

## The Impact of Blood Pressure on Carotid Artery Stiffness and Wave Intensity in Patients with Resistant Hypertension after Renal Sympathetic Denervation

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### Abstract

**Objective:** The study investigated the impact of renal sympathetic denervation on office blood pressure and ambulatory blood pressure monitoring in patients with resistant hypertension. We evaluated whether a decrease in blood pressure may improve local carotid stiffness and parameters of wave intensity.

**Methods:** Renal sympathetic denervation was performed in 17 patients (age 55 ± 9 years) with true resistant hypertension. Measurements of carotid stiffness and wave intensity were performed using ultrasound combined with echo-tracking.

**Results:** We found significantly improved office systolic blood pressure changes 1 month (p=0.023) and together with pulse pressure changes at the 6 month follow up (p=0.041; p=0.016). Changes in systolic blood pressure during the daytime were significantly decreased at 1 month and diastolic blood pressure changes during the daytime were significantly reduced at 1 and 3 months. Stiffness parameters beta stiffness and pressure-strain elastic modulus were significantly reduced (p=0.04; p=0.03) and arterial compliance was increased (p=0.03), especially 1 and 3 months. The changes in negative area were significantly reduced after 1 month (p=0.041) and the ejection period was significantly increased at the 6 month follow-up (p=0.011). According to linear regression analysis systolic blood pressure correlated positively with the beta stiffness, pressure-strain elastic modulus, pulse wave velocity, and negatively with arterial compliance.

**Conclusions:** We found significantly lower office blood pressure as well as blood pressure from ambulatory blood pressure monitoring in patients with resistant hypertension 6 months after renal sympathetic denervation. The decrease in blood pressure was followed by improvement of carotid stiffness and wave intensity. That may be reflected in enhancement of ventricular-arterial coupling.

**Keywords:** Carotid stiffness; Renal sympathetic denervation; Resistant hypertension; Wave intensity analysis

### Summary

The study investigated the impact of renal sympathetic denervation on blood pressure, carotid stiffness and wave intensity in 17 patients with resistant hypertension. We found improved blood pressure and stiffness parameters. Negative area was reduced and the ejection period increased.

### Introduction

In recent years many authors have pointed out that arterial stiffness is considered to be an independent predictor of total and cardiovascular (CV) morbidity and mortality [1]. Arterial stiffening is closely related to age and arterial hypertension (AH), together with CV risk factors involved in the progression of stiffness. Recently published ESH/ESC Guidelines for the diagnosis and treatment of hypertension recommended the assessment of arterial stiffness as evidence of target

organ damage [2]. Arterial stiffening should be considered together with cardiac function, as it is known that the interaction between the heart and the arterial system, the “ventricular-arterial (V-A) coupling”, could be the key factor in CV performance [3].

Resistant hypertension (RH) is defined when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses fails to lower systolic BP and diastolic BP levels to <140 and 90 mmHg, respectively. The prevalence has been reported to range from 5 to 30% of the overall hypertensive population, with the incidence of true RH less than 10% according to the latest ESH/ESC Guidelines [2]. This form of AH is characterized by excessive activity in the sympathetic nervous system. Interventional treatment with catheter-based renal sympathetic denervation (RDN) has been shown to be a promising and available therapeutic approach [4]. Several studies have reported the blood pressure (BP) lowering effect of RDN [5,6]. Until now, only a few studies have detected the possible favourable effect of RDN on arterial stiffness and central hemodynamics [7,8].

The aim of the presented study was to determine the impact of RDN on office BP and ambulatory BP monitoring (ABPM) in patients with RH. Subsequently, we evaluated whether a decrease in BP has a positive effect on carotid stiffness as well as on V-A coupling using wave intensity analysis.

## Methods

### Patients

Between March 2012 and March 2013 we performed RDN in 17 patients (age  $55 \pm 9$  years, M: F=12:5) with true RH at the National Institute of Cardiovascular Disease (NUSCH) in Bratislava. The procedure was approved by the Ethics Committee of NUSCH. All physicians on the RDN team have received the international certificate for RDN (University of Heidelberg, Germany). In Slovakia RDN procedure is covered by the health insurance. All patients signed an informed consent.

The baseline characteristics of the patients are shown in Table 1. All patients fulfilled the eligibility criteria for RDN [2,9]. The patients were followed at 1, 3 and 6 months after the procedure. Three patients failed the follow-up at 3 and 6 months (causes unrelated to RDN). Routine blood tests, focused mainly on kidney functions, and renal duplex ultrasound examinations were performed during each visit. Control computed tomographic angiogram was performed one month after RDN. Echocardiography was performed immediately before RDN and at the 6 month follow-up.

Parameter, unit	Baseline (n=17)	6 months after RDN (n=14)
Age $\pm$ SD (years)	$55 \pm 9$	
Men/Women (n)	12/5	9/5
BMI (kg/m <sup>2</sup> )	$36 \pm 6$	
Type 2 diabetes mellitus [n (%)]	4 (23)	
Hyperlipidemia [n (%)]	10 (59)	
CAD [n (%)]	2 (12)	
Antihypertensive drugs: n	6 (5-7)	6 (5-8)
Beta-blockers (%)	82	79
RAS blockers (%)	100	100
Calcium antagonists (%)	100	86
Diuretics (%)	94	93
Aldosterone antagonists (%)	35	36
Other antihypertensive drugs (%)	100	100
Heart rate (b.p.m.)	$67 \pm 13$	$62 \pm 10$
eGFR (mL/min per 1.73 m <sup>2</sup> )	$81.9 \pm 19$	$78 \pm 8$
LVEF (%)	$63 \pm 9$	$62 \pm 9$

**Table 1:** General patient's characteristics, Data are expressed as means  $\pm$  SEM; BMI: Body Mass Index; CAD: Coronary Artery Disease; RAS: Renin-Angiotensin-System; eGFR: Calculated Glomerular Filtration

Rate; LVEF: left Ventricular Ejection Fraction; RDN: Renal Sympathetic Denervation

### BP measurements

The office BP was measured in a supine position on the left brachial artery during ultrasound examination with an automatic oscillometric device Microlife BP100 PLUS (Microlife AG, Switzerland). All patients underwent ABPM using a validated SunTech-Oscar device (SunTech Medical, Inc., New Carolina, USA). BP measurements were taken at baseline before RDN and during each visit at follow-up.

### High resolution echo-tracking of common carotid arteries

Measurement of carotid stiffness was performed with ALOKA Prosound Alpha 10 equipment (ALOKA Co., Ltd., Tokyo, Japan). This unit is equipped with an integrated and automated ultrasound, Doppler and an echo-tracking system. The echo-tracking system allowed real-time measurement of the diameter changes between the near and far wall of the common carotid artery (CCA). On the basis of experimental studies have been demonstrated that arterial pressure waveforms and diameter-change waveforms are similar [10,11]. Sugawara and coworkers [12] reported in humans the similarity between carotid arterial pressure waveforms measured with a catheter-tipped micromanometer and carotid arterial diameter-change waveforms measured by echo-tracking. Brachial systolic and diastolic BP was used to calibrate the maximum and minimum values of the diameter-change waveforms. We used 5 consecutive beats to obtain a representative waveform.

The stiffness parameters were measured on both sides of the CCA in its longitudinal axis and after applying echo-tracking to the adventitia of the near and far wall. The following stiffness values were measured [3,13] :

Stiffness index (beta), calculated from changes in vessel diameter and BP:

$$\text{Beta} = \ln(Ps/Pd) / [(Ds - Dd) / Dd]$$

Where: ln=the logarithm, Ps=systolic BP, Pd=diastolic BP,

Ds=arterial systolic diameter, Dd=arterial diastolic diameter

Pressure-strain elasticity modulus (Ep), an index of vessel elasticity, calculated from changes in vessel diameter and BP:

$$\text{Ep} = (Ps - Pd) / [(Ds - Dd) / Dd]$$

Arterial compliance (AC), an index of blood vessel compliance, calculated from the arterial cross sectional area and BP:

$$\text{AC} = Ad / R (Ps - Pd)$$

Where: Ad=the area under the BP diastolic decay curve from end-systole to end-diastole,

R=total peripheral resistance, Ps=the end-systolic BP, Pd=the end-diastolic BP

One-point pulse wave velocity (PWV), calculated from the time delay between two adjacent distension waveforms from the water hammer equation for forward traveling waves using the  $\beta$ -stiffness parameter

AIx=augmentation index, calculated as the ratio between the augmentation pressure (AP) and PP (pulse pressure):

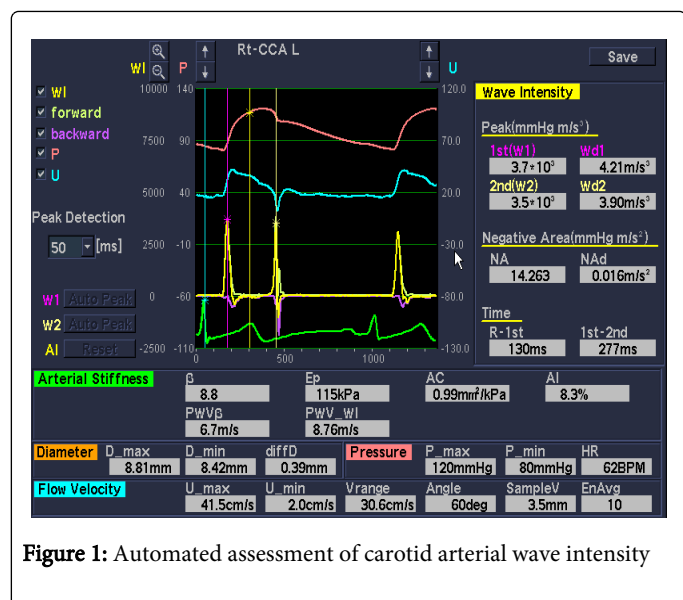
**AIx=AP/PP**

Stiffness values were assessed at baseline and during each visit after RDN. During the ultrasound examination, we evaluated parameters of wave intensity (WI) too. The WI methodology provided us with information about the forward and backward travelling waves.

The time-normalized WI is the product of derivatives of P (BP) and U (blood velocity) with respect to time [13]:

$$WI=(dP/dt) \times (dU/dt)$$

Two indices of intensity can be derived, W1 and W2. The first index, W1, appears during early systole. There is evidence that W1 correlates with the maximum rate of left ventricular () pressure. The second index, W2, occurs towards the end of ejection. It is known that W2 relates to the ability of LV to actively stop aortic blood flow, and correlates with the time constant of relaxation [14]. The negative area parameter (NA) indicates the effects of reflected waves. The interval between the R wave on ECG and the peak of W1 (R-W1) is known as the pre-ejection period and the interval between the peaks W1 and W2 (W1-W2) as the ejection time (Figure 1) [13].



**Figure 1:** Automated assessment of carotid arterial wave intensity

**Catheter-based renal denervation**

A radiofrequency ablation catheter (Catheter Symplicity; Medtronic Ardian Inc., California, ) was advanced into each renal artery via femoral access. Low-power radiofrequency treatments were applied along the length of both main renal arteries as described elsewhere [15,16]. Patients were given heparin in an i.v. bolus to achieve a prolonged activated clotting time. Intra-procedural diffuse visceral pain was managed with i.v. anxiolytics and narcotics. We have not observed serious intra-procedural or peri-procedural complications. No important adverse events related to the procedure were noted in any of the treated patients during the follow-up.

**Statistical analysis**

Demographic characteristics, systolic BP, diastolic BP and all other analysed parameters were summarised with descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequency and percentage for categorical variables. The statistical

significance of changes in continuous parameters over time was analysed by mean of the Wilcoxon Signed Rank test for dependent data. Spearman rank correlation was used to assess whether there was a relationship between variables. Using the linear regression model we examined the simultaneous effects of systolic BP and PP on the other analysed parameters. All tests were two-sided tests with the criteria set at  $\alpha=0.05$ . A p-value of  $<0.05$  was considered statistically significant.

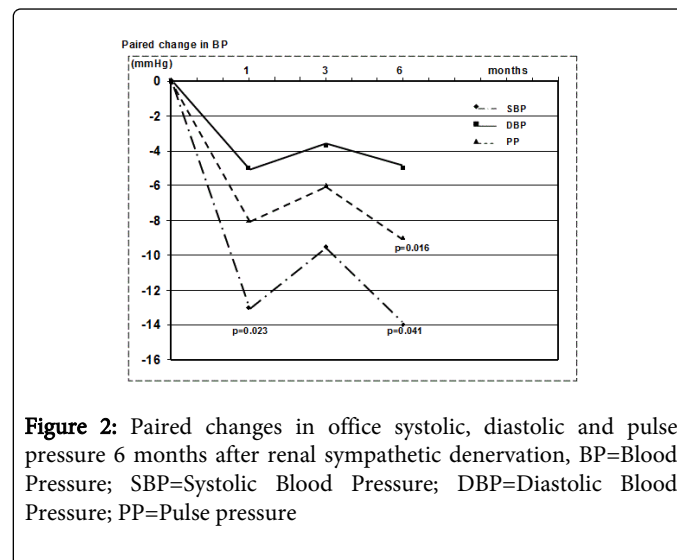
**Results**

**Baseline Characteristics**

Table 1 presents baseline clinical characteristics of 17 patients with RH before RDN and at the 6 month follow-up.

**Blood pressure**

The changes in office systolic BP were significantly improved after 1 month and at the 6 month follow-up. We found significant changes in pulse pressure (PP) 6 months after RDN too (Figure 2).



**Figure 2:** Paired changes in office systolic, diastolic and pulse pressure 6 months after renal sympathetic denervation, BP=Blood Pressure; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; PP=Pulse pressure

Changes in systolic BP during the daytime derived from ABPM were significantly decreased at 1 month and diastolic BP changes during the daytime were significantly reduced at 1 and 3 months after the procedure as well (Table 2).

	Paired changes			P-value (two sided test)		
	1	3	6	1	3	6
<b>Months</b>						
<b>SBP daytime</b>	-13	-9	-8	0.026	0.14	0.162
<b>(mmHg)</b>	± 20	± 20	± 20			
<b>SBP night-time</b>	-2	4	7	0.733	0.724	0.396
<b>(mmHg)</b>	± 19	± 25	± 24			
<b>DBP daytime</b>	-12	-10	-8	0.003	0.036	0.263
<b>(mmHg)</b>	± 19	± 19	± 22			
<b>DBP night-time</b>	-1	0	3	0.426	0.937	0.594
<b>(mmHg)</b>	± 9	± 13	± 14			

<b>PP daytime</b>	-5	-3	-5	0.14	0.345	0.234
<b>(mmHg)</b>	± 14	± 14	± 13			
<b>PP night-time</b>	-2	1	0	0.363	0.959	0.666
<b>(mmHg)</b>	± 9	± 12	± 11			

**Table 2:** Paired changes in ambulatory blood pressure monitoring before and after renal sympathetic denervation. Data are expressed as means ± SD; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure

### Indices of carotid stiffness and wave intensity

Stiffness indices were changed on both sides of the CCA; therefore, we evaluated the results of the right CCA. The changes in Ep were significantly reduced and in index AC increased at 1 month after RDN. The changes in beta and Ep values were significantly decreased after 3 months too. The changes in PWV declined slightly during the 3 months. Aix values, on the contrary, did not change significantly during this period (Table 3).

Months	Paired changes			P-value (two sided test)		
	1	3	6	1	3	6
<b>Beta</b>	-1.4	-1.5	-0.6	0.162	0.041	0.53
<b>(%)</b>	± 3.5	± 3.3	± 3.8			
<b>Ep</b>	-35	-36	-7	0.039	0.033	0.594
<b>(kPa)</b>	± 58	± 65	± 83			
<b>AC,</b>	0.11	0.12	0.05	0.03	0.069	0.167
<b>(mm<sup>2</sup>/kPa)</b>	± 0.19	± 0.23	± 0.19			
<b>Aix</b>	2.4	5.8	2	0.364	0.637	0.753
	± 9.5	± 16.8	± 10.5			
<b>PWV</b>	-0.5	-0.6	-0.1	0.099	0.169	0.593
<b>(m/s)</b>	± 1.1	± 1.8	± 2.2			

**Table 3:** Paired changes in indices of carotid artery stiffness before and after renal sympathetic denervation. Data are expressed as means ± SD; Beta: Stiffness Index; Ep: Pressure-Strain Elasticity Modulus; AC:

	beta		Ep		AC		Aix		PWV	
	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p
<b>SBP</b>	0.398	0.159	0.613	0.02	-0.674	0.008	0.175	0.55	0.559	0.038
<b>DBP</b>	0.346	0.226	0.617	0.019	-0.693	0.006	0.127	0.664	0.673	0.008
<b>PP</b>	0.524	0.054	0.491	0.074	-0.394	0.163	0.061	0.836	0.374	0.188

**Table 5:** The correlations between carotid stiffness parameters and office blood pressure at 6 months after renal sympathetic denervation

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; Beta: Stiffness Index; Ep: Pressure-Strain Elasticity

Arterial Compliance; Aix: Augmentation Index; PWV: One-Point Pulse Wave Velocity

The changes in NA were significantly reduced after one month and significantly increased in W1-W2 at the 6 month follow-up (Table 4).

Months	Paired changes			P-value (two sided test)		
	1	3	6	1	3	6
<b>W1</b>	0.2	6.5	-6.6	0.57	0.239	0.328
<b>(mmHgm/s<sup>3</sup>)</b>	± 27.3	± 36	± 22.5			
<b>W2</b>	-0.4	-1.2	-1.3	0.691	0.182	0.059
<b>(mmHg m/s<sup>3</sup>)</b>	± 2.6	± 2.3	± 2.0			
<b>NA</b>	-21	46	-36	0.041	0.388	0.345
<b>(mmHg m/s<sup>3</sup>)</b>	± 160	± 212	± 122			
<b>R-W1</b>	34	2	-3	0.003	0.722	0.255
<b>(ms)</b>	± 27	± 32	± 19			
<b>W1-W2</b>	-3	11	27	0.293	0.071	0.011
<b>(ms)</b>	± 35	± 19	± 29			

**Table 4:** Paired changes in indices of wave intensity before and after renal sympathetic denervation

Data are expressed as means ± SD; Wave intensity: first peak W1 correlates with maximum rate of left ventricular pressure; second peak W2 correlates with the time constant of left ventricular relaxation; NA: Negative Area, determines the effects of reflected waves; R-W1: the interval between the R wave on ECG and the peak of W1 (R-W1) corresponds to pre-ejection period; W1-W2: corresponds to ejection time.

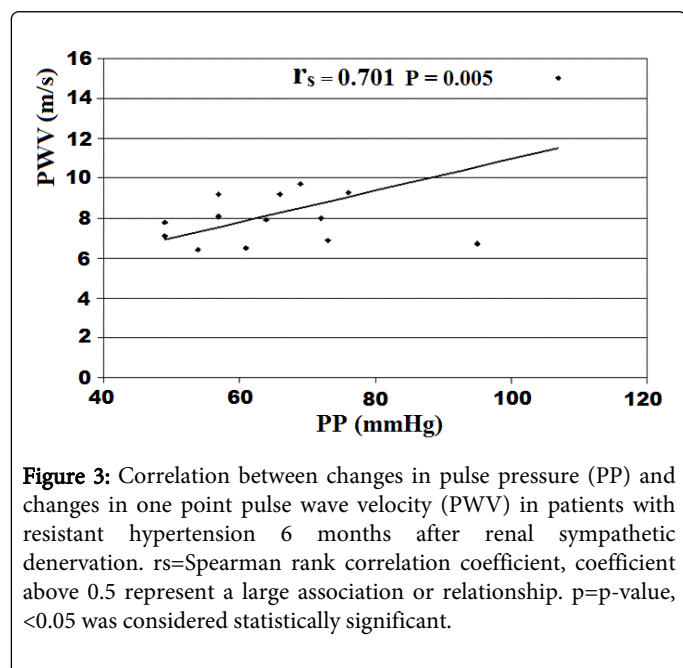
Using the Spearman rank correlation, we found significant correlations between office BP and the stiffness indexes. At the baseline correlated only PP with Ep (r<sub>s</sub>=0.499, p=0.041). At the 6 months SBP and DBP correlated positive with indexes Ep, PWV and negative with AC (Table 5). Similarly we found positive correlations between the changes in SBP, DBP and the changes in indexes EP, PWV (Table 6). The changes in PP correlated positive with changes in indexes Ep and PWV 6 months after RDN (Table 6, Figure 3).

Modulus; AC: Arterial Compliance; PWV: One-Point Pulse Wave Velocity; Aix: Augmentation Index; RDN: Renal Sympathetic Denervation; r<sub>s</sub>=Spearman Rank Correlation Coefficient; p=p-value;

	Changes in beta		Changes in Ep		Changes in AC		Changes in Aix		Changes in PWV	
	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p	r <sub>s</sub>	p
Changes in SBP	0.449	0.107	0.762	0.002	-0.466	0.093	0.11	0.708	0.774	0.001
Changes in DBP	0.471	0.089	0.74	0.002	-0.482	0.081	0.075	0.799	0.782	0.001
Changes in PP	0.424	0.13	0.737	0.003	-0.513	0.061	0.015	0.958	0.701	0.005

**Table 6:** The correlations between changes in carotid stiffness parameters and changes in office blood pressure at 6 months after renal sympathetic denervation

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; beta: Stiffness Index; Ep: Pressure-Strain Elasticity Modulus; AC: Arterial Compliance; PWV: one-Point Pulse Wave Velocity; Aix: Augmentation Index; RDN: Renal Sympathetic Denervation; rs=Spearman Rank Correlation Coefficient; p=p-value;



Office systolic BP and PP correlated to W1 (r<sub>s</sub>=0.781, p<0.0001; r<sub>s</sub>=0.867, p<0.0001) and to NA (r<sub>s</sub>=0.618, p=0.011; r<sub>s</sub>=0.576, p=0.002) only at baseline.

Systolic BP during the night-time and PP during the daytime and night-time derived from ABPM correlated to index Ep only at baseline (r<sub>s</sub>=0.504, p=0.047; r<sub>s</sub>=0.556, p=0.021; r<sub>s</sub>=0.511, p=0.043).

Linear regression analysis was used to detect the interrelations between office BP, carotid stiffness, and WI. Systolic BP correlated positively with the beta index (β=0.18, p=0.01; 95% CI 0.053-0.307) and with Ep (β=5.592, p<0.0001, 95% CI 3.796-7.388), negatively with AC (β=-0.009, p<0.0001, 95% CI -0.013-0.006), and positively with PWV (β=0.07, p=0.001, 95% CI 0.034-0.106). We did not detect correlations with WI.

## Discussion

In the study we have found significantly lower values of office BP as well as values of ABPM in patients with RH at the 6 month after RDN. In the same period, we found improvement in carotid stiffness values. Many factors are known to affect carotid stiffness, including low grade inflammation and age among others [17,18]. In this study we have focused on BP. Relationships between BP and stiffness indices have emphasized the impact of BP, particularly of systolic BP and PP, on carotid stiffness. Recent studies have reported that RDN improved BP as well as arterial stiffness. Brandt and co-workers [19] found significantly reduced carotid-femoral PWV in 110 patients 6 months after RDN. Other study demonstrated in responders an improvement of two-point PWV by 13.7% 6 months after the procedure [8]. Most of the studies have used the method of applanation tonometry for the measurement of arterial stiffness. Very few studies were done with method of the local carotid artery stiffness measurement using the ultrasound with echo-tracking, but without an association with RDN. The main advantage of the echo-tracking method is that carotid stiffness is determined directly from the change in pressure and the change in volume without the use modeling of the circulation [20].

The mechanisms of BP reduction after RDN are not completely known. Reduced sympathetic activity after RDN is the main recognized mechanism responsible for lowering BP [21]. It is known that the procedure is followed by reduced efferent sympathetic stimulation, by lowering of norepinephrine spillover, by reduced plasma renin activity, and by increased natriuresis and renal blood flow. The decrease in renal afferent signalling is associated with lowering of central sympathetic activity [22]. We found significantly improved carotid stiffness parameters. We affirmed the relationships between BP values and stiffness parameters at 6 months after RDN. According to these results we may suppose that the BP reduction together with modification of sympathetic tone after RDN may lead to attenuation of carotid stiffening.

The clinical effectiveness of the RDN procedure is mainly known from the Simplicity Clinical Trial Program. To date Simplicity HTN-1 and Simplicity HTN-2 are the largest trials on this topic, which have confirmed the effect of RDN on lowering BP [16,23]. On the other hand, the results of the Simplicity HTN-3 trial did not show a significant reduction of office systolic BP as compared with a sham control [24]. Other single centre studies have mostly included a small number of patients. The RDN method raises a number of questions, the correct clinical selection of patients who will the real benefit from RDN being one of the key issues [25].

In our previous study we found increased carotid stiffness indices in hypertensive patients and, based on the relations between BP and

indices of carotid stiffness as well as WI, we assumed an effect of BP on V-A coupling [26]. In the present study we have used WI to analyse V-A coupling in patients after RDN. The NA index, which signifies reflections from the cerebral circulation, was significantly reduced at 1 month after RDN. On the other hand, we found the relation between BP and NA only at the baseline. Systolic BP and PP correlated with NA and with W1. On the basis on these findings, we may consider that the relationship between BP and WI may reflect the impact of BP on the reflected waves returning to the heart and consequently affect the rise in LV pressure. There is evidence that increased stiffness in conduit arteries is associated with early arrival of reflected waves to the proximal aorta during mid-to-late systole. The load caused by the reflected wave may result in shortening of the ejection period [27]. We observed a significantly prolonged W1-W2 index 6 months after RDN. Therefore, we may assume that the decrease in BP was followed by a reduction in NA and consequently by prolongation of the LV ejection period. We suggest that improvement in carotid stiffness and WI may be reflected in the enhancement of V-A coupling.

Some limitations of this study may be noted. We have evaluated a relatively small group of patients with RH (17 subjects) and over a shorter follow-up period (6 months). For these reasons we have not analysed the impact of BP value on carotid stiffness in responders and non-responders. It is therefore necessary to continue to monitor our patients for a longer period.

## Conclusion

We have found improvement in office BP as well as ABPM in patients with RH 6 months after RDN. The decrease in BP was followed by improvement of carotid stiffness and WI. That may be reflected in the enhancement of V-A coupling.

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