DOI: 10.4149/BLL_2022_113

Bratisl Med J 2022; 123 (10)
710 – 715

CLINICAL STUDY

Renal denervation in resistant hypertension treatment

OREKHOV Andrey U, SABITOV Yersyn T, KARAZHANOVA Ludmila K

Non-Commercial Joint-Stock Company "Semey Medical University", Department of Cardiology and Interventional Arrhythmology, Semey, Republic of Kazakhstan. **orekhov-andrei@list.ru**

ABSTRACT

BACKGROUND AND OBJECTIVES: Purpose of the study is the assessment of the effectiveness of renal denervation with different types of catheters, as well as its long-term effects, in the patients with resistant hypertension.

MATERIALS AND METHODS: This single-center prospective study included 81 patients who underwent a renal denervation procedure using 2 types of catheters: monopolar and helical (Medtronic Inc., Minneapolis, Minnesota, the USA) between 2015 and 2018. Baseline demographics, clinical, functional and laboratory characteristics of the patients were assessed. A comparative analysis of the dynamics of office systolic and diastolic blood pressure during 5 years of follow-up was carried out. The Kaplan–Meier method was used to study the survival of the patients with resistant hypertension after renal denervation.

RESULTS: A total of 81 patients with a mean age of 57.79±9.87 years, of whom 37.04 % were men, were included in the 2-stage study (first stage using monopolar catheters and second stage using spiral catheters). At the time of inclusion, study participants were receiving an average of 4.5±1.4 antihypertensive medications. In 36 (or 44.4 %), the procedure was performed using a monopolar catheter; in 45 (or 55.6 %), a spiral catheter was used. There were no statistically significant differences between the two groups of the patients. The analysis established statistically significant changes in the dynamics of office SBP and DBP ($p < 0.001$) assessed 1, 2, 3, 4, and 5 years after the renal denervation procedure. The analysis demonstrated a stability in the reduction of office SBP and DBP during the 5-year follow-up. The results of the study showed that the median survival time was 1061 days from the beginning of follow-up (95% CI: 728.03 to 1 393.97 days); the median survival time in the monopolar catheter group was 777 days (95% CI: 692.314 to 861.686) and in the spiral catheter group 1 294 days (95% CI: 713.079 to 1 874.921).

FINDINGS: Our results demonstrated the efficiency and safety of renal denervation in both short-term and long-term follow-up using monopolar and spiral catheters in the treatment of uncontrolled hypertension with combined antihypertensive therapy. The most significant is the demonstrated stability of the effect after the procedure. In addition, the survival rate of the patients with resistant hypertension after the intervention has been carried out *(Tab. 2, Fig. 3, Ref. 22)*. Text in PDF *www.elis.sk*

KEY WORDS: renal denervation, device-based therapy, hypertension, sympathetic nervous system, resistant.

Introduction

Hypertension is the most common chronic noncommunicable disease and the leading risk factor for disability and premature mortality worldwide accounting for 10.8 million deaths (95% CI 9.51–12.1) or 19.2 % (16.9–21.3 %) (1). One of the most effective management strategies is to achieve a target blood pressure (BP) (2). According to SPRINT study results, reduction of systolic BP (SBP) to the target level less than 120 mmHg reduces the probability of death and severe complications of cardiovascular disease (CVD) in the patients with hypertension, especially at high cardiovascular risk (3). Resistant hypertension is one of the reasons for the failure to achieve the target BP (4). The large prospective study conducted in the UK demonstrated an increase in the incidence of resistant AH from 0.93 to 2.07 per 100 patient-years from 1996 to 2004 (5).

The technique of sympathetic denervation of the renal arteries (RD), suggested in 2003 by H. Levin and M. Gelfand, can act today as an additional, and sometimes alternative, method of uncontrolled hypertension treatment (6, 7).

The results of the first and certainly significant studies Symplicity HTN-1 (8) and Symplicity HTN-2 (9) were of great importance in determining the role of sympathetic denervation of the renal arteries in uncontrolled hypertension treatment. The findings have promoted the interest to study the role of sympathetic nervous system in resistance genesis (10), and promoted catheter techniques as one of the most perspective treatment approaches.

Non-Commercial Joint-Stock Company "Semey Medical University", Department of Cardiology and Interventional Arrhythmology, Semey, Republic of Kazakhstan

Address for correspondence: Andrey OREKHOV, Non-Commercial Joint-Stock Company "Semey Medical University", Department of Cardiology and Interventional Arrhythmology, Molodogvardeyskaya 34-1 street, Semey, Republic of Kazakhstan.
Phone: +87774141476

In view of this, the results of Symplicity HTN-3 – the first sham-controlled randomized study (11) showing no reliable advantage in the reduction of office BP in the patients after renal denervation in comparison with sham procedure were unexpected.

A kind of Renaissance of renal denervation is a series of SPYRAL Pivotal studies where the second generation of electrodes – a spiral catheter – was used. The results of SPYRAL HTN-OFF MED (12) showed a reliable effectiveness of the procedure in comparison with sham intervention; thus, the difference in treatment between the two groups for 24-hour SBP was –3.9 mmHg (95% CI from –6.2 to –1.6).

Purpose of the study is the assessment of the effectiveness of renal denervation with different types of catheters, as well as its long-term effects, in the patients with resistant hypertension.

Materials and methods

This prospective study included 81 patients with resistant hypertension, who were hospitalized in the Department of Cardiology of University Hospital of NCJSC "Semey Medical University" (the Republic of Kazakhstan) during the period from 2015 to 2018. The study was conducted in accordance with the Declaration of Helsinki, the study protocol was approved by the local ethical committee. All the participants signed a voluntary informed consent. The study used the ESC definition of resistant hypertension, which refers to the inability to achieve target SBP or DBP, despite the recommended treatment tactics, i.e., lifestyle modification and the use of optimal or maximum tolerated doses of three or more drugs, including a diuretic (2). All the patients were taking at least 3 antihypertensive drugs before renal denervation. Secondary forms of hypertension were excluded during selection. Other exclusion criteria were an acute myocardial infarction and acute cerebral circulation disorder 6 months before the procedure, a defined renal artery pathology (hemodynamically significant renal artery stenosis, fibromuscular dysplasia).

Renal denervation procedure was performed using Siemens Artiz Zee angiographic unit (Germany). Premedication was performed 30–40 minutes before the intervention. In all the cases RD was performed by right or left transfemoral access. After local anesthesia with 0.5 % Novocaine or 2 % Lidocaine solution, we performed an arterial puncture according to the Seldinger method with a 6 Fr introducer. Visualization of the renal arteries was performed in the anteroposterior view by means of aortography of the abdominal aorta using a PigTail 5 Fr diagnostic catheter. For all RDN procedures, a Sherpa 6 Fr. guidewire renal catheter and a 0.014 hydrophilic coronary guidewire were used. Renal denervation procedures were performed using 2 types of catheters – monopolar Symplicity Renal Denervation System Catheter (Medtronic Inc., Minneapolis, Minnesota, the USA) and spiral Symplicity Spyral Renal Denervation System Catheter (Medtronic Inc., Minneapolis, Minnesota, the USA). In each case at least 8 ablations were performed in each renal artery. The study did not involve blind randomization for the use of a particular type of catheter; patients were included in the groups as the catheters were modified. In this study by analogy with previously published studies (13) the patients in whom BP reduction of 10 mmHg or more was achieved were considered as responders.

In each case there were performed routine investigations including office blood pressure registration by Korotkoff method, laboratory tests (clinical blood test, urinalysis, biochemical blood test with analysis of lipid spectrum, glucose). In addition, we investigated the renal filtration function by serum creatinine level, calculation of glomerular filtration rate (GFR) according to CKD-EPI formula, 2011 (14). Repeated assessment was performed on the 7th day, then after 1, 2, 3, 4 and 5 years.

Tab. 1. General clinical characteristics of patients.

Indication	All patients	Monopolar catheter, 36	Spiral catheter, 45	p
Age, years	57.79±9.87	55.33±9.26	59.76±9.99	0.044[a]
Women, n (%)	51 (63%)	20 (55.6%)	31 (69.9%)	0.217[c]
Diabetes mellitus type 2, n (%)	23 (28.4%)	9 (25%)	14 (31.1%)	0.720[e]
Chronic ischemic heart disease, n (%)	30 (37%)	14 (38.9%)	16 (35.6%)	0.758[c]
Previous myocardial infarction, n (%)	20 (24.7%)	11 (30.6%)	9 (20%)	0.403[e]
Atrial fibrillation, n (%)	8 (9.9%)	2 (5.6%)	6(13.3%)	0.290[d]
Stroke, n (%)	12 (14.8%)	7 (19.4%)	5 (11.1%)	0.354[d]
Postponed revascularization, n (%)	19 (23.5%)	8 (22.2%)	11 (24.4%)	0.815[e]
Office SBP, mmHg	190 (140; 240)	180 (160; 240)	190 (140; 240)	0.588[b]
Office DBP, mmHg	100 (80; 140)	100 (80; 130)	100 (80; 140)	0.666[b]
Heart rate, beats per minute	69 (46; 110)	69 (46; 100)	70 (50; 110)	0.444[b]
Left ventricular ejection fraction, %	63 (37; 77)	63 (51; 77)	63 (37; 69)	0.238[b]
Creatinine, μmol /l	121 (53; 250)	121 (53; 169)	121 (70; 250)	0.342[b]
GFR, Ml/min/1.73m^2	59 (24; 116)	59 (26; 116)	59 (24; 102)	0.137[b]
Blood glucose, mmol/l	5.7 (3.4; 13.2)	6.05 (3.4; 13.2)	5.3 (3.5; 12.8)	0.183[b]
Total cholesterol, mmol/l	5 (3; 9.7)	5 (3.6; 6.2)	5 (3.0; 9.7)	0.612[b]
Triglycerides, mmol/l	2.14 (0.8; 6)	2.14 (0.8; 4.4)	2.14 (1.03; 6)	0.945[b]
Haemoglobin, g/l	139.3±17.15	142.64±14.64	136.8±14.49	0.126[a]
Urine protein, g/l	0 (0; 1.984)	0 (0; 0.99)	0 (0; 1.984)	0.713[b]
Left renal artery, cm	4.8 (4; 6)	4.805 (4; 6)	4.805 (4; 6)	0.451[b]
Right renal artery, cm	5.29 (3; 7)	5.144 (4; 6)	5.288 (3; 7)	0.2[b]
Received therapy				
ACE inhibitor /ARA, n (%)	76 (93.8%)	35 (97.2%)	41 (91.1%)	0.375[d]
Beta-blockers, n (%)	43 (53.1%)	21 (58.3%)	22 (48.9%)	0.397[c]
Diuretics, n (%)	73 (90.1%)	31 (86.1%)	42 (93.3%)	0.279[c]
Calcium channel blockers, n (%)	47 (58%)	20 (55.6%)	27 (60%)	0.687[c]
Aldosterone antagonists,	23 (28.4%)	14 (38.9%)	9 (20%)	0.104[e]
Agonists imidazoline receptors, n (%)	36 (44.4%)	13 (36.1%)	23 (51.1%)	0.177[c]
Other drug, n (%)	5 (6.2%)	4 (11.1%)	1 (2.2%)	0.166[d]

[a] – Parametric criteria: Student's test, M ± SD (mean ± standard deviation); [b] – Nonparametric criteria: Mann-Whitney U-test, Me (IQR) (median (interquartile range)); min and max values, [with] – χ2 Pearson, [d] – Fisher test, [e] – correction for continuity

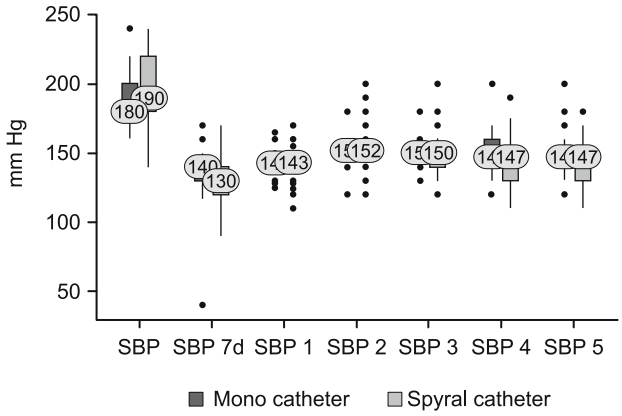

Fig. 1. Analysis of SBP dynamics depending on the type of catheter.

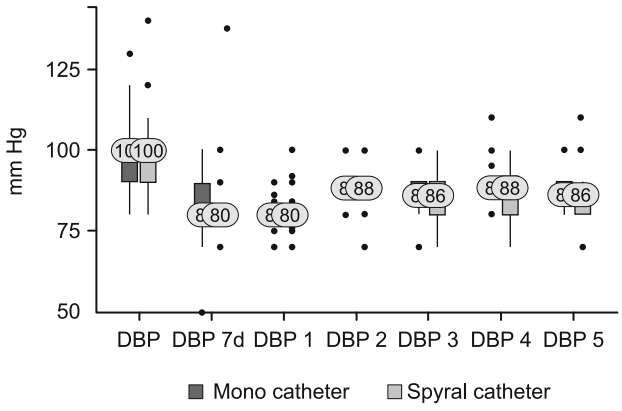

Fig. 2. Analysis of DBP dynamics depending on the type of catheter.

Statistical analysis

Statistical processing of the data was performed using SPSS 20.0 software. Quantitative data were assessed for their correspondence to the normal distribution using the Kolmogorov-Smirnov criterion. Quantitative measures with a normal distribution were described with arithmetic mean (M) and standard deviations (SD), 95% confidence interval (95% CI) limits; Student's test for independent samples was used for comparison. If there was no normal distribution, quantitative data were described using the median (Me), minimum and maximum values. Comparison of the two groups for a quantitative data whose distribution differed from normal was performed using the Mann-Whitney U-test. Categorical data were described with absolute values and percentages, and Pearson's $\chi 2$, continuity correction, and Fisher's test were used to identify relationships between nominal variables. When comparing three or more dependent populations whose distribution differed from normal, the non-parametric Friedman criterion with a posteriori comparison using the Conover-Iman criterion with Holm correction was used. Patient survival function was assessed by the Kaplan-Meier method. One-factor Cox regression analysis was used to estimate the factors associated with 5-year survival. Differences between compared variables were considered significant at $p < 0.05$.

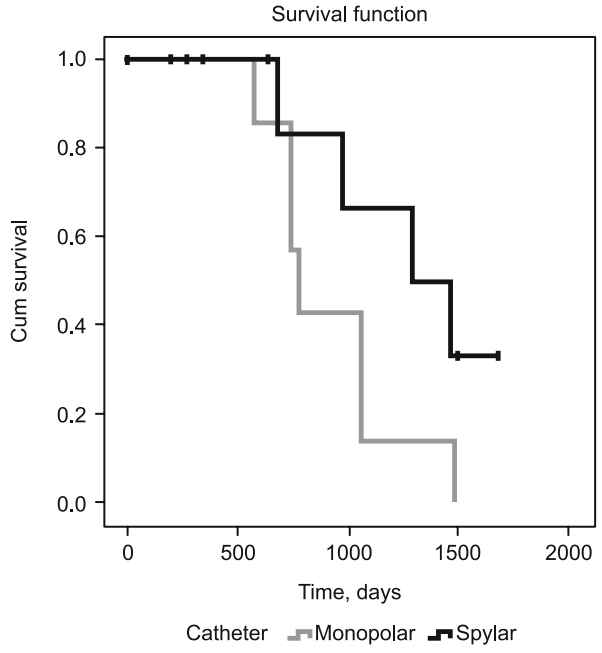

Fig. 3. Survival of patients with resistant hypertension depending on the type of catheter.

Results

General characteristics

The present study included 81 patients whose mean age was 57.79 ± 9.87 years, with a maximum and minimum of 77 and 34 years, respectively. Among them, there were 30 (37.04 %) men (mean age 57.79 ± 9.78) and 51 (62.96 %) women (mean age 59.71 ± 9.4 years), with men being statistically significantly younger ($p = 0.022$). 28.4 % of patients had type 2 diabetes mellitus (DM), coronary heart disease was registered in 37 %, including 24.7 % who had had a myocardial infarction at the time of the inclusion in the study.

Renal denervation procedure was performed using 2 types of catheters – monopolar (36 or 44.4 %) and spiral (45 or 55.6 %). The main clinical and demographic parameters did not differ in the two groups. At baseline, the patients received the average of 4.5 ± 1.4 antihypertensive medications. Importantly, more than 90 % received ACE inhibitors or angiotensin receptor antagonist in combination with diuretics and beta-adrenoblockers or calcium antagonists. However, only 28.4 % were taking mineralocorticoid receptor antagonists, with 44.4 % of the patients receiving moxonidine as their 4th drug. This can be explained by the lack of recommendations for the widespread use of spironolactone in the treatment of resistant hypertension at the time of the study initiation.

Tab. 2. Cox regression results to predict 5-year survival.

Indicator	B (SE)	95% CI for exp B			R
		Lower	Exp B	Upper	
Age, years	–5.838 (2.594)	0	0.003	0.470	0.024
Stroke	–14.83 (7.81)	0.001	1.01	1.611	0.058
Diabetes mellitus type 2	–88.402 (63.665)	0.0001	0.0001	6.301	0.165
SBP, mmHg	0.836 (0.554)	0.778	2.306	6.836	0.132
Creatinine, μmol/l	–3.588 (3.279)	0.001	0.028	17.084	0.274
GFR	0.372 (1.118)	0.077	0.690	6.172	0.740
Albuminuria	76.225 (81.379)	0.0001	1.27	2.366	0.349

B – regression coefficient, SE – standard error, CI – confidence interval

The general clinical characteristics of the patients participating in the study are presented in Table 1.

Blood pressure dynamics

The baseline office SBP was 190 (IQR 100; 140, 240) mmHg, BP 100 (IQR 60; 80, 140) mmHg. There were no differences between the baseline BP levels between the two groups ($p = 0.588$ for SBP and $p = 0.666$ for DBP). The analysis established statistically significant changes in the dynamics of office SBP (Fig. 1) and DBP (Fig. 2) ($p < 0.001$) assessed 1, 2, 3, 4 and 5 years after the renal denervation procedure. Immediate intervention results obtained on day 7 demonstrated statistically significant differences for SBP (140 mmHg in group 1 and 130 mmHg in group 2, $p = 0.024$). There were no significant changes depending on the type of catheter used in the dynamics of SBP (p (1st year) = 0.673; p (2nd year) = 0.405; p (3rd year) = 0.618; p (4th year) = 0.082; p (5th years) = 0.153) and DBP (p (1st year) = 0.805; p (2nd year) = 0.849; p (3rd year) = 0.206; p (4th year) = 0.116; p (5th years) = 0.028).

The presented analysis demonstrated a stability in the reduction of office SBP and DBP during the 5-year follow-up.

Survival

Survival of the patients with resistant hypertension, who underwent renal denervation was assessed by the Kaplan–Meier method. We studied the occurrence of major adverse cardiovascular events (MACE, i.e., heart attack, stroke, and death from cardiovascular disease) 5 years after the intervention. The analysis showed that the median survival time was 1 061 days from the start of follow-up (95% CI: 728.03 to 1 393.97 days). The analysis also showed a longer period in the onset of MACE in the group of the patients in whom a spiral catheter was used during the procedure (Fig. 3). Thus, the median survival time in the monopolar catheter group was 777 days (95% CI: 692.314 to 861.686), in the spiral catheter group 1294 days (95% CI: 713.079 to 1874.921).

During the 5-year follow-up, MACE was reported in 11 patients (13.6 %), among whom 9 patients developed stroke, resulting in death in 7 cases (8.6 %), and 2 patients (2.5 %) had an acute myocardial infarction.

To assess the factors associated with 5-year survival, one-way Cox regression analysis was used (Tab. 2). The result showed that only age had a statistically significant predictive value in the selected model (95% CI 0.0001–0.470, $p = 0.024$).

Discussion

The study demonstrated that renal denervation is an effective and safe treatment for uncontrolled hypertension; the long-term maintenance of the obtained effect is remarkable (Median SBP and DBP after 1 and 5 years 143/80 and 147/86 mmHg, respectively, $p = 0.0001$). It is worth noting a peculiarity of this observation design, where patients received multicomponent antihypertensive therapy before the study (on average, patients received 4.5 ± 1.4 drugs), further correction of taken drugs was performed as needed (ON MED design). At the same time, the volume and individual components of the therapy did not change significantly during the follow-up. The general characteristics of the patients, who took part in our work corresponded to those in previously conducted large studies, including randomized ones (8, 9, 12).

One of the peculiarities of the presented results is a comparison of two technical aspects of the procedure, namely the use of first- and second-generation catheters (unipolar and spiral catheters).

Our results are comparable to those published in the period, when interest in this procedure was growing (8, 9). For example, the results of the Symplicity HTN-1 study demonstrated a 27/17 mmHg decrease in office BP 1 year after the intervention ($p = 0.026$ for SBP and $p = 0.027$ for DBP) (8). However, this study used 1st generation catheters, and there was no randomization of the patients. In the Symplicity HTN-1 study, the safety of the procedure was convincingly demonstrated in our work as well.

In this work we have shown the effectiveness in reducing office SBP and DBP in using 2nd generation catheters, so in 45 patients the procedure was performed with a spiral catheter. In this group we managed to achieve a stability in the dynamics of SBP and DBP during 5 years of follow-up (Median SBP and DBP after 1 and 5 years 143/80 and 147/86 mmHg, respectively, $p = 0.0001$). The last large randomized SPYRAL HTN-ON study (15) also showed a reduction in SBP after 36 months –18.7 mmHg, 95% CI 16.6–3.3; $p = 0.0039$). The data we obtained can be compared to the results of this study.

A separate task of our study was to investigate the survival rate of the patients with uncontrolled hypertension after renal denervation in terms of its impact on the development of NSCLC, such as MACE (i.e., acute myocardial infarction, stroke and death from cardiovascular causes) (16). According to the available data, resistant hypertension is associated with an increased risk of adverse cardiovascular events. For example, in one registry of 205,750 patients with hypertension, the risk of cardiovascular complications was higher among those with drug-resistant therapy with (HR 1.47, 95% CI 1.33–1.62) (17). In addition, one large cohort study (n = 470 386 patients) examined the relationship of resistant hypertension with the risk of developing major cardiovascular diseases. Thus, a significant relationship was determined between

the resistant hypertension and overall mortality (HR 1.06, 95% CI 1.03–1.08), coronary heart disease (HR 1.24, 95% CI1.20–1. 28), heart failure (HR 1.46, 95% CI 1.40–1.52), cerebrovascular complications (HR 1.14, 95% CI 1.10–1.19), and end-stage renal disease (HR 1.32, 95% CI 1.27–1.37) (18). In our study, the survival function of the patients assessed by the Kaplan-Meier method showed that the median survival with spiral catheters was 1 294 days (95% CI: 713.079 to 1874.921), which was 517 days longer than in the monopolar catheter group (777 days, 95% CI: 692.314 to 861.686).

The result of distant consequences of resistant hypertension is very important; it has been demonstrated that 13.6 % of the patients after renal denervation developed stroke, acute myocardial infarction and death from cardiovascular causes. However, a limited number of studies are devoted to this issue. Thus, it is worth noting the results of the Global SYMPLICITY Registry (19), which included 2 237 patients, who underwent a renal denervation using a flexible unipolar catheter. In this registry study, after 3 years, 4.1 % (or 59) of the patients had a fatal outcome and 3.2 % (or 47) of the patients had a stroke.

A limited number of studies have examined the effects of the renal denervation procedure among persons of Asian race. Selected results are based on SYMPLICITY registry subanalysis data (20, 21). Among the Asian population, renal denervation was shown to reduce SBP and DBP by –26.7 ± 18.5, –30.1 ± 21.6, and –32.5 ± 18.8 mm Hg after 12, 24, and 36 months, respectively (21). On this basis, a major international consensus has suggested Asian race as a possible predictor of response to intervention (22). In our study, there was a predominance of Asian race (57 or 70.4 %). At the same time, there were no significant differences in SBP and DBP dynamics.

However, it should be recognized that our study has certain significant limitations, which should be considered, when assessing the results. Firstly, based on the design, there was no sham intervention group (sham-control), as well as randomization procedure that was adopted in the recent published studies (11, 12, 15).

Also, very important is the fact that the final analysis reflected the results of office BP measurement only, the indicators of daily BP monitoring were not available at each stage of the analysis. Although Korotkoff blood pressure measurement is the gold standard, in modern studies, the main endpoint of effectiveness was the mean daily BP (12, 15).

Conclusion

The results of our study demonstrated the efficiency and safety of renal denervation with both monopolar and spiral catheters in the treatment of uncontrolled hypertension during a combined antihypertensive therapy. The most significant is the demonstrated stability of the effect after the procedure was carried out, as well as the survival of the patients with resistant hypertension after the intervention. The analysis revealed that only age can act as a predictor of the development of adverse events in the patients after sympathetic denervation of the renal arteries.

Learning points

1. The analysis established the changes in the dynamics of office SBP and DBP assessed 1, 2, 3, 4, and 5 years after the renal denervation procedure.
2. The analysis demonstrated a stability in the reduction of office SBP and DBP during the 5-year follow-up.
3. The analysis also showed a longer period in the onset of MACE in the group of patients in whom a spiral catheter was used during the procedure.

References

1. Abbafati C et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396 (10258): 1223–1249.

2. Williams B, Mancia G, Spiering W et al 2018 practice guidelines for the management of arterial hypertension of the European society of cardiology and the European society of hypertension ESC/ESH task force for the management of arterial hypertension. Journal of Hypertension 2018; 36 (12): 2284–2309.

3. Wright JT, Williamson JD, Whelton PK et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015; 26; 373 (22): 2103–2016.

4. Carey RM, Calhoun DA, Bakris GL et al. Resistant hypertension: Detection, evaluation, and management a scientific statement from the American Heart Association. Hypertension 2018; 72 (5): e53–e90.

5. Sinnott SJ, Smeeth L, Williamson E, Douglas IJ. Trends for prevalence and incidence of resistant hypertension: Population based cohort study in the UK 1995–2015. BMJ 2017; 358: j3984

6. Murray E. Renal denervation for hypertension: observations and predictions of a founder. Eur Heart J 2014; 35 (18): 1178–1185.

7. Mahfoud F, Azizi M, Ewen S et al. Proceedings from the 3rd European Clinical Consensus Conference for clinical trials in device-based hypertension therapies. Eur Heart J 2020; 41 (16): 1588–1599.

8. Krum H, Schlaich M, Whitbourn R et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373 (9671): 1275–1281.

9. Esler MD, Krum H, Sobotka PA et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A randomised controlled trial. Lancet 2010; 376 (9756): 1903–1909.

10. Grassi G, Ram VS. Evidence for a critical role of the sympathetic nervous system in hypertension. J Am Soc Hypertens 2016; 10 (5): 457–466.

11. Bhatt DL, Kandzari DE, O'Neill WW et al. A Controlled Trial of Renal Denervation for Resistant Hypertension. N Engl J Med 2014; 370 (15): 1393–1401.

12. Böhm M, Kario K, Kandzari DE et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet 2020; 395 (10234): 1444–1451.

13. Reshetnik A, Gohlisch C, Scheurig-Münkler C, Bucourt MD, Zidek W, Tölle M, Giet M. Predictors for success in renal denervation – a single centre retrospective analysis. Sci. Rep 2018; 8 (1): 15505.

14. KDIGO 2021. Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. Kidney Int 2021; 99 (3S): 1–87.

15. Mahfoud F, Kandzari DE, Kario K et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet 2022; 399 (10333): 1401–1410.

16. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol 2021; 21: 241.

17. Daugherty SL, Powers JD, Magid DJ et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012; 125: 1635–1642.

18. Sim JJ, Bhandari SK, Shi J et al. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int 2015; 88 (3): 622–632.

19. Mahfoud F, Böhm M, Schmieder R. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. Eur Heart J 2019; 40 (42): 3474–3482.

20. Chih-Kuo Lee, Tzung-Dau Wang, Ying-Hsiang Lee et al. Efficacy and Safety of Renal Denervation for Patients with Uncontrolled Hypertension in Taiwan: 3-Year Results from the Global SYMPLICITY Registry-Taiwan (GSR-Taiwan). Acta Cardiol Sin 2019; 35 (6): 618–626.

21. Byeong-Keuk Kim, Hyo-Soo Kim, Seung-Jung Park et al. Long-term outcomes after renal denervation in an Asian population: results from the Global SYMPLICITY Registry in South Korea (GSR Korea). Hypertension Res 2021; 44: 1099–1104.

22. Kario K, Kim B.K, Aoki J et al. Renal Denervation in Asia. Consensus Statement of the Asia Renal Denervation Consortium. Hypertension 2020; 75 (3): 590–602.

Received May 11, 2022.
Accepted May 25, 2022.