One year follow-up effect of renal sympathetic denervation in patients with resistant hypertension

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Short Communication

Abstract

BACKGROUND: Resistant hypertension is a common clinical problem of blood pressure that is not controlled despite the simultaneous application of multiple antihypertensive agents. Ablation of renal afferent nerves has been applied and proved to decrease hypertension and injuries produced by severe sympathetic hyperactivity. The main objective of this study was to investigate the long-term effect of renal artery sympathetic ablation and its complications in patients with treatment-resistant hypertension.

METHODS: In this prospective study which done between March 2012 and November 2013, 30 patients with resistant arterial hypertension despite treatment with ≥3 antihypertensive drugs-were randomly enrolled in this self-control clinical study in Isfahan, Iran. The patients were treated with the renal denervation procedure; the femoral artery was accessed with the standard endovascular technique and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator. Before and 12 months after renal denervation procedure waist, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), metabolic syndrome, fasting blood sugar (FBS), high-density lipoprotein (HDL), and triglyceride were measured in all patients.

RESULTS: Both mean SBP and DBP were significantly decreased, 12 months after renal denervation ($P < 0.001$). The frequency of metabolic syndrome was not significantly different after renal denervation in compare to baseline ($P = 0.174$). Furthermore, a significant decreased in FBS and triglyceride was observed in compare to baseline ($P = 0.001$).

CONCLUSION: This study highlighted the role of renal sympathetic denervation as a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases.

Keywords: Hypertension Resistant; Renal Sympathetic Denervation; Renal Artery Ablation; Angiography; Renal Sympathectomy

Introduction

Hypertension is one of the severe public health problems worldwide and one of the leading causes of cardiovascular disease and death.[1,2] Annually, about 7.5 million deaths (13% of all deaths) are caused by hypertension.[3,4] Report given by the global burden of hypertension, expressed that, almost one billion adults suffer of hypertension in 2000, and it is expected to enlarge to 1.56 billion until 2025.[5] In spite of wide efforts to handle hypertension, just half of treated individuals are controlled and the rest is cases with resistant hypertension.[6,7] Resistant hypertension is a common clinical problem of blood pressure that is not controlled despite the simultaneous application of multiple antihypertensive agents.[8,9] Physician inertia, medication side effects, non-conformity to lifetime pharmacological remedy by patients, and drug incompetence have been expressed as reasons of failure in the pharmacological strategy.[10,11]

Several studies have indicated that kidney has an important impact on blood pressure regulation; it has

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been proved that augmented activity in the sympathetic nervous system contributes to the hypertension pathogenesis.[12,13] Hence, ablation of renal afferent nerves has been applied and proved to decrease hypertension and injuries produced by severe sympathetic hyperactivity.[14,15] Traditionally, surgical sympathectomy had been successfully applied in decreasing blood pressure in individuals with chronic hypertension.[16] Given that, this method was founded to have abundant large scale perioperative mortality and long-lasting complications, was forsaken until the advent of catheter-based method.[17] Catheter-based renal sympathetic denervation has been expressed as a safe, helpful, and cost-effective intervention in patients with resistant hypertension.[18,19] Reduction in blood pressure and diminishing the possibility of stroke, left ventricular hypertrophy, chronic renal, and heart failure by catheter-based renal sympathetic denervation in combination with pharmacologic remedy have been reported.[20]

However, the long-term effect of renal sympathetic denervation and its complications in patients with treatment-resistant hypertension is not clearly understood. Toward this end, the present survey tries to investigate the long-term effect of renal artery sympathetic ablation and its complications in patients with treatment-resistant hypertension. This study designed to assess the feasibility, safety, and effectiveness of renal sympathetic denervation in patients with resistant arterial hypertension.

Materials and Methods

This single-center, prospective study was approved by the Ethical Review Committees of Isfahan University of Medical Sciences, Isfahan, Iran. After a full explanation of the study, written informed consent was obtained from all the patients.

In total 30 patients with resistant arterial hypertension despite treatment with ≥ 3 antihypertensive drugs (at least one of the antihypertensive medications was required to be a diuretic) were enrolled in this study. Inclusion criteria were age more than 15 years in both sex, with systolic blood pressure (SBP) ≥ 160 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg. Exclusion criteria were pregnancy; have any known secondary cause of hypertension; severe renal artery stenosis, previous renal stenting or angioplasty, or known dual renal arteries type 1 diabetes, hemodynamically major renal artery stenosis, previous renal artery intervention, renal artery anatomy that precluded treatment (< 4 mm

diameter, or < 20 mm length), an estimated glomerular filtration rate of < 45 ml/minutes, heart disease, planned pregnancy during the study, and a history of myocardial infarction (MI) and unstable angina in the previous 6 months.

Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.[1] Patients whose blood pressure is controlled with four or more medications are considered to have resistant hypertension.

Selected patients were treated with the renal denervation procedure, the femoral artery was accessed with the standard endovascular technique, and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator. Blood pressure was measured twice in sitting position after 5 minutes resting by mercury sphygmomanometer. The mean of the two recordings was reported as patient's blood pressure. Subjects who had three or more of the criteria defined by National Cholesterol Education Program (NCEP) were diagnosed with metabolic syndrome. The criteria of NCEP include: (1) Central obesity as the waist circumference > 102 cm in men and > 88 cm in women; (2) fasting plasma triglycerides ≥ 150 mg/dl; (3) low high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl in men and < 50 mg/dl in women; (4) SBP ≥ 130 mm Hg and/or DBP 85 mm Hg and/or antihypertensive agents (5) hyperglycemia with fasting plasma glucose (FPG) ≥ 100 mg/dl and/or hypoglycemic medications.[10]

Before and 12 months after renal denervation procedure waist, body mass index (BMI), SBP, DBP, metabolic syndrome, fasting blood sugar (FBS), HDL, and triglyceride were measured in all patients. Change in the mean of measurements of SBP and DBP from baseline to 12 months after renal denervation were the main effectiveness endpoint of this study, also, chronic procedural safety such as death, MI, stroke, congestive heart failure (CHF), and renal arterial stenosis were assessed in all patients after 12 months. To measure renal arterial stenosis 12 months after renal denervation, angiography performed in any of patients who were willing and ready.

With a sample of 30 patients, we calculated that the study would have at least 80% power to show benefit of renal denervation, assuming at least a 10 mm Hg difference with a 21 mm Hg standard deviation (SD) of the change in SBP from baseline to 12 months.

The pattern of medication use was defined

Table 1. Clinical characteristics of studied patients at baseline and 12 months follow-up after renal denervation

Variable	Baseline	12 months after renal denervation	P	Δ between two phase
	Mean ± SD	Mean ± SD		Mean ± SD
BMI (kg/m^2)	28.3 ± 2.8	27.9 ± 2.5	0.008	-0.90 ± 1.20
Waist circumference (cm)	92.3 ± 10.4	91.1 ± 10.2	0.003	-0.34 ± 0.02
SBP (mm Hg)	169.8 ± 10.5	147.5 ± 14.9	< 0.001	-22.30 ± 10.04
DBP (mm Hg)	95.7 ± 9.7	83.8 ± 7.5	< 0.001	-11.83 ± 5.63
FBS (mg/dl)	111.7 ± 15.7	107.2 ± 12.9	0.001	-4.50 ± 2.31
HDL (mg/dl)	45.1 ± 5.5	48.3 ± 5.4	0.002	3.27 ± 1.03
Triglyceride (mg/dl)	165.9 ± 53.8	146.5 ± 38.1	0.001	-19.43 ± 10.02

P values calculated by pair t-test.
SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High-density lipoprotein

according to the type of drugs used to control and/or treat hypertension. Medicines were classified according to pharmacological category.

The collected data were analyzed statistically with SPSS software (version 20, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov normality test was used before analysis, and in case of abnormality in data transformation was used. Continuous variables present as mean ± SD and categorical variables as number (%). Studied variables after renal denervation in compare to baseline were assessed using pair t-test. The frequency of metabolic syndrome was tested by McNamara's test. P < 0.050 was considered significant.

Results

During the study period (March 2012 to November 2013), a total of 37 patients were consented for enrollment. During the screening process, seven patients were excluded (three patients did not met inclusion criteria and four refused informed consent). In total, 30 patients completed baseline evaluation and underwent the renal denervation procedure. Within the 12 months follow-up period one patient died, and finally, 29 patients completed the study and analyzed. The mean age of studied patients was 56.3 ± 10.8 years old, 14 of patients (47%) were male and 16 patients (53%) were female.

Clinical characteristics of studied patients at baseline in compare to 12 months follow-up after renal denervation are shown in table 1. BMI and waist after renal denervation significantly decreased in compare to baseline (P < 0.050). SBP at baseline was 169.8 mm Hg and after renal denervation meaningfully reduced to 147.5 mm Hg (P < 0.001). DBP was significantly decreased of 95.7 mm Hg at baseline to 83.8 mm Hg after renal denervation (P < 0.001). The distribution of metabolic

syndrome was not significantly different after renal denervation in compare to baseline (P = 0.170). Moreover, a significant decreased in FBS and triglyceride after renal denervation was observed in compare to baseline (P = 0.001). HDL significantly increased in compare to baseline (P = 0.002).

Distribution of SBP levels at baseline in compare to 12 months post-renal denervation. At baseline, all studied patients had SBP higher than 140 mm Hg and only 7% had SBP between 140 and 160 mm Hg and 93% had SBP higher than 160 mm Hg. 12 months after renal denervation 3.3% of subjects had SBP lower than 140 mm Hg and 20.0% had SBP between 140 and 160 mm Hg. Decline in SBP in 7% of patients was lower than 10 mm Hg, which were defined as no decrease in SBP. 93% of patients had the SBP reduction of ≥ 10 mm Hg. Moreover, also 12 months after renal denervation 23.3% of patients achieved the SBP of < 140 mm Hg. Table 2 shows there are no significant differences in the pattern of ntihypertensive medication at baseline and 12 months follow-up after renal denervation.

Table 2. Prevalence of antihypertensive medication at baseline and 12 months follow-up after renal denervation

Drug	Value (%)	Value (%)
ACE inhibitor	51.0	49.9
Angiotensin receptor blocker	67.3	67.5
Calcium channel blocker	27.6	28.1
Diuretic	58.8	59.2
Aldosterone antagonist	18.4	17.8
β blocker	81.6	82.2
α androgenic blocker	8.2	8.3
Direct renin inhibitor	16.3	16.7
Thiazides	4.0	4.3

ACE: Angiotensin-converting-enzyme

The mean of decreases in both SBP and DBP was 22.3 and 11.83 mm Hg, respectively. The mean of decreases in BMI, waist, FBS and triglyceride after follow-up was 0.9, 0.34, 4.5 and 19.4, respectively; and the mean of increased in the level of HDL was 3.27. Post-procedure within the follow-up period we detected the following side effects: MI was occurred in two patients. One of patient's died from a MI. One of the patients had stroke and one patient had CHF. Angiography was done in eight patients who were willing and renal arterial stenosis (50%) was observed in two of them.

Discussion

In present single-center, prospective study showed renal sympathetic denervation as a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases is useful method so renal denervation provides harmless and continued drop of blood pressure to 2 years. Similar to our results Esler et al. demonstrated control hypertensive subjects who crossed over to renal denervation with the Symplicity system demonstrated a meaningful decline in blood pressure alike to that observed in subjects obtaining urgent denervation.[21]

As with the former available reports concerning this method, our findings, reaffirm the effectiveness of catheter-based therapy for hypertension resistant subjects and clarified that renal sympathetic denervation creates a secure and sustained blood pressure reduction during 12 months after treatment follow-up. A highly significant reduction of SBP and DBP were observed. SBP at baseline was 169.8 mm Hg and after renal denervation significantly decreased to 147.5 mm Hg (P < 0.001). Furthermore, DBP was significantly decreased from 95.7 mm Hg at baseline to 83.8 mm Hg after renal denervation (P < 0.001). Our findings are keeping with Katholi and Rocha-Singh,[19] they have expressed that catheter-based renal denervation offers sustained and considerable reduction of blood pressure in resistant hypertension patients. They also reported that catheter-based renal denervation causes no severe unpleasant complication, and mentioned the necessities of prospective randomized clinical trials for proving their findings.[19]

Hypertension reduction using catheter-based renal sympathetic denervation along with pharmaceutical remedy have been shown to be effective in decreasing the stroke risk, heart failure, left ventricular hypertrophy, and severe renal failure.[21]

Moreover, it has been suggested that after 6 months, analogs significant reduction in blood pressure like as individuals receiving immediate renal sympathetic denervation were observed and the secure and sustained reduction of blood pressure exist in 1 year follow-up. Our results confirm this safety and sustainability of renal sympathetic denervation method in 21 months follow-up period.[21]

It's worth noting that we measured the amount of triglyceride, HDL and FBS after renal sympathetic denervation according to the results triglyceride, HDL, and FBS meaningfully decreased from baseline to 21 months after renal sympathetic denervation. We have to acknowledge the investigation limitation due to the fact that inasmuch as, there are no other therapeutic strategies to be compared with renal sympathetic denervation, we are not capable to judge against the renal sympathetic denervation effectiveness with other remedy options. Another study limitation possibly will be the relatively little sample size.

Conclusion

Renal sympathetic denervation presents a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases. We demonstrate for the first time to our knowledge that triglyceride, HDL, and FBS are also controlled by renal sympathetic denervation.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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