Long-term quality of life and clinical outcomes in patients with resistant hypertension treated with renal denervation

Agata Krawczyk-Ożóg[1], Tomasz Tokarek[1], Katarzyna Moczała[1], Zbigniew Siudak[1], Artur Dziewierz[2], Waldemar Mielecki[2], Tomasz Górecki[1], Karolina Gerba[1], Dariusz Dudek[1,2]

[1]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[2]2nd Department of Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

Adv Interv Cardiol 2016; 12, 4 (46): 329–333
DOI: 10.5114/aic.2016.63633

Abstract

Introduction: Pharmacological treatment combined with lifestyle modifications is an effective treatment for arterial hypertension. However, there are still patients who do not respond to standard treatments. Patients with pharmacologically resistant hypertension may benefit from renal denervation (RDN).

Aim: To assess long-term quality of life (QoL) after RDN and effectiveness in reduction of blood pressure (BP) in patients with resistant hypertension.

Material and methods: From 2011 to 2014, 12 patients with previously diagnosed resistant hypertension, treated by RDN, were included in this study. The QoL was assessed using a standardized Polish version of the Nottingham Health Profile questionnaire (NHP).

Results: The median age was 54 (IQR: 51–57.5) years. Mean baseline ambulatory pre-procedural systolic/diastolic BP was 188/115 ±29.7/18 mm Hg. The mean values of systolic/diastolic BP measured perioperatively and 3, 6, 12 and 24 months postoperatively were 138/86, 138/85, 146/82, 152/86, and 157/91. All *p*-values for mean systolic and diastolic BP before versus successive time points after RDN were statistically significant; *p*-value for all comparisons < 0.05. Improvement of QoL was only observed in two sections of the NHP questionnaire: emotional reaction and sleep disturbance. The analysis of the NHP index of Distress (NHP-D) showed a lower distress level perioperatively and 3, 6, 12 and 24 months after RDN as compared to baseline. The RDN was not associated with any significant adverse events.

Conclusions: Patients with pharmacologically resistant hypertension treated with RDN achieved significant reduction in BP during 24-month follow-up. Furthermore, a significant improvement in the QoL was observed in those patients.

Key words: resistant hypertension, blood pressure, quality of life, catheter-based renal denervation.

Introduction

Renal denervation (RDN) is a percutaneous procedure that uses radio-frequency energy to ablate the nerves in renal arteries. This method decreases arterial blood pressure (BP), protects against hypertension-related complications and improves quality of life (QoL). Resistant hypertension is defined as BP that remains above the goal in spite of the concurrent use of three optimally dosed antihypertensive agents of different classes, one of which should be a diuretic [1]. Importantly, an increasing number of people are affected by resistant hypertension each year [2]. Renal denervation is based on ablation of two types of nerves: afferent and efferent. Afferent signaling in the posterior hypothalamus increases central sympathetic system activity. The consequences of efferent signaling are activation of the renin-angiotensin-aldosterone system and vasoconstriction of renal arteries, which results in increased BP values. Recently published data on RDN are not consistent. Despite the benefits reported in previous studies [3, 4], the SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension) clinical trial failed to confirm the effectiveness of RDN in patients with resistant hypertension [5]. However, definitive conclusions on its inefficacy cannot be drawn due to a number of study limitations. Also, benefits of RDN may be limited to a selected group of patients which has not yet been clearly defined. Fortunately, the long-term effectiveness of RDN in terms of BP lowering

Corresponding author:
Prof. Dariusz Dudek MD, PhD, Department of Interventional Cardiology, 2nd Department of Cardiology, Institute of Cardiology, Jagiellonian University Medical College, 17 Kopernika St, 31-501 Krakow, Poland, phone: +48 12 424 71 81, e-mail: mcdudek@cyfronet.pl
Received: 31.07.2016, **accepted:** 30.09.2016.

as well as other clinical endpoints is still under investigation. There is growing interest in the assessment of QoL, which seems to be an important outcome measure also in patients with resistant hypertension. However, QoL with assessment of the treatment effectiveness in patients after RDN has not been widely evaluated. In this study we analyzed the long-term results (24 months) of RDN, and obtained patients' subjective QoL assessment 24 months following RDN using the Nottingham Health Profile (NHP) questionnaire. The NHP scale is a generic QoL questionnaire and is capable of measuring changes in perceived health following introduced treatment [6]. More importantly, its performance has not reported in other studies dealing with the issue of QoL in patients with resistant hypertension.

Aim

The aim of the study was to evaluate long-term QoL after RDN as well as its effectiveness in reduction of BP in patients with resistant hypertension.

Material and methods

The study group consisted of 12 consecutive patients enrolled from January 2011 to December 2014. These patients have been diagnosed with resistant arterial hypertension. Resistant arterial hypertension was defined as hypertension present despite the concurrent use of at least three antihypertensive medications, including diuretics. Previously to the procedure and in successive follow-up periods after RDN all patients have been regularly taking antihypertensive medications. Patients were qualified for RDN and underwent the procedure in accordance with current guidelines [7]. The procedure is performed with the Symplicity renal denervation catheter (Medtronic, Minneapolis, MN, USA), which is introduced through the femoral artery to the renal arteries bilaterally, where it emits radiofrequency energy in range of 5–8 W to damage the nerves present in the adventitia of the renal artery. The first ablation is applied to the distal part of the truncus of the renal artery, and then the catheter is withdrawn 5 mm to the outside and rotated around 90°. Further applications cover all the circuit of the artery [8]. Clinical and procedural data were obtained prospectively before the intervention and subsequently during in-hospital stay after RDN and at 3, 6, 12 and 24 months following the procedure. For the evaluation of QoL, the standardized Polish version of the NHP questionnaire was used. This questionnaire consists of six sections, referring to separate areas of functioning: energy, pain, emotional reactions, sleep disturbance, social isolation and physical mobility. The NHP index of Distress (NHP-D) was devised from the NHP questionnaire, consisting of 24 yes/no items; higher scores indicate greater distress [9]. The follow-up interviews were conducted via telephone before RDN, and 3, 6, 12, and 24 months following the procedure. The periprocedural data were obtained from the medical history of patients. Blood pressure measurements were taken by the patients themselves at their place of residence. Patients were asked to provide measurements of BP after RDN at least twice a day and write down the values.

Statistical analysis

Standard descriptive statistics were used. The normality of the data was assessed with the Shapiro-Wilk test. Quantitative variables were described using means and standard deviations or medians with interquartile (IQR) ranges as appropriate. Categorical variables were presented as percentages. The Wilcoxon signed-rank test (for non-normally distributed data) or paired Student's *t*-test (for normally distributed data) were applied for assessment of changes in particular dimensions of the questionnaire and NHP-D at successive time points of follow-up. The level of statistical significance was set at $p \leq 0.05$. All analyses were carried out with the software StatSoft, Inc. Statistica (data analysis software system), version 10 (Tulsa, OK, USA).

Results

The median age of included patients was 54 (IQR: 51–57.5) years. Men constituted 58% (7 patients) of patients. Four (33%) patients suffered from diabetes mellitus, 7 (58%) from hypercholesterolemia, 2 (16.6%) had previous stroke and 6 (50%) were active smokers or have recently quitted. The mean body mass index (BMI) was 29.9 ±3.9 kg/m^2 with overweight in 5 (41.7%) patients and obesity in 5 (41.7%) patients. There was no patient with diagnosed obstructive sleep apnea syndrome. The mean duration of energy delivery was 18.1 ±6.7 min. The mean radiation dose and contrast load were 0.58 ±0.29 Gy and 243.57 ±73.3 ml, respectively. The mean number of successful ablations applied to the right and left renal artery was 6.6 ±4.4 and 5.6 ±1.7, respectively. There were no changes in the levels of sodium $p = 0.5$, potassium ($p = 0.9$), urea ($p = 0.5$), or creatinine ($p = 0.7$) after the procedure as compared to baseline. There were no procedure-related complications. No difference between kidney function estimated by glomerular filtration rate (eGFR) before and after the procedure was found (53 ±9.9 vs. 55.8 ±8.9 ml; $p = 0.4$). In the study population there was no significant change in the number or type of antihypertensive drugs. Mean baseline pre-procedural systolic/diastolic BP for the whole group was 188/115 ±29.7/18 mm Hg. Median follow-up was 872 (IQR: 499–1187) days. The mean BP after the procedure was reduced to 138/86 ±29.2/19.9, 138/85 ±16.9/8.9, 146/82 ±16.4/5.9, 152/86 ±14/11.6, and 157/91 ±12.2/10.3 mm Hg perioperatively and 3, 6, 12 and 24 months after the procedure, respectively. The analysis shows significant differences between mean values of pre-procedural BP in compari-

son with those obtained in successive periods after RDN. All *p*-values for mean systolic and diastolic BP before versus successive time points after RDN were statistically significant; p-value for all comparisons < 0.05. The mean value of the highest observed BP before the procedure was 229/132 ±37.9/26.5 mm Hg. The maximal BP obtained perioperatively and 3, 6, 12 and 24 months after the procedure was 161/98 ±29/21.7, 159/95 ±25.3/17.1, 166/97 ±26.7/17.9, 177/104 ±24.8/12.4, and 203/121 ±38.4/25.4 mm Hg, respectively. A significant reduction of maximum systolic and diastolic BP in comparison with baseline was observed perioperatively and 3, 6 and 12 months following RDN (*p*-values for maximum systolic and diastolic BP before versus perioperatively and 3, 6 and 12 months after RDN were < 0.5). This effect was not observed 24 months after the procedure (systolic and diastolic BP before vs. 24 months after RDN: $p = 0.2$, $p = 0.5$, respectively). Results are presented in Figure 1.

Table I shows a detailed distribution of the scores from NHP. A significant improvement of QoL was observed in the sections of emotional reactions (answers of patients before RDN versus all successive periods of follow-up) and sleep disturbance (answers of patients before RDN versus perioperatively and 3 and 24 months following RDN) in the NHP questionnaire. Total score of NHP-D was significantly lower perioperatively and at 3, 6, 12, and 24 months after RDN as compared to baseline.

Discussion

Patients treated with RDN in the studied group achieved significant reduction in mean systolic and diastolic BP during 24-month follow-up and in mean value of the highest BP perioperatively and 3, 6 and 12 months following the procedure. Patients with resistant hypertension are at a higher risk of cardiovascular events and end-organ damage as compared to patients with adequately controlled hypertension [10]. The efficacy of the RDN procedure has been assessed in several large studies. The Symplicity HTN-1 and randomized Symplicity HTN-2 trial demonstrated that RDN is feasible, effective and safe in the treatment of resistant hypertension. In both studies, no adverse effects of RDN on renal function were observed [3, 4]. The Symplicity HTN-3 trial suggested that 6 months after RDN there were no significant dif-

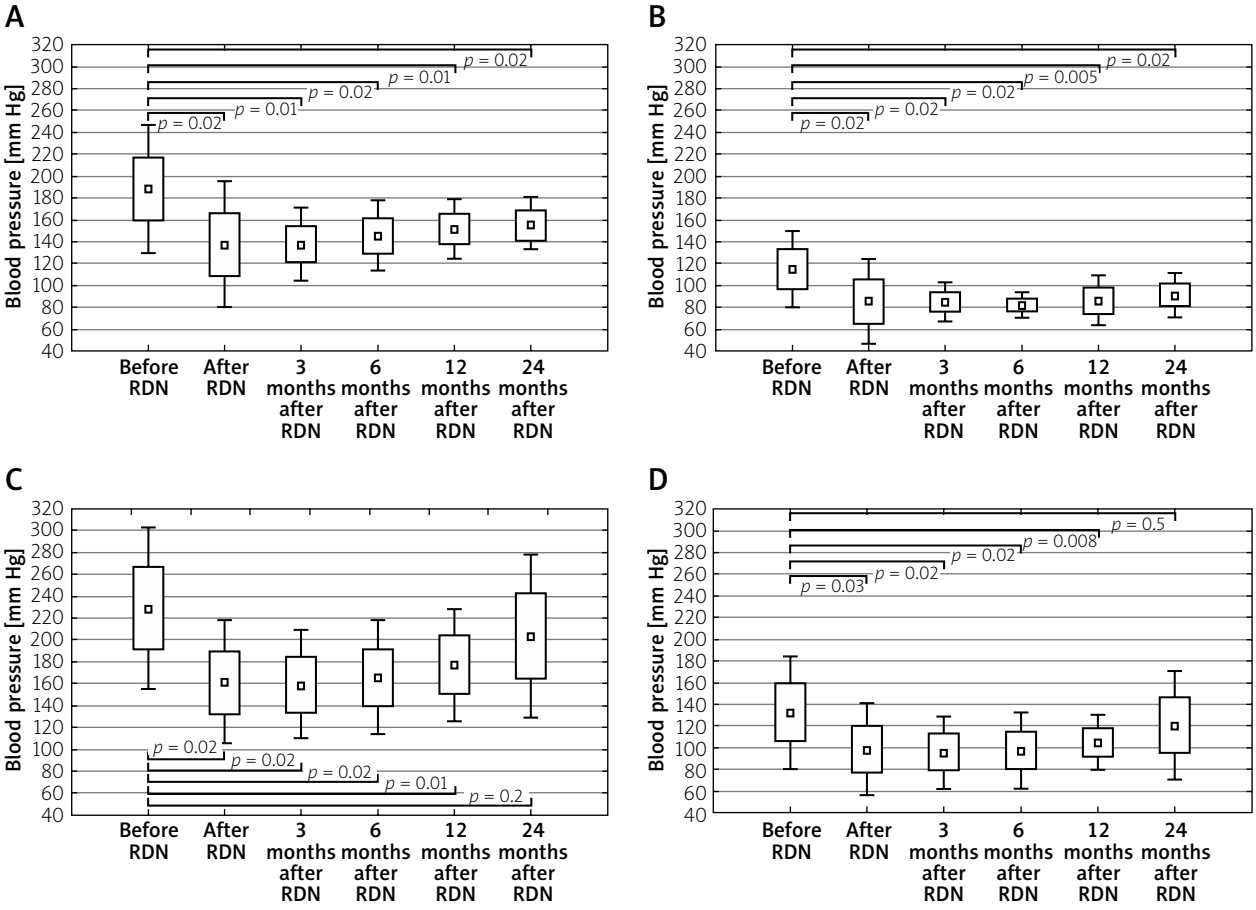

Figure 1. Mean and maximal systolic and diastolic blood pressure before and after renal denervation: **A** – mean systolic blood pressure, **B** – mean diastolic blood pressure, **C** – maximal systolic blood pressure, **D** – maximal diastolic blood pressure. Results presented as mean values (squares), SD (box), and minimum and maximum values (whiskers)

Table I. Detailed results from Nottingham Health Profile (NHP) Questionnaire

Variable	Before RDN	Perioperatively	*P*-value[a]	3 months after RDN	*P*-value[b]	6 months after RDN	*P*-value[c]	12 months after RDN	*P*-value[d]	24 months after RDN	*P*-value[e]
Energy	22.2 ±41.0	8.3 ±20.7	0.2	5.6 ±19.3	0.2	8.3 ±20.7	0.3	25.0 ±32.2	0.8	27.8 ±37.2	0.6
Pain	13.5 ±24.7	15.6 ±28.8	0.7	15.6 ±28.8	0.7	15.6 ±28.8	0.7	15.6 ±27.2	0.7	15.6 ±28.8	0.7
Emotional reactions	19.4 ±23.3	9.3 ±13.3	0.02	4.6 ±11.1	0.02	4.6 ±11.1	0.02	5.6 ±11.1	0.02	7.4 ±17.3	0.02
Sleep disturbance	40.0 ±37.2	21.7 ±30.1	0.04	21.7 ±30.1	0.04	23.3 ±30.6	0.07	30.0 ±26.3	0.2	23.3 ±32.8	0.03
Social isolation	1.7 ±5.8	0	0.3	0	0.3	0	0.3	1.7 ±5.8	1	1.7 ±5.8	1
Physical mobility	6.3 ±14.6	9.4 ±17.0	0.3	9.4 ±17.0	0.3	9.4 ±17.0	0.3	10.4 ±16.7	0.2	9.4 ±17.0	0.3
NHP-D	4.2 ±4.7	2.2 ±3.0	0.01	1.7 ±2.9	0.005	1.8 ±2.8	0.006	2.8 ±3.4	0.04	2.8 ±4.5	0.03

Mean values of total score for each section expressed as a percentage and mean values of the NHP index of Distress (NHP-D). Comparison of response before the procedure versus perioperatively and at 3, 6, 12 and 24 months after renal denervation (RDN). [a]Before RDN vs. perioperatively, [b]before RDN vs. 3 months after RDN, [c]before vs. 6 months after RDN, [d]before vs. 12 months after RDN, [e]before vs. 24 months after RDN.

ferences in reduction of systolic BP in office or 24-hour ambulatory measurements as compared with a sham control [5]. The results of the Symplicity HTN-3 trial did not confirm the results of previous registries and trials with a potentially overestimated treatment effect; however, several limitations of the study design might have influenced the clinical outcomes [11–13]. On the other hand, Symplicity HTN-3 confirmed the safety of the RDN procedure. Based on the results of individual analyses, we can conclude that the final effect of RDN will depend on many factors and this procedure may not be suitable for all patients. Identifying predictors which make RDN effective is important to select patients who will respond to treatment. Due to important uncertainties about RDN, more research is required to provide conclusive evidence for antihypertensive long-term effects, safety, clinical outcomes and QoL improvement after RDN. The additional benefits of RDN observed in other studies were reduction of left ventricle mass and improvement of diastolic function. These might have important prognostic implications for patients with resistant hypertension at high cardiovascular risk [14]. Other studies have suggested a reduction in heart rate over 6 months [15, 16], as well as a positive effect on renal function [17], glucose metabolism and insulin sensitivity [18] after RDN. In the present study an improvement in QoL was observed. A significantly lower level of distress (NHP-D) and amelioration of the emotional reactions and sleep disturbance sections were reported. However, they were not observed at all successive time points, probably due to the size of the group and possible observational error. The effects of RDN in patients with obstructive sleep apnea syndrome are the subject of several studies. In these patients hypertension is caused by increased sympathetic overdrive. The RDN may provide greater BP reduction and might reduce sleep-onset cardiovascular events by suppressing hypoxia-induced nocturnal BP peaks [19]. The RDN also improves the severity of obstructive sleep apnea syndrome in patients with resistant hypertension by a reduction of the apnea-hypopnea index, fewer nocturnal awakenings and improvement of nocturnal oxygen saturation [20]. It might explain better outcomes in the section of sleep disturbances in the NHP questionnaire after the RDN as compared to baseline. The QoL after RDN has been assessed in several studies [21–24]. Lenski *et al.* observed reduction of anxiety and depression, intensity of headache and improved QoL and stress tolerance in 119 patients treated with RDN. In that study, the Hospital Anxiety and Depression Scale and Short Form-12 Health Survey were used to assessed QoL at baseline and at 3 and 6 months following RDN [21]. In other studies RDN improved subjective QoL in several aspects examined by Beck Depression Inventory-II and without a detrimental effect on any elements of the 36-Item Short-Form Health Survey 3 months after RDN. However, there was no correlation between improvement of QoL and the magnitude of BP reduction [22]. A recently published study assessed the effect of RDN on BP and health-related QoL 12 months after RDN and revealed that RDN in patients with confirmed resistant hypertension is associated with a reduction in BP and a sustained improvement in mental health-related aspects of QoL [23]. Another study reported that sufficient BP reduction by RDN and time following therapeutic success lead to significant improvements in patient QoL and a loss of anxiety in 93% of recipients [24]. Several studies have revealed improvement of the QoL using different questionnaires, especially in terms of depression and anxiety. It is consistent with our results concerning the emotional reactions section and the index of distress from the NHP questionnaire.

The results of the present study were obtained at one center, which potentially limits their generalizability. An-

other limitation is the lack of a control group and small sample size related to the limited number of RDN procedures performed in our center. Twenty-four-month follow- up was not available in all the patients. In addition, measurements of BP values were taken by the patients themselves at their place of residence, and this fact could be a potential source of inaccurate results. Ambulatory blood pressure monitoring was not performed. There are potential limitations associated with the tool for QoL assessment. The NHP is a generic questionnaire which is not specific for cardiovascular diseases and interventions.

Conclusions

Patients with pharmacologically resistant hypertension treated with RDN achieved significant reduction of mean values of BP during 24-month follow-up. Furthermore, a significant improvement in the QoL was observed in the emotional reactions as well as sleep disturbance sections of the NHP questionnaire and in the NHP-D.

Conflict of interest

The authors declare no conflict of interest.

References

1. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension – its identification and epidemiology. Nat Rev Nephrol 2013; 9: 51-8.
2. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008; 51: 1403-19.
3. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension durability of blood pressure reduction out to 24 months. Hypertension 2011; 57: 911-7.
4. Esler MD, Krum H, Sobotka PA, et al. (Symplicity HTN-2 Investigators). Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet 2010; 376: 1903-9.
5. Bhatt DL, Kandzari DE, O'Neill WW, et al. (SYMPLICITY HTN-3 Investigators). A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370: 1393-401.
6. Wann-Hansson C, Hallberg IR, Risberg B, et al. A comparison of the Nottingham Health Profile and Short Form 36 Health Survey in patients with chronic lower limb ischaemia in a longitudinal perspective. Health Qual Life Outcomes 2004; 2: 9.
7. Mancia G, Fagard R, Narkiewicz K, et al. 2013 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159-219.
8. Witkowski A, Januszewicz A, Imiela J, et al. Catheter-based renal sympathetic denervation for the treatment of resistant arterial hypertension in Poland – experts consensus statement. Kardiol Pol 2011; 69: 1208-11.
9. Hunt SM, McKenna SP, McEwen J, et al. The Nottingham Health Profile: subjective health status and medical consultations. Soc Sci Med 1981; 15: 221-9.
10. Januszewicz A, Witkowski A. Renal denervation – where do we stand in 2014? Postep Kardiol Inter 2014, 10: 1.
11. Warchoł-Celińska E, Januszewicz A, Prejbisz A, et al. Renal denervation after the symplicity HTN-3 trial. Postep Kardiol Inter 2014; 10: 75-7.
12. Luscher TF, Mahfoud F. Renal nerve ablation after SYMPLICITY HTN-3: confused at the higher level? Eur Heart J 2014; 35: 1706-11.
13. Mahfoud F, Bhatt DL. Catheter-based renal denervation: the black box procedure. JACC Cardiovasc Interv 2013; 6: 1092-94.
14. Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 2012; 59: 901-9.
15. 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: 1275-81.
16. Ukena C, Mahfoud F, Spies A, et al. Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. Int J Cardiol 2013; 167: 2846-51.
17. Mahfoud F, Cremers B, Janker J, et al. Renal haemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. Hypertension 2012; 60: 419-24.
18. Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 2011; 123: 1940-6.
19. Kario K, Ikemoto T, Kuwabara M, et al. Catheter-based renal denervation reduces hypoxia-triggered nocturnal blood pressure peak in obstructive sleep apnea syndrome. J Clin Hypertens (Greenwich) 2016; 18: 707-9.
20. Jaén-Águila F, Vargas-Hitos JA, Mediavilla-García JD. Implications of renal denervation therapy in patients with sleep apnea. Int J Hypertens 2015; 2015: 408574.
21. Lenski D, Kindermann I, Lenski M, et al. Anxiety, depression, quality of life and stress in patients with resistant hypertension before and after catheter-based renal sympathetic denervation. EuroIntervention 2013; 9: 700-8.
22. Lambert GW, Hering D, Esler MD, et al. Health-related quality of life after renal denervation in patients with treatment-resistant hypertension. Hypertension 2012; 60: 1479-84.
23. Lambert GW, Hering D, Marusic P, et al. Health-related quality of life and blood pressure 12 months after renal denervation. J Hypertens 2015; 33: 2350-8.
24. Dörr O, Liebetrau C, Möllmann H, et al. Influence of renal sympathetic denervation on quality of life. J Interv Cardiol 2013; 26: 536-41.