RENAL DENERVATION AND RESISTANT HYPERTENSION: BACK TO THE FUTURE

INGRID PRKAČIN[1,2], BORNA VRHOVEC[1], ANA LEGOVIĆ[1], VESNA ĐERMANOVIĆ DOBROTA[2], TOMISLAV BULUM[2] and VINKO VIDJAK[2,3]

[1]University of Zagreb, School of Medicine, Merkur University Hospital, Department of Internal Medicine, [2]University of Zagreb, School of Medicine, Merkur University Hospital, Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, [3]University of Zagreb, School of Medicine, Merkur University Hospital, Department of Radiology, Zagreb, Croatia

Renal sympathetic denervation (RDN) with radiofrequency (RF) is being used to treat resistant hypertension in seven non-responder patients (62±6 years for age, 5F/2M) despite treatment with >4 different antihypertensive drugs in optimal doses. Prior to diagnosing a patient as having resistant hypertension, we document adherence and exclude white-coat hypertension, inaccurate measurement of blood pressure and secondary causes. Office blood pressure (BP) measurements at 1, 3, 6, 12 and 18 months follow-up visits were compared to baseline. We used STATISTICA 10, 2011 software (Stat Soft Inc., Tulsa, OK, USA). Values are mean SD and considered statistically significant if P <0.001. At baseline, values were 184±21 and 106±26 mmHg for systolic (SBP) and diastolic (DBP), 6.7±1 for number of antihypertensive drug classes. One, 3, 6, 12 and 18 months after RDN, office SBP values were significantly lower (144±13 mmHg, 140±17, 141± 15, 139±12 and 135±11 mmHg; P <0.001), with no significant reduction in DBP values at 1, 3, 6, 12 and 18 months after RDN (81±6, 82±9, 79±9, 78±6, and 76±7 mmHg). The number of antihypertensive drug classes before and 6, 12, 18 months after RDN were evaluated. Six months after RDN the number of antihypertensive drug classes required was 6.5±1, after 12 and 18 months was 5.5±1 and 4.5±1. During RDA no complications occurred (the pain during the procedure was well tolerated) and the renal function remained stabile. Renal sympathetic denervation is being a concomitant treatment of drug-resistant hypertension (rHT). The sustained reduction of SBP was observed after the RDN. Patients have benefit the most from procedure after 6-12 months. Further meta-analysis will evaluate the importance of new devices for less pain treatment of RDN.

Key words: resistant hypertension, renal sympathetic denervation

Address for correspondence: Ingrid Prkačin, MD, PhD,
University Hospital Merkur,
School of Medicine,
University of Zagreb, Croatia
I.Zajca 19
10 000 Zagreb, Croatia
Tel: +385 1 2253 231; Fax: +385 1 2253 393
E-mail:ingrid.prkacin@gmail.com

INTRODUCTION

If pharmacological therapy with at least three antihypertensive drugs in optimal doses, including a diuretic, fails to reduce the office blood pressure to below 140/90mmHg, patients are considered to suffer from drug resistant hypertension (rHT)[(1,2)]. The prevalence of rHT has been estimated between 8 to 13% of all antihypertensive drug treated patients[(2)]. In recent decades, the use of antihypertensive drugs has revolutionised the therapy of hypertension. Despite the available pharmacological inhibition of the sympathetic nervous system, about 50% of patients show suboptimal control and pharmacotherapy does not provide adequate effects in clinical practice[(3-5)]. Although the most common causes of therapeutic failure are undiscovered secondary causes of hypertension and lack of patient/doctors compliance,

in about 10% of cases it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system,condition that confers a high cardiovascular risk to the patient[6,7,8]. Renal sympathetic denervation (RDN) produce multilevel inhibition of the sympathetic nervous system, and trigers additional positive metabolic effects[9,10,11].

The reason for the rapid introduction of RDN in the therapy of rHT were the reported high efficiency and safety of the procedure[9]. The effectiveness was demonstrated in the studies Symplicity HTN-1 and HTN-2, and in the EnligHTN-1 Study (by using special RF ablation catheters)[10,11]. According to the results of different trials, including Symplicity HTN-3 (this study did not show differences in SBP reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there are several concerns about inexperienced doctors in the field of RDN, the study population and the medical treatment), RDN seems to be safe and procedure-related complications of catheter-based RDN were rare[11,12].

Based on these findings the objective of this study was to investigate long term effects of RDN on BP control and renal function parameters in our patients.

SUBJECTS, MATERIALS AND METHODS

Study included 7 patients with proven resistant hypertension (rHT) from a cohort of 101 patients referred to ambulance due to suspected rHT. Prior to diagnosing a patient as having rHT, we document adherence and exclude white-coat hypertension, inaccurate measurement of blood pressure and secondary causes. In order to qualify patients as rHT (defined as BP that remains >140/90 mmHg in spite of the use of >4 different antihypertensive agents in optimal dose, including diuretic, and lifestyle changes), patients for RDN had to show a mean systolic BP >150 mmHg in the 24 hr ambulatory blood pressure measurement (ABPM).

Data collection

Basic anthropometric measurements were performed on all subjects. Office Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 5-10 minutes. Fasting venous blood samples were collected in the morning between 08:00 and 09:30 hours after an overnight fast for the determination of basic blood chemistries. Data on serum creatinine levels, age, sex and race were used to calculate the estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which has been shown to be accurate in determining kidney function in rHT[6].

Study procedure

In our Center RDN was performed using standard radiofrequency system with ablation catheter (5F system/ 6F guide catheter; Symplicity TM RDN System) inserted through the femoral artery, engaging the renal artery bilaterally. Five to six nerve ablations of 100 second duration on each side were performed without any complications. During the RDN patients received intravenous narcotic and sedative drugs agains the abdominal pain. Office BP measurements at 1, 3, 6, 12 and 18 months follow-up visits were compared to baseline. At six months after RDN duplex sonography was performed. The number of antihypertensive drug classes before and 6, 12, 18 months after RDN were evaluated.

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethics committees.

Statistical Analysis

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage.
Level of statistical significance was considered statistically significant if $P < 0.001$. Statistical analysis was performed by statistical package STATISTICA 10, 2011 software (Stat Soft Inc., Tulsa, OK, USA).

RESULTS

Purpose of this Study was to evaluate efficacy and safety of renal sympathetic denervation (RDN) with radiofrequency (RF) as additional therapy for rHT pt during the 18-month follow-up. RDN is being used to treat rHT in seven non-drug responder patients (62±6 years for age, two male) with >4 different antihypertensive drugs in optimal doses, with a severe comorbidity (four patients (2F/2M) with well controled diabetes mellitus type 2, one male patient with coronary artery disease, two male patients with chronic kidney disease (defined as eGFR CKD EPI <60 ml/min/1.73m2). At baseline, before RDN, values were 184±21 and 106±26 mmHg for systolic (SBP) and diastolic (DBP), heart rate 67±6 beats/min, 6.7±1 for number of different antihypertensive drug classes. One, 3, 6, 12 and 18 months after RDN, office SBP values were significantly lower (144±13, 140±17, 141±15, 139±12 and 135±11 mmHg; $P < 0.001$), with no significant reduction in DBP values at 1, 3, 6, 12 and 18 months after RDN (81±6, 82±9, 79±9, 78±6, and 76±7 mmHg).
The characteristics of the study subjects are listed in Table 1.

During RDA no complications occurred (the pain during the procedure was well tolerated) and the mean renal function at baseline was eGFR CKD-EPI stage G2 (65±38 ml/min/1.73m^2).

Table 1.

Baseline clinical characteristics and biochemical measures of all patients treated with RDN method (n =7)

Variable	Data
Age (yrs)	62 ± 6
Women	5/7
Type 2 diabetes	4/7
Body mass index (kg/m^2)	32± 2
Antihypertensive drugs (n)	6.7 ± 1
ACEI	2/7
ARB	5/7
ACEI and ARB	0/7
β - blocker	5/7
Calcium-channel blocker	7/7
α - blockers	5/7
Diuretic	7/7
Direct renin inhibitor	0/7
Vasodilator	2/7
Central acting sympatholytic	7/7
Office SBP (mmHg)	184 ± 21
Office DBP (mmHg)	106 ± 26
Heart rate (beats/min)	67 ± 6
eGFR (ml/min per 1.73m^2)	65 ± 38
Serum creatinine (μmol/L)	108± 61

Values are mean SD or number/number of patients
ACEI - angiotensin-converting enzyme inhibitor
ARB - angiotensin II receptor blocker
DBP - diastolic blood pressure
eGFR - estimated glomerular filtration rate (CKD-EPI formula)
SBP - systolic blood pressure

All patients show a small reduction of the mean ABPM but not show a reduction of systolic BP >10 mmHg at 6 months following RDN therapy.

Six months after RDN the number of antihypertensive drug classes required was 6.5±1, after 12 and 18 months was 5.5±1 and 4.5±1. Values of HbA1c were stabile before and (6.5-7.1 and 6.7-7.0%) after RDN on oral hypoglicemic drugs in 50% of patients.

At six months duplex sonography was performed in all patients (to exclude renal artery stenosis after RDN). We did not observe any renal vascular complications during the 18 months of follow up. The renal function remained stabile during 18-month follow up with mean eGFR CKD-EPI stage G2 (61±36 ml/min/1.73m^2).

DISCUSSION

The resistant hypertension treatment is achieved with nonpharmacological and pharmacological approach, treating secondary hypertension causes and invasive procedures such as RDN[1]. Many observational studies and our results have shown that RDN is a safe and effective method of reducing office BP in patients with rHT, with an additional positive effect on blood glucose metabolism, obstructive sleep apnea and signs of hypertensive end organ damage[2-4]. In support of these data, we documented that RDN was associated with good response in SBP regulation and improved stabile kidney function after RDN without complications such as renal stenosis or a pseudoaneurysm of the femoral artery after the procedure.

It is very important to select patients most likely to have benefit from invasive procedures such as RDN, because patients with rHT represent a very mixed group of diagnoses[5]. Chronic kidney disease (CKD) patients have sympathetic nervous system hyperactivation that leads to fluid overload, aggravation of hypertension and further deterioration and loss of renal function, and it has been demonstrated that RDN is associated with stabile kidney function[5]. The most obvious explanation relating effect of stabile kidney function could be that after RDN treatment increase renal blood flow which result in increase in GFR. Studies that have measured kidney function in pt with rHT with gold standard methods (CKD-EPI, MDRD) also found high prevalence of CKD in rHT patients[6-8]. Our results support these observations, we also found mean eGFR CKD-EPI stage G2 (65±38 ml/min/1.73m^2) on beginning, and after 18-month follow up eGFR was stabile.

The present study has a number of potential limitations. First, our study is obviously limited by the small number of patients. Furthermore our analyses were based on measurement of office blood pressure and we did not have performed ABPM in all patients in 12/18-month follow up.

To the best of our knowledge, this is the first report of beneficial RDN treatment for 18-month follow up in rHT patients in Croatia. However, our data show additional effect of treatmen in slowing natural progression of CKD.

In this study RDN with radiofrequency (RF) ablation is being used to treat rHT, with good safety profil and no complications occurred, the pain during the procedure was well tolerated. From other studies as 15-13% of treated patients are non-responders to RDN with radiofrequency, option is to repeat RF or perform RDN with cryoenergy as second line option[9].

CONCLUSIONS

Our results suggest that sustained reduction of SBP after the RDN was observed in 18-month follow-up.
Renal sympathetic denervation is being a concomitant treatment of drug-resistant hypertension (rHT). High risk patients with resistant hypertension have benefit the most from procedure after 6-12 months. Further meta-analysis will evaluate the optimal target population and importance of RDN as rHT treatment.
The future of the RDN systems are noninvasive, delivering externally focused ultrasound energy to the renal nerves using Doppler-based ultrasound image guidance to track and correct for renal artery motion during treatment.

Conflict of Interest: None to declare.

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SAŽETAK

DENERVACIJA BUBREŽNIH ARTERIJA I REZISTENTNA HIPERTENZIJA

I. PRKAČIN[1,2], B. VRHOVEC[1], A. LEGOVIĆ[1], V. ĐERMANOVIĆ DOBROTA[2], T. BULUM[2] i V. VIDJAK[2,3]

Sveučilište u Zagrebu, Medicinski fakultet, Klinička bolnica Merkur, [1]Klinika za interne bolesti, Zagreb, [2]Klinika za dijabetes, endokrinologiju i bolesti metabolizma Vuk Vrhovac, Zagreb i [3]Sveučilište u Zagrebu, Medicinski fakultet, Klinička bolnica Merkur, Klinika za radiologiju, Zagreb, Hrvatska

Denervacija bubrežnih arterija (DBA) radiofrekvencijom jedna je od obećavajućih novih metoda liječenja rezistentne hipertenzije refraktorne (RH) na optimalno liječenje kombiniranom antihipertenzivnom terapijom koja uključuje 3 i više lijekova iz različitih antihipertenzivnih skupina od kojih jedan mora biti diuretik. Nakon isključenja sekundarnih uzroka, neadekvatnog mjerenja tlaka te nesuradljivosti prikazujemo učinak DBA u 7 bolesnika (62±6 years for age, 5F/2M) tijekom razdoblja od 18 mjeseci praćenja. Za statističku analizu korišten je program STATISTICA 10, 2011 softwer (Stat Soft Inc., Tulsa, OK, USA), uz razinu značajnosti P <0,001.

Bolesnici su praćeni na redovitim ambulantnim kontrolama 1, 3, 6, 12 i 18 mjeseci nakon DBA uz mjerenje krvnog tlaka i praćenje laboratorijskih parametara. Od početnih izmjerenih vrijednosti tlaka u ambulanti 184±21 za sistolički i 106±26 mm Hg za dijastolički tlak, uz prosječni broj antihipertenzivnih lijekova od 6,7±1 nakon DBA 1, 3, 6, 12 i 18 mjeseci prati se značajno smanjenje sistoličkih vrijednosti tlaka (144±13, 140±17, 141±15, 139±12, 135±11 mm Hg; P <0,001), bez značajnog smanjenja dijastoličkih vrijednosti (81±6, 82±9, 79±9, 78±6, 76±7 mmHg). Nakon 6 mjeseci prosječan broj antihipertenzivnih lijekova ostao je nepromijenjen (važno da se objektivizira učinak DBA) i iznosio je 6.5±1, dok je nakon 12 i 18 mjeseci došlo do smanjenja broja antihipertenzivnih lijekova (5.5±1 i 4.5±1). Tijekom DBA bolest je bila podnošljiva, nije zabilježeno neposrednih ni kasnijih komplikacija DBA, bubrežna funkcija je bila stabilna tijekom praćenja. Dokazana je dugoročna sigurnost DBA i učinkovitost na smanjenje sistoličkog krvnog tlaka u bolesnika s refraktornom RH.

Ključne riječi: denervacija bubrežnih arterija, hipertenzija