

Physiological Research Pre-Press Article

Renal denervation in the most serious form of resistant arterial hypertension.

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Short title: Renal denervation in the resistant arterial hypertension.

Abstract

Aims

The aim of our observation was to establish whether or not renal sympathetic denervation (RSD) may help control blood pressure (BP) levels in patients with severe hypertension refractory to pharmacological therapy.

Methods

Out of a group of 12 patients, candidates for RSD, with uncontrolled hypertension and a systolic BP over 190 mmHg on repeated measurements despite optimal medication, four patients were excluded for multiple renal arteries and one for hyperaldosteronism. Seven patients had RSD using a Symplicity device (5M, 2 F) with a mean age of 64.9 years. While all were followed up for a minimum of 6 months, follow-up duration in the majority of them was substantially longer (12 - 20 months).

Results

At six months post-RSD, six of the seven patients showed a decrease in systolic BP by at least 15 mmHg while receiving the same or fewer doses of antihypertensive agents. A similar response was seen in diastolic BP. The BP decrease was maintained throughout whole follow-up.

Conclusion

In a small group of patients with severe hypertension, we demonstrated that renal sympathetic denervation is capable of reducing blood pressure even in patients with severe hypertension.

Key words

Hypertension - renal sympathetic denervation – Symplicity device – uncontrolled blood pressure

Introduction

Renal sympathetic denervation (RSD) in resistant arterial hypertension has recently been a hotly debated topic. While, based on data from the SYMPPLICITY HTN-1 and SYMPPLICITY HTN-2 trials, investigators pinned hopes on RSD as an option in the treatment of hypertension, conclusions of the subsequent SYMPPLICITY HTN-3 trial brought about disillusionment. To date, unanimity has not been reached regarding its efficacy, with opinions ranging from completely positive to completely negative [Krum H, 2009; Esler MD, 2010; Kandzari DE, 2012; Bhatt DL, 2014]. Still, while it is almost certain that there are patients who may benefit from RSD, we are apparently not yet able to reliably identify this specific patient population. The aim of our study was to find out whether it is possible to identify, even among those with the most severe forms of hypertension, patients who would respond to this technique at all. Systolic blood pressure decrease by at least 15 mmHg was considered as positive response.

Material and Methods

In our limited group of patients, RSD was performed using a Symplicity device (Medtronic, Mountain View, CA, USA). We sought to select patients experiencing major clinical problems with the antihypertensive therapy. These patients were characterized by long-term follow-up in an outpatient clinic of cardiology before their inclusion in the group selected for RSD. They had to meet the usual requirements of use of a combination of several antihypertensive drugs; also, they had to repeatedly have systolic blood pressure (SBP) levels above 200 mmHg as measured by professional health workers and a documented episode of hypertensive crisis. To rule out a potential secondary cause of arterial hypertension, all these patients had basic laboratory tests and whenever possible, ambulatory blood pressure monitoring (ABPM), echocardiography, renal artery CTA with simultaneous visualization and

evaluation of renal parenchyma. Irrespective of the documented highest blood pressure (BP) levels and their fluctuations, the baseline value used in subsequent comparisons was that measured closest to the date of the procedure. In 2012, when RSD was introduced in our center, we identified a total of 11 patients. Prior to becoming candidates for RSD, they were individuals followed up on an outpatient basis in our department (these patients were demonstrably compliant to proper use of medication) while also meeting anatomical criteria for RSD (see below).

Actual RSD was performed in all patients meeting all criteria for inclusion in the study and signing informed consent. The renal variables monitored on a regular basis included changes in glomerular filtration rate (GFR-CCr, GFR-MDRD), serum creatinine (SCr), urea, urinary albumin/creatinine ratio (UAlb/ UCrea), 24-hour urinary sodium and potassium excretion (UNaV, UKV), fraction excretion of sodium and potassium (FENa, FEK), and urinary Na/K ratio (UNa/UK). Further, we sought to find out whether RSD, performed in patients with such an extreme degree of hypertension, can affect the levels of some novel biomarkers reflecting processes within the cardiovascular system [Sun RR, 2014]. Hence, we also focused our attention on proatrial natriuretic peptide (proANP), midregional proadrenomedullin (proADM), and copeptin (COP).

Patient characteristics

Based on their clinical status as specified above, a total of 12 patients were initially selected since 2012. Four patients were excluded because of their renal vascular anatomy, with multiple renal arteries (measuring ≤ 4 mm in diameter) currently not recommended to catheter-based ablation [Krum H, 2009; Esler MD, 2010; Kandzari DE, 2012; Bhatt DL, 2014], in one patient a micronodular primary hyperaldosteronism was found. The remaining group of seven patients included 5 men and 2 women, with a mean age of 64.9 years at the time of RSD. Table I presents more detailed patient characteristics.

The pharmacotherapy instituted prior to RSD should be considered optimal as the patients had been previously receiving other drugs and combinations thereof but did not tolerate them. Essentially, all patients were taking a beta-blocker (metoprolol at a dose of 100–300 mg/day), an angiotensin-receptor blocker (predominantly telmisartan at doses of 80–160 mg/day), and a diuretic (hydrochlorothiazide at an average dose of 25 mg/day). Add-on therapy included a selective inhibitor of alpha 1 subtype of alpha-adrenergic receptors (doxazosin), alpha 1-adrenoceptor antagonist with central agonistic action at serotonin 5-HT_{1A} receptors (urapidil), and calcium-channel blockers. Those additional drugs were uptitrated to maximum tolerated doses (specifically, the highest doses of doxazosin and urapidil were 8 mg and 180 mg, respectively). Comorbidities included cases of suprarenal ulceration/abdominal aortic aneurysm (managed by endovascular approach immediately prior to RSD), atrial fibrillation (paroxysmal, resolving after BP normalization), and metabolic syndrome with coronary arterial disease. One patient undergoing RSD with coronary arterial disease and metabolic syndrome had a solitary kidney. In principle, all patients were classified as overweight to degree I obesity, with a BMI \geq 35 in two patients.

The mean level of office SBP was 170.9 (\pm SD 15.0) mmHg (the primary focus on SBP was because of the greater impact of the catecholaminergic system on subsequent RSD outcome). The mean value of SBPA derived from ambulatory BP monitoring (ABPM) (overall in-study value; unfortunately unavailable from all patients in our group) was 158.2 mmHg (\pm SD 10.2). On average, the patients were taking combinations of five drugs (\pm SD 0.9). Follow-up visits were scheduled at 3, 6, and 12 months post-RSD, with follow-up still under way.

Description of procedure

A 6 F guiding catheter was manipulated from the femoral artery approach to the renal artery ostium and a radiofrequency (RF) catheter was introduced into the artery lumen (Simplicity, Medtronic, Mountain View, CA, USA). All procedures were performed in analgosedation. All patients were heparinized to reach an ACT level of 200–250 seconds. The Simplicity catheter

tip was advanced as distally to the main renal artery as the anatomy allowed and the tip of the catheter was brought into contact with the renal artery endothelium. Five to eight RF ablations were performed, after each ablation the catheter was rotated and slightly withdrawn within the lumen of the renal artery. The tip of the catheter reached a temperature of 58–69°C. Since the relationship between the RF generator output and the tip catheter temperature depends on variable parameters, impedance, temperature power and length of the ablation were continuously monitored. In cases where one of these parameters differed from the recommended/predicted values, treatment was automatically stopped and the tip of the catheter was repositioned.

After the procedure, patients were followed up on a regular basis at outpatient clinics of cardiology and nephrology. Monitored variables included current BP values, laboratory parameters, and evolution of health status over time. The main renal variables are identified above.

Statistical analysis

Given the small number of patients, the non-parametric paired Wilcoxon (for two measurements over time) and Friedman tests (for 3-4 repeated measurements at a time) were used for statistical analysis of data.

Results

In all cases, RSD was performed without any complications. As a rule, the procedure required a two-day hospitalization. The procedure was well tolerated by all patients, with subjective improvement (particularly in terms of reduced incidence of headache, dizziness, and increased exercise tolerance) reported by all but one patient at follow-up visits.

Likewise, there was no change in medication or the number of drugs and/or doses used even decreased (Graph 1).

Office BP measurements in all patients at 6 months documented a decrease in SBP by at least 15 mmHg, with the effect maintained (Graph 2). Only one patient (VN) showed a different course on follow-up: as found later, the differences in terms of BP fluctuations were due to specific and enhanced psychological/emotional distress. However, overall, there was a statistically significant difference between SBP and DBP levels pre-RSD and all post-procedural values ($p = 0.05$) (Graphs 2 - 5).

Regrettably, and for a variety of reasons, ABPM values for all patients throughout the study are unavailable; given the small number of patients, it made no sense to analyze them.

No significant changes were seen in GFR- C_{Cr} , GFR-MDRD, S_{Cr} or U_{Alb}/U_{Crea} , not even in CKD patients. There was a significant increase in $U_{Na}V$, FE_{Na} , and U_{Na}/U_K ($p < 0.025$), whereas urinary potassium excretion remained unchanged. The extremely high values of the fractional excretion of urea and sodium suggested high dietary protein and salt intake. Long-term (12-month) follow-up of renal function did not reveal any significant changes both in measured and estimated GFR values. However, there was a significant decrease in $U_{Na}V$ ($p < 0.025$) reflecting the reduction of dietary salt intake. No statistically significant changes were noted in selected biomarkers (COP, proADM, and proANP) at the six consecutive follow-up visits.

Discussion

What We Do Know

Clinicians are well aware that there are individuals resistant to long-term multi-drug combination therapy. If disregarding a minority view that there is no such a thing as resistant hypertension, this category may include even relatively “milder” patients meeting the following criteria: use of two different antihypertensive agents (each from a different class) and a diuretic have failed to achieve adequate BP control so SBP and DBP levels do not decrease below 140 mmHg and 90 mmHg, respectively [Mancia G, 2013]. In diabetic

patients, the values are 10 mmHg lower both for SBP and DBP. In diabetic candidates for RSD, GFR should be $> 45 \text{ ml/min/1.73m}^2$.

In fact, it is widely recognized that both animals in models of arterial hypertension and patients with established hypertension show increased renal sympathetic activity [Dibona GF, 2002]. Renal sympathetic denervation procedures have been associated with BP reduction both in large and small laboratory animals regardless of the technique of inducing hypertension: identical outcomes have been reported for genetically modified rat populations [Katholi RE, 1985], sodium-sensitive miniature swine [O'Hagan KP, 1990], one-kidney renal hypertension [Katholi RE, 1981] and established two-kidney, one-clip Goldblatt hypertension [Katholi RE, 1982]. In these animal models, just as in patients with arterial hypertension, enhanced sympathetic activity is a consistent response and can thus serve as a target for therapeutic intervention.

As such, renal denervation is a well-known approach in the management of refractory hypertension; however, while employed by surgeons in the past, it was gradually discarded because of its high morbidity and mortality rates [Smithwick RH, 1953; Grimson KS, 1949]. The idea has only been revisited by the SYMPLICITY trials using RF ablation for RSD. Initial results were most promising with the technique quickly gaining acceptance in clinical practice [Krum H, 2009; Esler MD, 2010; Kandzari DE, 2012]. However, regrettably, the SYMPLICITY HTN-3 results [Bhatt DL, 2014] challenged the value of RSD and the technique seemed to be doomed to fall into oblivion as quickly as it became accepted. Still, a thorough search of the relevant literature clearly shows that some patients did benefit from RSD; the problem was that the investigators were unable to identify those who would [Bhatt DL, 2014; Nathan S, 2014; Desch S, 2015; Azizi M, 2015].

What We Do Not Know

There may be a myriad of reasons why RSD simply “failed to work” in some individuals:

(a) Inadequate ablation– there is no graphic, biochemical or other piece of evidence showing that all sympathetic nerves have indeed been transected. It remains unclear whether the Medtronic device design allows all thermal energy to pass through the arterial wall. As the technique involves application of single RF pulses and given the variable course of nerve fibers, we do not know whether the course of nerves has been adequately targeted along the whole circumference of the artery [Nathan S, 2014]. At least some models of new-generation catheters feature a circumferential source of RF pulses thus likely eliminating this problem. Data from initial reports of small patient series are most encouraging; studies with RF techniques include the 12-month RHAS trial using a OneShot™ device (Covidien, Culver City, CA, USA) [Ormiston JA, 2013] and 6-month follow-up within the REDUCE HTN project (Vessix V2™ device, Boston Scientific, Natick, MA, USA) [Sievert H, 2015]. Likewise, it is unknown whether the nerve fibers have been adequately severed. Besides, the periarterial renal innervation system is most variable and the target nerve fibers or ganglia may be located at a distance that RF pulses cannot reach [Tzafriri AR, 2014]. Some reports have suggested the behavior of the sympathoadrenal plexus in the region of the kidney differs in lean individuals compared with overweight/obese ones [Lambert E, 2007; Middlekauf HR, 2015]. Still, these and a host of other considerations, in light of the discouraging results of SYMPPLICITY HTN-3, should not lead to departure from the concept of RSD once for all [Middlekauf HR, 2015; Reddy VY, 2014]. Also, it is currently unknown whether RSD will consistently induce nerve fiber necrosis (as an irreversible type of lesion) or whether only its partial injury such as demyelination or hypertrophy to atrophy will occur. No information is available as to the process of healing of such injured fibers and/or re-innervation. In an ovine model, re-innervation has been documented at 11 months post-RSD using a Symplicity Flex catheter [Booth LC, 2015]. Furthermore, no data are available about the duration of the release of catecholamines accumulated in periarterial deposits.

The above gaps in our knowledge may contrast, for example, with a model of vincristine-based denervation, which demonstrably and reliably destroys nerve fibers both circumferentially and across the index area (based on the balloon surface) [Stefanidis C, 2014; Stefanidis C, 2013].

(b) A patient may have had undiagnosed secondary hypertension.

(c) Standard BP monitoring was not performed. There is no evidence of patient compliance to drugs treatment (with only scarce data about the plasma levels of the drugs prescribed available).

Our results clearly show that RSD does have a role to play in the treatment of patients with severe hypertension. While there was decrease in SBP in all our patients, it should be acknowledged this occurred only after a substantial lifestyle modification in one patient (VN) making the effect of RSD at least disputable. Still, the decrease in BP seen after RSD in the remaining six patients is unquestionable. Among the selected novel biomarkers, a sufficient wealth of data are available about the family of natriuretic peptides, which may enhance cardiac wall stress potentially impacting a patient's prognosis in terms of developing heart failure [Sun RR, 2014].

Today, the adrenomedullin family of peptides is believed to be, among other things, a marker of vascular tone regulation [Yuan M, 2015]. While copeptin has been reported to closely reflect both SBP and DBP levels, it has been suggested copeptin may also serve as a predictor of pre-eclampsia before it becomes clinically overt [Tenderenda-Banasiuk E, 2014; Yeung EH, 2014]. However, we did not observe any consistent and statistically demonstrable changes in BP levels, either population-wide or in individuals experiencing a favorable change in BP post-RSD.

While no authoritative conclusions can be derived from our data (undoubted beneficial effect in resistant hypertension in six out of seven patients) due to the limited number of our patients, they do support the concept of RSD. In our view, the question to be asked regarding

RSD should definitely not be YES or NO but, IN WHOM? And, perhaps, also HOW?

Needless to say, further and better designed studies using new-generation catheters are warranted to identify the patient population potentially benefitting from renal sympathetic denervation.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and in its later amendments or comparable ethical standards.

Informed consent was obtained from all included participants.

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Table I Characteristics of 7 patients with resistant hypertension who underwent RSD

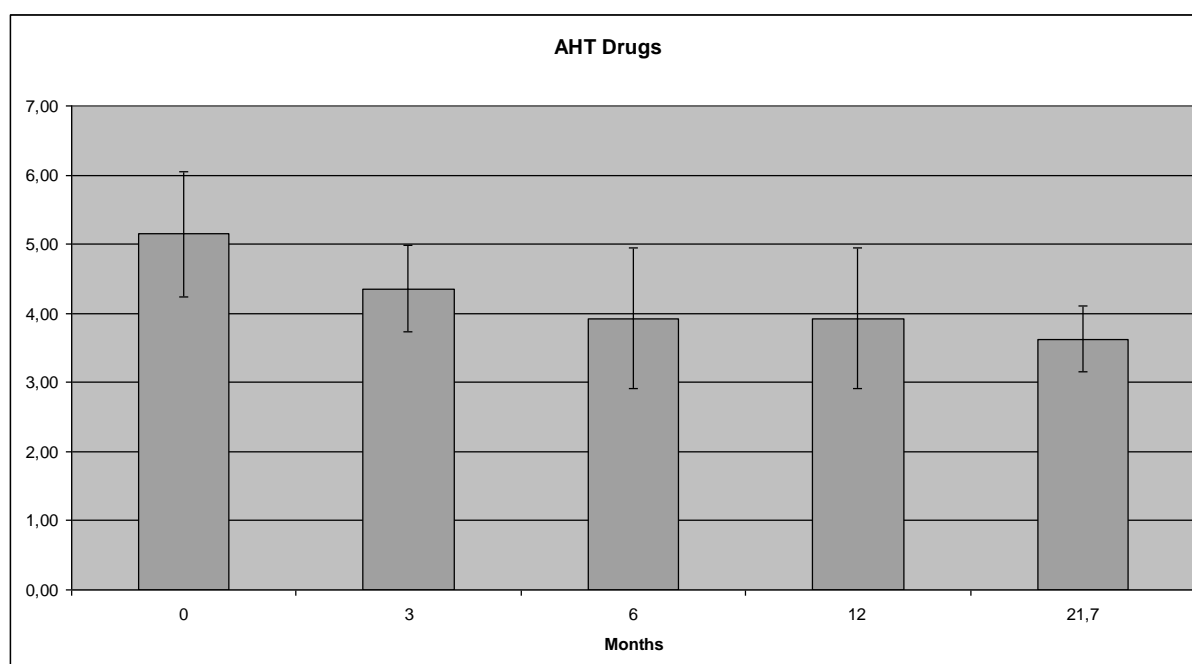
		Note
Gender ♂ / ♀	5/2	
Mean age (range, 61–68), years	64.9	
Average BMI, kg/m ²	32.3 ± 4.5	
<i>Medication:</i>		
Beta-blocker	7/7	
Angiotensin receptor blocker	7/7	
Calcium-channel blocker	6/7	
Alpha 1 adrenergic receptor blocker	5/7	
α blocker + central 5HXT receptor agonist	4/7	
Diuretic	7/7	
Comorbidities, n/patients	5/7	AAA, MS, SL, CAD, O
Mean creatinine (μmol/l)	86.7 ± 15.9	
Mean cholesterol (mmol/l)	5.25 ± 0.7	
Mean glycemia (mmol/l)	5.65 ± 0.45	
Mean COP (pmol/l)	7.26 ± 3.55	No change in levels at follow-up visits
Mean proADM (nmol/l)	0.67 ± 0.15	No change in levels at follow-up visits
Mean proANP (pmol/l)	118.59 ± 55.14	No change in levels at follow-up visits

Abbreviations: BMI – body mass index; 5HXT – 5-hydroxytryptamine; AAA, abdominal aortic aneurysm; MS –metabolic syndrome with overweight; SL – solitary kidney; CAD – coronary artery disease; O – obesity; COP – copeptin; proADM – proadrenomedullin; proANP – pronatriuretic peptide

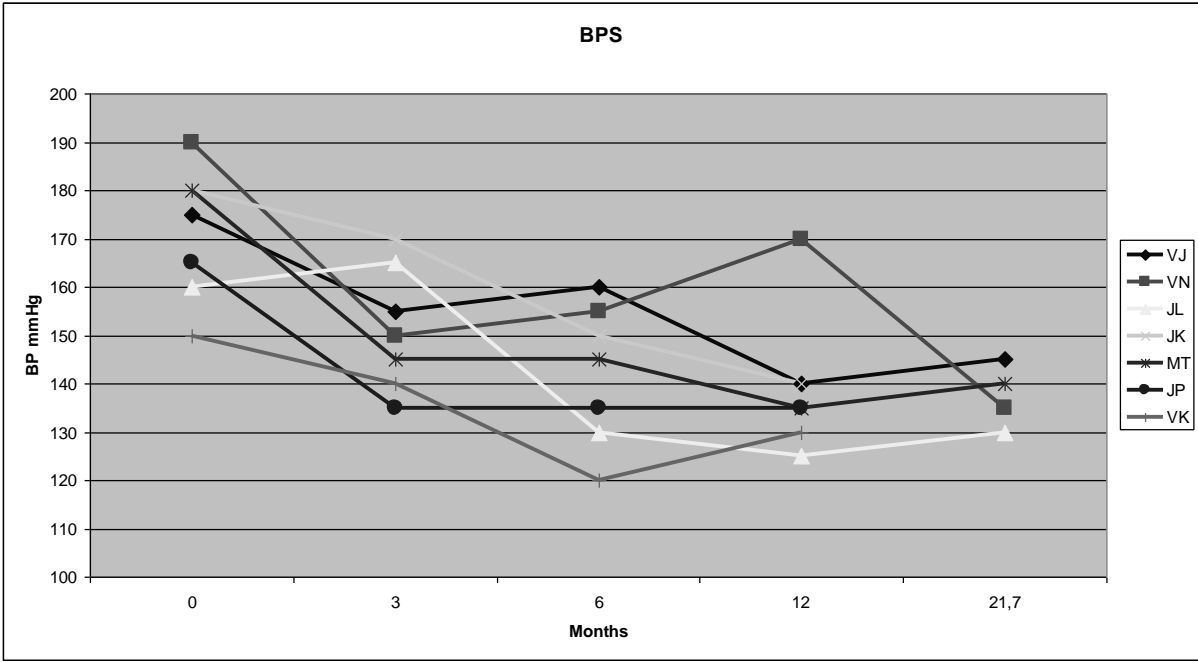
Table 2 Changes in renal variables post RSD (n = 7)

	Pre-RSD	1 month post-RSD	12 months post-RSD	p
	x ± SD	x ± SD	x ± SD	
S _{cr} , mmol/l	144.3 ± 28.4	146.4 ± 22.1	152.2 ± 38.6	n.s.
GFR-C _{cr} , ml/s/1.73m ²	0.92 ± 0.63	0.90 ± 0.73	0.85 ± 0.64	n.s.
GFR-MDRD, ml/s/1.73m ²	0.82 ± 0.43	0.78 ± 0.37	0.76 ± 0.41	n.s.
U _{alb/creat} , g/mol)	2.72 ± 3.18	2.60 ± 4.35	2.64 ± 3.82	n.s.
U _{Na} V, mmol/24h	280.2 ± 45.4	336.3 ± 42.8	240.2 ± 36.4	< 0.025
U _K V, mmol/24h	77.7 ± 27.3	81.7 ± 22.2	68.2 ± 31.0	n.s.
U _{urea} V, mmol/24h	437.4 ± 150.6	464.3 ± 60.3	420.3 ± 86.2	0.05
FE _{Na} , %	1.44 ± 0.36	1.57 ± 0.35	1.58 ± 0.40	< 0.025
FE _K , %	12.8 ± 1.61	11.5 ± 3.82	13.0 ± 4.20	n.s.
U _{Na} /U _K	3.17 ± 1.89	4.39 ± 1.72	3.52 ± 1.68	< 0.025

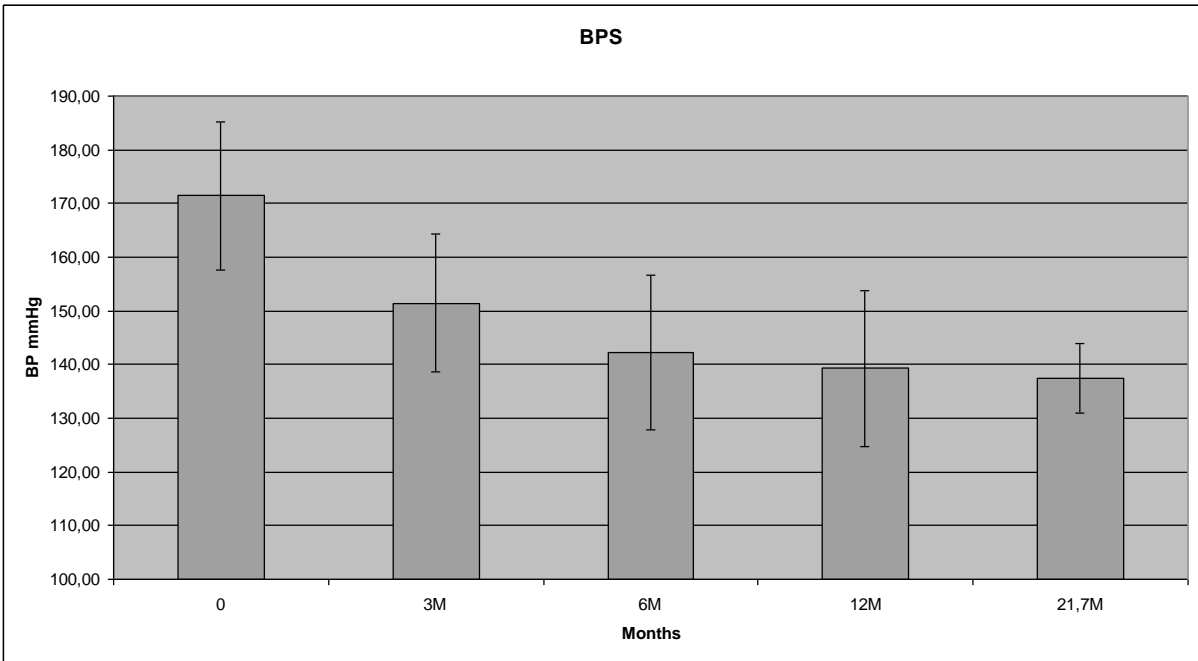
Abbreviations: S_{cr} – serum creatinine, GFR-C_{cr} - glomerular filtration rate, U_{alb/creat} - urinary albumin/creatinine ratio, U_{Na}V – urinary sodium excretion, U_KV – urinary potassium excretion, U_{urea}V - urinary urea excretion, FE_{Na} - sodium excretion fraction, FE_K – potassium excretion fraction, U_{Na}/U_K sodium/potassium excretion ratio



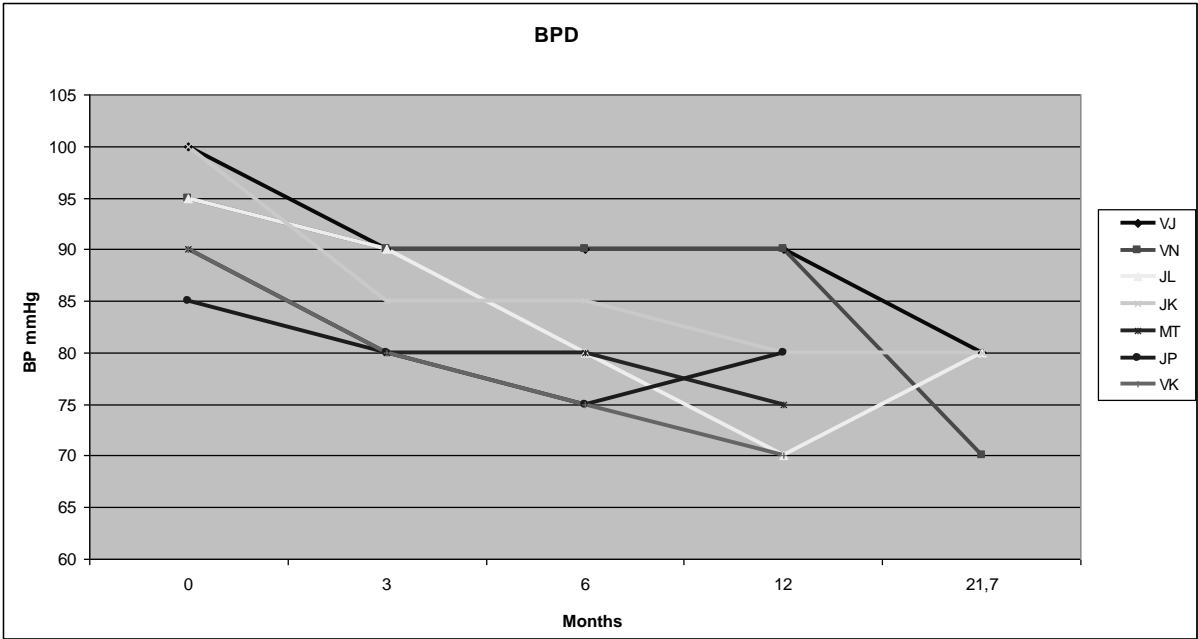
Graph 1. Graph 1. Decreasing numbers of drugs taken. All values differed statistically significantly from pre-RSD values ($p = 0.05$).



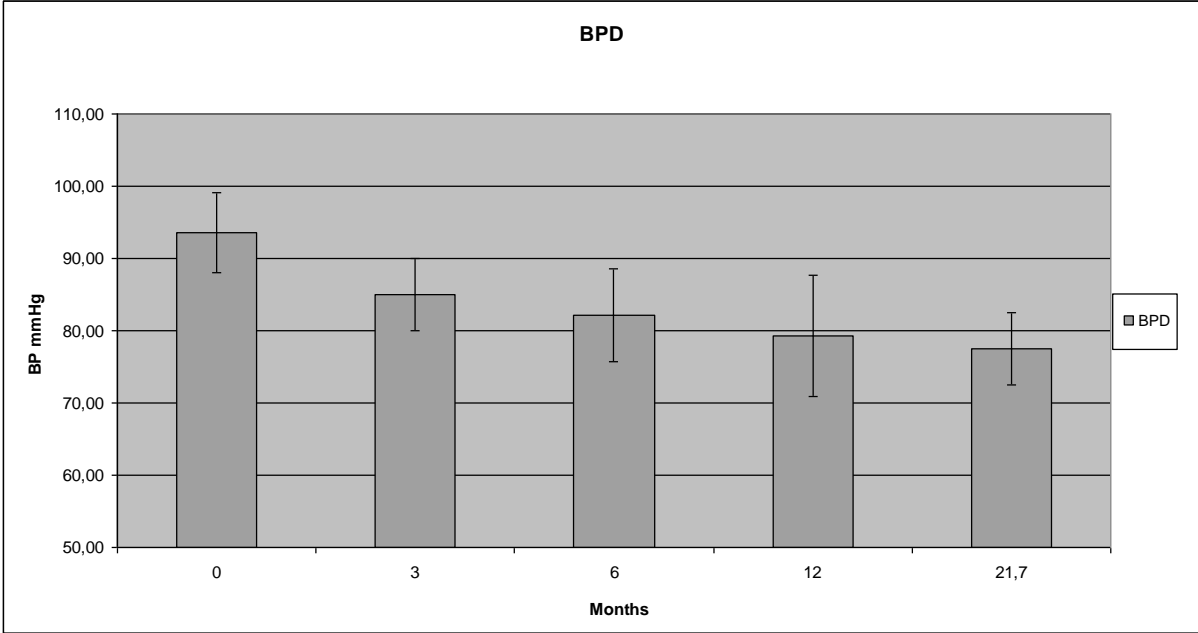
Graph 2. Graph 2. Changes in clinic systolic blood pressure (BPS) levels in individual patients post RSD (mmHg).



Graf 3. Graph 3. Changes in clinic systolic blood pressure (BPS) levels in the group of seven patients post RSD (mmHg). All post-RSD values differ significantly ($p = 0.05$) from pre-RSD values.



Graph 4. Graph 4. Changes in clinic diastolic blood pressure (DBP) levels in individual patients post RSD (mmHg).



Graph 5. Graph5. Changes in clinic diastolic blood pressure (DBP) levels in the group of seven patients post RSD (mmHg). All post-RSD values differ significantly ($p = 0.05$) from pre-RSD values.

