposure in 35 patients with hypertension and atrial fibrillation [12]. Combined treatment (renal denervation in combination with radiofrequency isolation of the mouth of the pulmonary veins) not only leads to a BP reduction, but also to a significantly greater reduction in recurrences of atrial fibrillation, compared to the patients who only underwent the isolation of the mouth of the renal veins.

In conclusion, it should be noted that, given the latest scientific data, the use of renal denervation is not limited to the treatment of resistant hypertension and its complications, and possibly clinically effective in various pathologies caused by abnormal activation of the sympathetic nervous system. Given the relative «youth» of the method, long-term observations are limited to a short period and there is no compelling scientific evidence on the improvement of long-term outcome after renal denervation. Nevertheless, all of the clinical studies, including randomized, demonstrate safety of the method and absence of complications related to the technical features of the procedure. All this justifies the usefulness of renal ablation in addition to drug therapy in treatment of various cardiovascular pathologies.

Conflict of interest: None declared

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