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CIRCADIAN RHYTHM OF BLOOD PRESSURE RESTORATION AND NEPHROTIC PROTEINURIA ALLEVIATION IN A PATIENT WITH CHRONIC KIDNEY DISEASE AFTER RENAL SYMPATHETIC DENERVATION

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SUMMARY – Renal sympathetic denervation (RSD) could be an effective antihypertensive treatment of resistant hypertension that triggers additional positive effects on glucose metabolism and insulin sensitivity in type 2 diabetes mellitus. We report the effects of RSD in a patient with chronic kidney disease, type 2 diabetes mellitus and resistant hypertension, manifesting as blood pressure reduction with dipping pattern restoration, followed by nephrotic proteinuria alleviation. The non-dipping blood pressure pattern and proteinuria increase the risk of cardiovascular complications and accelerate kidney disease progression. Thus, further research documenting the frequency and investigating the mechanisms of these effects reported after RSD in chronic kidney disease patients with type 2 diabetes mellitus and resistant hypertension is necessary for the benefit of this high-risk patient population.

Key words: *Circadian rhythm; Diabetic nephropathies; Proteinuria; Hypertension – drug therapy; Kidney – innervation; Sympathectomy – methods; Case reports*

Introduction

Diabetic nephropathy is characterized by hypertension, albuminuria (macroalbuminuria/proteinuria) and progressive loss of renal function. The available data suggest that afferent signals from affected kidneys to integrative structures in the brain result in chronic elevation of sympathetic outflow. Increased sympathetic activity inducing vasoconstriction, renin-angiotensin-aldosterone system (RAAS) activation, sodium and fluid reapportion and proteinuria plays an important role in the aggravation of hypertension and further deterioration of renal function[1]. Therefore, pharmacological inhibition of the sympathetic nervous system with lowering blood pressure and/or RAAS activity reduction through proteinuria alleviation exerts renoprotective effect in type 2 diabetic (T2DM) patients with hypertension and chronic kidney disease (CKD)[2-5]. Although frequently used in such patient populations, pharmacological inhibitors do not provide adequate antihypertensive or renoprotective effect in clinical practice[6]. Renal sympathetic denervation (RSD) as endovascular catheter-based intervention by providing multilevel inhibition of the sympathetic nervous system could be an appealing concomitant therapeutic option for treating resistant hypertension in patients with diabetic nephropathy and CKD[7].

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Case Report

Here we describe a case of a 57-year-old male with diabetic nephropathy and CKD stage 3, submitted to RSD due to severe hypertension resistant to treatment with seven antihypertensive drugs from different (complementary) drug classes including an appropriately dosed diuretic. These drugs were: 10 mg ramipril qd (angiotensin-converting enzyme inhibitor), 40 mg nifedipine delayed-release bid (calcium channel blocker), 90 mg urapidil bid (direct vasodilator), 10 mg torsemide qd (diuretic), 320 mg valsartan qd (angiotensin receptor blocker), 0.6 mg in the evening moxonidine (centrally acting sympatholytic) and 50 mg spironolactone qd dose (aldosterone antagonist).

Before the intervention, antihypertensive treatment was optimized according to the BHS/NICE treatment algorithm adapted from CG127; non-concordance with pharmacotherapy as well as secondary forms of hypertension were excluded. The patient had had T2DM for seven years and was educated on self-management and treated with oral antidiabetic agents (OADs). In 2010, the patient was diagnosed with diabetic nephropathy based on increased urinary albumin excretion (UAE), with no hematuria and normal kidney ultrasound dimensions. Three months prior to RSD, the creatinine-based estimated glomerular filtration rate (eGFR) decreased to <60 mL/min/1.73m^2 and OADs therapy (metformin and glimepiride) was replaced with the insulin secretagogue gliquidone, 30 mg bid.

The RSD treatment method and its potential risks and benefits were explained to the patient and his written consent was obtained. RSD was performed with standard radiofrequency delivery system with ablation catheter (5F system/6F guide catheter; Symplicity™ RDN System, Medtronic Inc., Mountain View, CA, USA) inserted through the femoral artery. Additionally, multiple three-dimensional imaging and catheter monitoring were used to precisely pinpoint the sites of radiofrequency energy delivery, engaging the renal artery bilaterally. Five nerve ablations on each side were performed. The RSD procedure was completed without any complications. The 24-hour ambulatory blood pressure monitoring (ABPM), medication therapy and laboratory analysis were assessed at baseline (before RSD), and at 1-, 3- and 6-month follow up visits.

The ABPM data were divided into 3 eight-hour segments: morning (06.00-14.00 h), afternoon (14.00-22.00 h) and sleep-time (22.00-06.00 h). The mean arterial pressure (MAP = [(2 x diastolic) + systolic]/3) was calculated for each segment and expressed as mean ± standard deviation (SD). Comparison of two means was performed using the Student's t-test. Comparison of several means was performed using two-way (two factors tested) analysis of variance and the Newman-Keuls *post hoc* test. Changes between the baseline and consecutive follow up visits within the same eight-hour segment were considered statistically significant if $p<0.001$ (two-tailed). Statistical analysis was per-

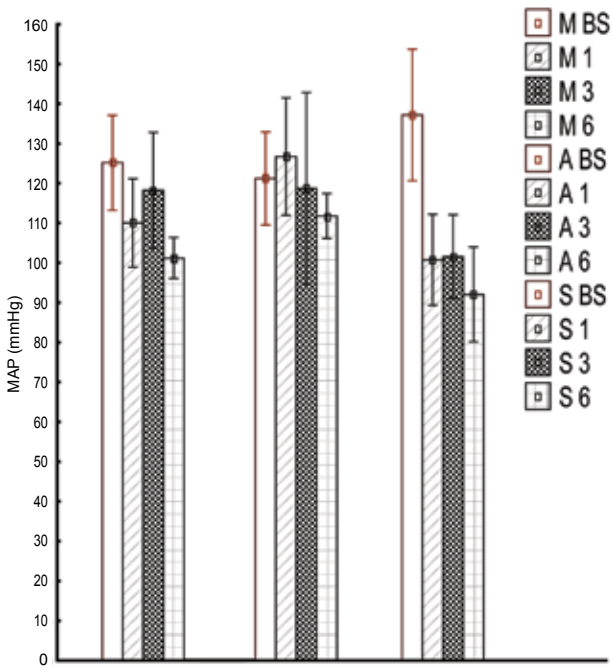
Table 1. Blood pressure and renal function before and after renal sympathetic denervation

Parameter	Before RSD	After RSD		
		1 month	3 months	6 months
Systolic ABPM (mm Hg)	198±24	172±20	174±17	178±16
Diastolic ABPM (mm Hg)	92±14	85±18	85±24	67±8
Heart rate (bpm)	74±8	74±11	74±20	60±6
Night/day ratio of MAP	1.11	0.85	0.86	0.86
Serum creatinine (mol/L)	154	174	217	171
eGFR (mL/min/1.73m^2)	39	35	32	33
Urinary protein (mg/day)	4605	1900	554	591
Urinary albumin (mg/day)	4325	1798	458	442

RSD = renal sympathetic denervation; ABPM = ambulatory blood pressure measurements (24-hour); eGFR (MDRD) = excretion glomerular filtration rate; MAP = mean arterial pressure; ABPM and heart rate values are expressed as mean standard deviation (SD); other data are presented as number.

formed using the STATISTICA 10, 2011 software (Stat Soft Inc., Tulsa, OK, USA).

The ABPM at baseline revealed hypertension with non-dipping BP pattern before RSD. The RSD significantly decreased MAP at month 1, 3 and 6 (100.8±11.4 mm Hg; 101.6±10.5 mm Hg; and 92.1±11.9 mm Hg, respectively) compared to baseline (137.2±16.5 mm Hg), significantly decreased morning MAP at month 1 and 6, and restored the dipping BP pattern (circadian blood pressure rhythm) (Fig. 1). An additional positive effect of RSD on nephrotic proteinuria alleviation was observed (Table 1), with better control of diabetes (HbA1c 7.1% before RSD, 6.8% at 3 months after RSD and 6.9% at 6 months after RSD). Moreover, we observed 87% serum renin reduction 6 months after RSD compared to baseline. Antihypertensive drug treatment dose and regimen remained the same throughout the 6-month period. There were no changes in antidiabetic treatment.



RSD = renal sympathetic denervation; BS = baseline (before RSD); MAP = mean arterial pressure; 1 = 1-month follow up visit, 3 = 3-month follow up visit; 6 = 6-month follow up visit; MAP values are mean ± SD; *statistically significant difference ($p<0.001$).

Fig. 1. Circadian blood pressure rhythm before and after renal sympathetic denervation.

Discussion

To the best of our knowledge, this is the first case report of a CKD patient with nephropathy and resistant hypertension having limiting effect on BP level optimization, but circadian rhythm restoration and nephrotic proteinuria alleviation after RSD treatment. Neither the Symplicity Trials nor the European Society of Cardiology Recommendations find CKD patients with eGFR 45 mL/min/1.73m^2 and resistant hypertension to be eligible for RSD treatment[8]. However, individual data show antihypertensive effects of RSD intervention in CKD patients with eGFR 45 mL/min/1.73m^2 and resistant hypertension[9].

Normal circadian BP rhythm includes nocturnal BP decline, i.e. the dipping BP pattern (more than 10% sleep-time relative BP decline). In T2DM patients, the non-dipping pattern is highly correlated with the rate of albumin excretion; 80% of T2DM patients with albuminuria A3 (macroalbuminuria) were found to have loss of sleep-time BP decline[10]. The non-dipping BP pattern was demonstrated to be related to a more prominent failure to respond to antihypertensive medication[11]. Moreover, it accelerates kidney disease progression to end-stage renal failure and increases the risk of cardiovascular complications[10,11]. Therefore, RSD elicited sleep-time BP decline is expected to have multiple long term benefits. In addition, proteinuria alleviation after RSD intervention is an important observation. Proteinuria is an independent risk factor for kidney disease progression and recognition of the antiproteinuric treatment is essential for providing renoprotection[12].

Further research documenting the frequency and investigating the mechanisms of these effects reported after RSD in CKD patients with T2DM and resistant hypertension is necessary, as RSD may constitute an effective treatment option to reduce cardiovascular risk and kidney failure progression.

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Sažetak

POBOLJŠANJE KRVNOG TLAKA, CIRKADIJALNOG RITMA I PROTEINURIJE U BOLESNIKA S KRONIČNOM BUBREŽNOM BOLEŠĆU NAKON POSTUPKA DENERVACIJE BUBREŽNIH ARTERIJA

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Denervacija bubrežnih arterija (DBA) je jedna od obećavajućih novih metoda liječenja rezistentne hipertenzije refraktorne na optimalno liječenje kombiniranom antihipertenzivnom terapijom koja uključuje 3 i više lijekova iz različitih antihipertenzivnih skupina, od kojih jedan mora biti diuretik. Uz učinak na sniženje tlaka, radiofrekventnom ablacijom periarterijskih simpatičkih niti denervacijom uočeni su dodatni pleotropni pozitivni učinci poput regulacije glikemije i inzulinske rezistencije u osoba sa šećernom bolešću tipa 2. U radu je prikazan učinak DBA u bolesnika s kroničnom bubrežnom bolešću (KBB), šećernom bolešću tipa 2 i refraktornom hipertenzijom: djelomično sniženje krvnog tlaka polučilo je dodatni učinak na snižavanje krvnog tlaka tijekom noći uz smanjenje nefrotičke proteinurije, bez pogoršanja KBB. Izostanak očekivanog sniženja krvnog tlaka tijekom noći i nefrotska proteinurija povećavaju kardiovaskularni rizik bolesnika i progresiju KBB. Daljnja prospektivna istraživanja mehanizama nastanka povoljnih učinaka DBA u bolesnika sa šećernom bolešću tipa 2, KBB i rezistentnom hipertenzijom su neophodna kako bi se dokazali dodatni učinci blokade simpatičkog sustava DBA u ove visoko rizične populacije.

Ključne riječi: *Cirkadijalni ritam; Dijabetička nefropatija; Proteinurija; Hipertenzija – farmakoterapija; Bubreg – inervacija; Simpatektomija – metode; Prikazi slučaja*