LONG TERM EFFECT OF RENAL DENERVATION ON 24 HOUR ABPM BLOOD PRESSURE VARIABILITY AND BLOOD PRESSURE LOAD PARAMETERS

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ДЪЛГОСРОЧЕН ЕФЕКТ ОТ ПРОВЕДЕНА РЕНАЛНА ДЕНЕРВАЦИЯ ВЪРХУ ПАРАМЕТРИ НА ВАРИАБИЛИТЕТА И ТОВАРА НА АРТЕРИАЛНОТО НАЛЯГАНЕ ОТ 24-ЧАСОВОТО АМБУЛАТОРНО МОНИТОРИРАНЕ

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Abstract. The aim of the study was to evaluate the long-term effect of renal sympathetic denervation (RSD) on 24h ambulatory blood pressure measurement (ABPM) and blood pressure load (BP load) in patients with resistant hypertension. The study included 32 patients with treatment-resistant hypertension and performed successful RSD. The effect of renal denervation was significant both in terms of daytime, nighttime and 24-hour arterial pressure, with the most pronounced effect on nocturnal blood pressure. In addition to mean BP reduction we found out a significant improvement of weighted 24 h SD and BP load during follow-up. A long-term effect of the RSD, reported as a reduction in 24-hour systolic blood pressure above 10 mm Hg at month 12, was found in 22 patients (68.8%). In multivariate regression analysis, two parameters remained predictive for successful renal denervation – higher nighttime systolic blood pressure (OR 0.9, 95% CI 0.8-1.005, p = 0.05) and lower pulse pressure (OR 1.13, 95% CI 1.01-1.26, p = 0.03).

Key words: resistant hypertension, renal denervation, ambulatory blood pressure monitoring, blood pressure variability, blood pressure load, arterial stiffness

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Резюме. Целта на настоящото проучване бе установяването на дългосрочния ефект от проведена ренална симпатикусова денервация върху параметри на вариабилитета на артериалното налягане и неговия товар при амбулаторно мониториране при пациенти с резистентна артериална хипертония. Проучването включва 32-ма пациенти с резистентна на медикаментозно лечение АХ и проведена успешна ренална денервация. Ефектът от проведената процедура е значим по отношение на всички показатели на АВРМ – дневно, нощно и 24-часово АН, като най-значим ефект отчитаме по отношение на редукция на нощното артериално налягане. В допълнение към благоприятния ефект на редукция на средните стойности на АН отчитаме и значимо подобрение на усредненото стандартно отклонение в рамките на 24-часов период, както и на товара на повишеното АН по време на наблюдението. Дългосрочен ефект, заложен като редукция на 24-часовото систолно артериално налягане с над 10 mm Hg на месец 12 след проведена ренална денервация, отчитаме при 22 пациенти (68.8%). В проведения многостъпален регресионен анализ два показателя предсказват успеха от проведената ренална денервация – високото нощно систолно артериално налягане (отношение на шансовете 0.9, 95% ИД 0.8-1.005, p = 0.05) и ниското пулсово налягане (отношение на шансовете 1.13, 95% ИД 1.01-1.26, p = 0.03).

Ключови думи: резистентна хипертония, ренална денервация, амбулаторно мониториране на артериалното налягане, вариабилитет на артериалното налягане, товар на артериалното налягане, артериален еластицитет

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INTRODUCTION

In recent years, there has been a significant interest in renal denervation as a possibility to optimize blood pressure control among patients with resistant arterial hypertension [1]. Randomized trials have clearly demonstrated the capabilities of the methodology among patients without and those taking multiple antihypertensive agents [2-12]. This was accompanied by clarification of diagnostic algorithms in patients with resistant hypertension, exclusion of secondary causes of hypertension, optimization of therapeutic approaches and assessment of adherence to antihypertensive therapy [13]. Apart from changes in office and home arterial pressure, 24-hour ambulatory blood pressure monitoring (24h ABPM) is currently the standard in the diagnostic algorithm and the monitoring of the effect of applied therapeutic regimens. As a consequence, in the majority of controlled trials in resistant hypertension, it was the change in 24-hour systolic blood pressure that emerged as the main primary efficacy endpoint [2-13]. Different criteria have been proposed – more than 5 or more than 10 mmHg reduction in 24-hour systolic arterial pressure to evaluate a favorable therapeutic response in serial follow-up after successful renal denervation. Other author groups focused their attention on separate components of 24-hour arterial pressure – daytime, nighttime, the entire 24-hour period. In this way, Azizi and Kario, and colleagues established the so-called always-on effect of renal denervation with an effect in the entire 24-hour period, with particular attention being paid to the reduction of nocturnal arterial pressure [10-11]. Beyond average blood pressure values in individual components of the day, the damaging effect of persistently elevated blood pressure can be attributed to its marked variability, as well as to the duration of periods of elevated values within the day. It is believed that the two indicators – arterial pressure variability and arterial pressure load reflect different aspects of uncontrolled arterial hypertension [14-15]. In the scientific literature, there is a lot of data on the relationship between the two indicators and the damage of target organs and the prediction of the risk of future cardiovascular complications [14-17]. Beyond the effect on office and out-of-office arterial pressure, studying the influence of performed renal denervation on BP variability and its burden is of considerable interest. This motivated us to carry out the present analysis, based on an algorithm for diagnosis and behavior in patients with resistant hypertension, developed at the Sveta Anna UMBAL, Sofia, an expert center for arterial hypertension of the European Society of Hypertension.

MATERIAL AND METHODS

Study population

Consecutive patients with resistant hypertension who underwent RSD workout at the University Hospital Saint Anna, Sofia, between January 2014 and December 2018 were included in the study. Based on the history taken, the available medical documentation and laboratory tests, the cardiovascular risk profile of the patients was assessed for the presence of other concomitant risk factors (RF) or previous cardiovascular or cerebrovascular events. RSD was performed on the grounds of resistant hypertension defined as mean daytime systolic BP ≥ 135 mm Hg or diastolic BP ≥ 90 mm Hg in 24-hr ambulatory blood pressure measurement (ABPM) despite the intake of at least three antihypertensive agents, including a diuretic. Patients with a renal anatomy unsuitable for denervation, severe renal artery stenosis, or an estimated glomerular filtration rate (eGFR) < 45 ml/min per 1.73 m² (Modification of Diet in Renal Disease equation) were excluded. The study was performed according to the 1975 Declaration of Helsinki and "good clinical practice" guidelines. All patients provided written informed consent.

Ambulatory blood pressure measurement, blood pressure variability and load

Conventional blood pressure was the average of 2 consecutive readings obtained either at the person's home (home BP) or at an examination center (office BP).

ABPM was performed using a validated oscillometric device (Riester® RI-CARDIO). BP recordings were performed every 15 minutes during the day (7.00 am–10.00 pm) and every 30 minutes during the night (10.00 pm–7.00 am) according to the guidelines [25].

In our main analyses, we defined daytime as the interval ranging from 0700 to 2200 hours and nighttime intervals ranged from 2200 to 0700 hours. The mean and standard deviation (SD) of daytime, nighttime and 24 hours systolic and diastolic blood pressure are presented in the following article. We assessed short term blood pressure variability by two indices – standard deviation of blood pressure and weighted 24 h SD. According to Bilo et al [18] the weighted 24 h SD (wSD) selectively removes the contribution provided by nighttime BP fall to 24 h SD, by weighting daytime and nighttime BP SD for the duration of the day- and nighttime periods, respectively, and by averaging the SD of these two time subperiods.

BP load was defined as the percentage of BP values exceeding 135 mm Hg systolic or 85 mm Hg diastolic during daytime, or 120 mm Hg systolic or 70 mm Hg diastolic during nighttime, or 130 mm Hg systolic or 80 mm Hg diastolic during entire 24 hours' period [19-20].

Renal denervation

RSD was performed with the Symplicity Flex™ catheter (Medtronic, Minneapolis, MN, USA) according to a standardized protocol, which has been used in large-scale clinical trials and has been described previously [21]. In brief, four to six complete ablation runs of two minutes were delivered to each renal artery. The ablation points were placed circumferentially to the renal artery wall. All patients received intravenous fentanyl to control pain. All procedures were performed by two experienced interventional cardiologists (> 20 supervised procedures).

Statistical analysis

Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as number of patients and percentage. Categorical variables were compared using Fisher's exact test and the independent samples t-test was used for continuous variables. Univariate and multivariate binary logistic regression analysis was performed to determine predictive factors of non-response. All variables with a probability value (p-value) < 0.05 in univariate analysis were included in multivariate analysis. A two-tailed p-value < 0.05 was defined as statistically significant. All analyses were performed with SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

For a period of 4 years between 2014 and 2018 in the excellence center of arterial hypertension at Cardiology Clinic of University hospital "Sveta Anna" (Sofia) was conducted a prospective follow-up of 62 patients with difficult to control arterial hypertension, defined as persistently high levels of office blood pressure despite taking triple antihypertensive therapy, including a diuretic. For this purpose, a predefined protocol was created, including history of hypertension; risk profile assessment; accompanying cardiovascular diseases; lipid profile; renal function; office, home and 24-hour ambulatory blood pressure monitoring; non-invasive assessment of arterial stiffness, renovasography and in the absence of contraindications, renal denervation (Figure 1). The follow-up group consisted of 62 patients – 32 men (51.6%) and 30 women (48.4%). In the first step, all patients underwent verification of the increased office blood pressure with out-of-office techniques – home and 24 hours ABPM. In 12.9% of the patients (n = 8) we found pseudoresistant arterial hypertension and normal values of home and 24-hour ABPM, regardless of the persistently high values of office BP. In the second group – 32.3% (n = 20), a correction was made in the antihypertensive therapy and the result was documented by normalization of both office and out of office repeated measurements at month 1 and 3. In the third group – 3.2% (n = 2) of patients, the performed renovasography identified renovasacular hypertension with significant renal artery stenosis, which was successfully intervened. In 51.6% (n = 32) the resistant hypertension was confirmed and in the absence of contraindications renal denervation performed. Office, home and ABPM were repeated every 3 months after RSD. Response to RSD was defined as a reduction of 10 mm Hg in systolic 24-hr blood pressure (ABPM) at month 12. Any patient who did not fulfil this criterion was considered a non-responder.

In the study, renal denervation as part of the treatment regimen was performed in 32 patients (51.6%). The baseline and 3 months after the procedure levels of office and out- off office blood pressure are shown in Table 1.
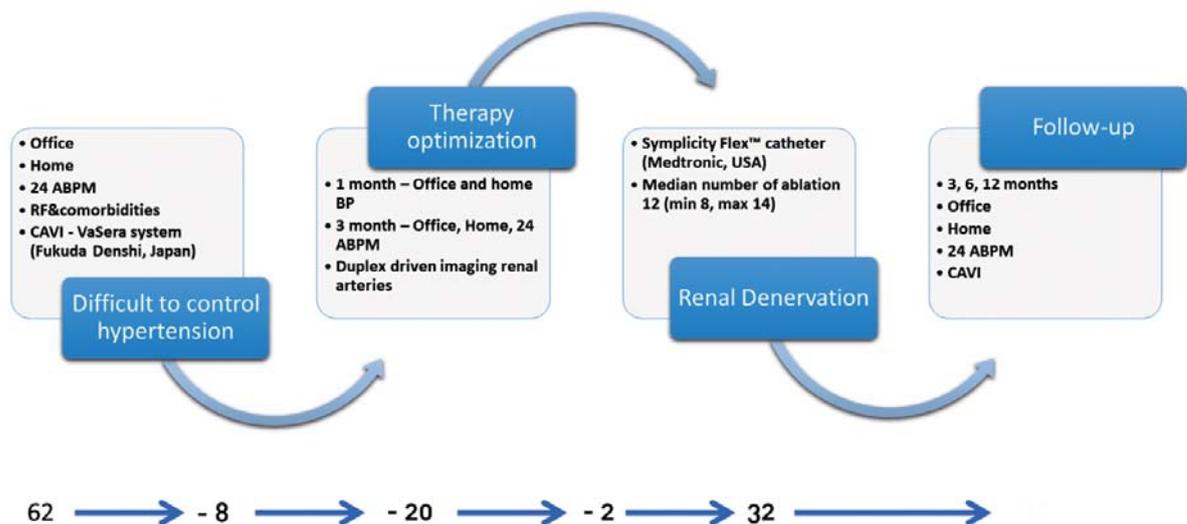

Fig. 1. Predefined protocol for the management of difficult to control arterial hypertension in excellence center of arterial hypertension at Cardiology Clinic of University Hospital "Sv. Anna", Sofia. The number of patients in each step are shown in the figure

Table 1. Office and out of office blood pressure values at baseline and 3 months after renal denervation (n = 32)

	Baseline	Month 3 after RSD	Reduction	p
Office BP				
Systolic	171.75 ± 21.32	160.91 ± 15.89	10.84 ± 17.90	0.002
Diastolic	94.66 ± 13.28	88.28 ± 11.89	6.38 ± 11.16	0.003
Home BP				
Sistolic	169.38 ± 15.86	157.38 ± 19.54	12.00 ± 15.72	0.000
Dyastolic	90.41 ± 12.01	85.78 ± 12.86	4.63 ± 8.23	0.003
24h. ABPM				
24h mean SBP	164.13 ± 14.29	155.06 ± 19.28	9.06 ± 14.21	0.001
12h mean DBP	88.16 ± 14.64	84.91 ± 16.75	3.25 ± 9.20	0.055
Daytime SBP	169.88 ± 13.78	161.59 ± 20.21	8.28 ± 14.80	0.003
Daytime DBP	91.16 ± 14.75	88.44 ± 16.34	2.72 ± 9.41	0.112
Nighttime SBP	156.66 ± 16.04	145.63 ± 23.43	11.03 ± 17.28	0.001
Nighttime DBP	83.28 ± 15.19	78.72 ± 19.32	4.56 ± 11.36	0.030
24 h Pulse Pressure	78.69 ± 11.26	73.16 ± 13.07	5.53 ± 9.13	0.002
Dipping				
Systolic	7.66 ± 6.22%	10.00 ± 6.15%	2.34 ± 6.66%	0.055
Diastolic	8.63 ± 7.65%	11.69 ± 7.80%	3.06 ± 7.54%	0.029
Number of medications	5.72 ± 1.09	5.25 ± 0.92	0.47 ± 0.98	0.011

Despite the very high baseline levels of blood pressure and number of antihypertensive medications the procedure was related with satisfactory long-term results – the percentage of patients normalizing office blood pressure 12 months after the procedure – 46.9%, normalizing home blood pressure values below 135/85 mm Hg – 18.8% and 24h ABPM < 130/80 mm Hg – 15.6%. A long-term effect of the procedure, reported as a reduction in 24-hour ABPM systolic blood pressure above 10 mmHg at month 12, was found in 22 patients (68.8%), Figure 2.

The median of the observed reduction of the 24-hour ABPM systolic blood pressure at month 12 was -16 mm Hg at 95% confidence interval -9.1 to -21 mm Hg. Although the effect of renal denervation was significant both in terms of daytime, nighttime and 24-hour arterial pressure, Figure 3 demonstrates the most pronounced effect on nocturnal blood pressure.

Additional data on the effect of the performed procedure within the whole day are obtained by analyzing serial ABPM recordings and changes in the variability of arterial pressure. We found out a significant improvement of weighted 24 h SD during follow-up of patients after renal denervation. The effect of the procedure on blood pressure variability is not immediate and it's mainly seen after 6 month of renal denervation (Figure 4).

A profound effect of the procedure on both systolic and diastolic blood pressure load was also noticed. In opposite to the dynamic of the mean blood pressure the main beneficial effect on the blood pressure load was seen for the daytime systolic and diastolic blood pressure (Figure 5).

As might be expected there is a direct linear relationship between the change in 24-hour systolic blood pressure and the change in systolic blood pressure
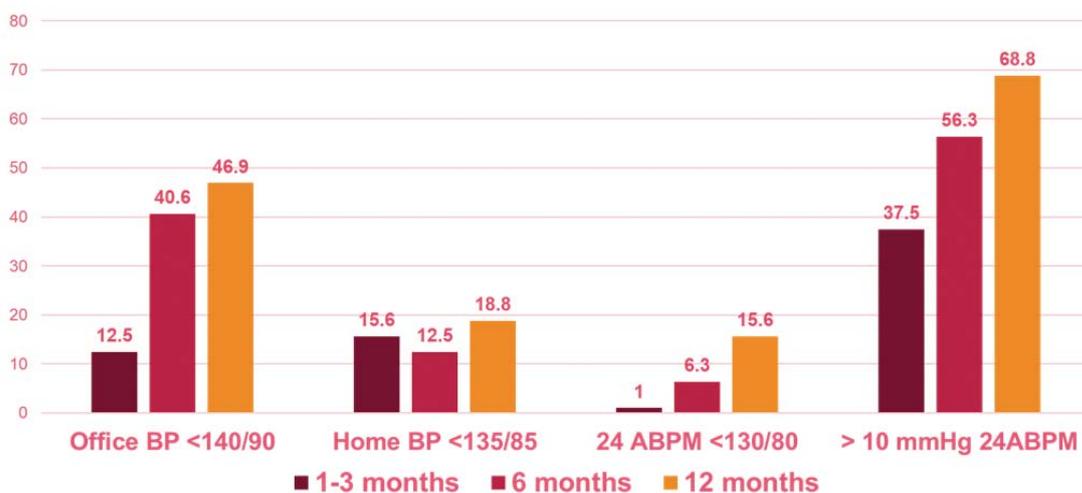
Fig. 2. Proportion of patients normalizing BP and responders (> 10 mm drop of SBP on 24h ABPM)
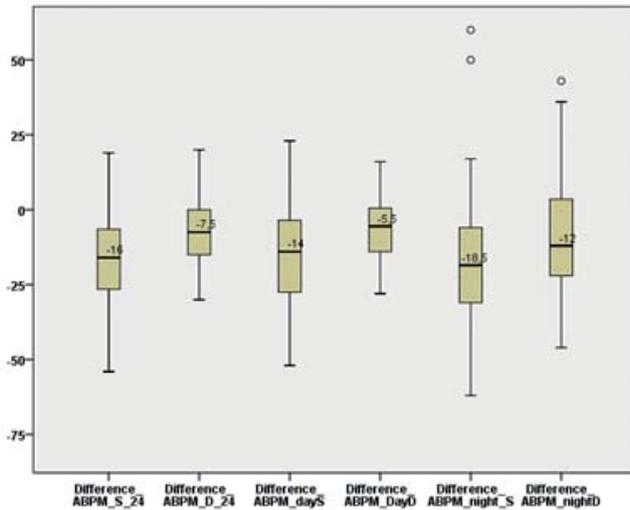
Fig. 3. Difference in 24 hours (24), daytime (Day) and nighttime (Night) systolic and diastolic blood pressure on ABPM during one-year follow-up, S-Systolic, D-Dyastolic, p < 0.001 for all comparisons vs baseline values
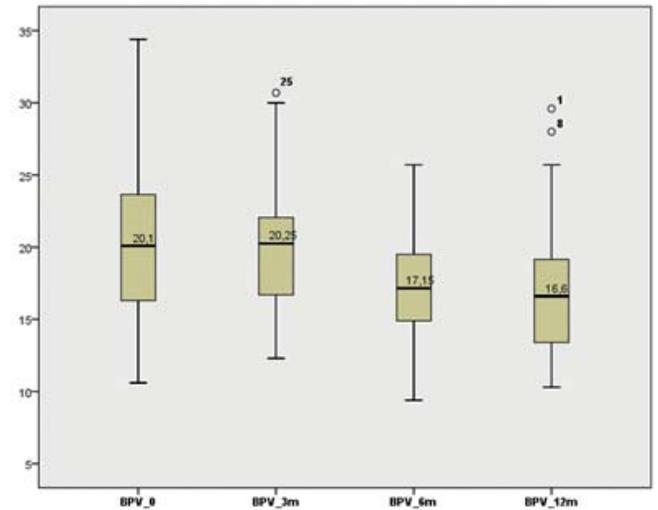

Fig. 4. Dynamics of weighted 24 h SD (BPV) before (0) and 3, 6 and 12 months after renal denervation. P = 0.3 in comparison of baseline values vs. 3-month, p = 0.002 in comparison of baseline values vs 6-month, p < 0.001 in comparison of baseline values vs 3 month
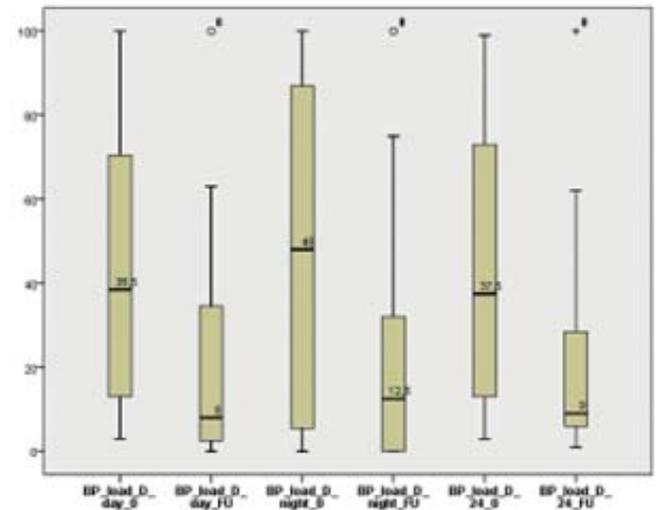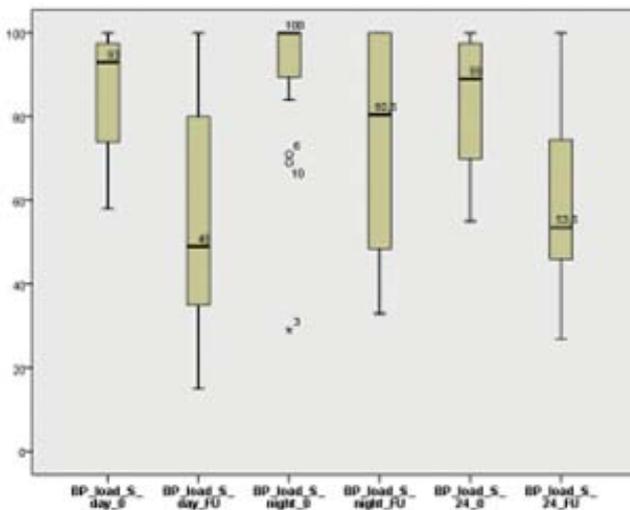
Fig. 5. Effect of renal denervation on blood pressure load during 12-month follow-up. On the left – effect on systolic BP load during the day, night and 24 h, on the right – effect on diastolic BP load during the day, night and 24 h, p < 0.001 for all comparisons. S – Systolic, D – Dyastolic, 0 – Baseline, FU – 12-month follow-up

load. Thus, the most beneficial effect on daytime, night-time, and 24-hour BP burden was observed in those patients who responded with a greater than 10 mmHg reduction in 24-hour systolic BP assessed at one-year follow-up with ABPM (Figure 6).

Similarly, this is the patient group in which the most significant favorable change in blood pressure variability is reported (Figure 7).

In our series of patients, univariate binary logistic regression analysis identified several non-invasive parameters with potential to predict the long-term outcome after renal denervation – higher baseline night-time systolic blood pressure (OR 0.9, p = 0.04) and higher standard deviation of nighttime SBP (OR 0.7, p = 0.09), number of ablation performed (OR 1.43, p = 0.05), lower nocturnal heart rate (OR 1.07, p = 0.07) and lower pulse pressure (OR 1.12, p = 0.02). In contrast, neither measures of blood pressure load nor baseline weighted 24 h SD were predictive of therapeutic response at 12-month follow-up. In multivariate analysis, two parameters remained predictive – higher nighttime systolic blood pressure (OR 0.9, 95% CI 0.8-1.005, p = 0.05) and lower pulse pressure (OR 1.13, 95% CI 1.01-1.26, p = 0.03).
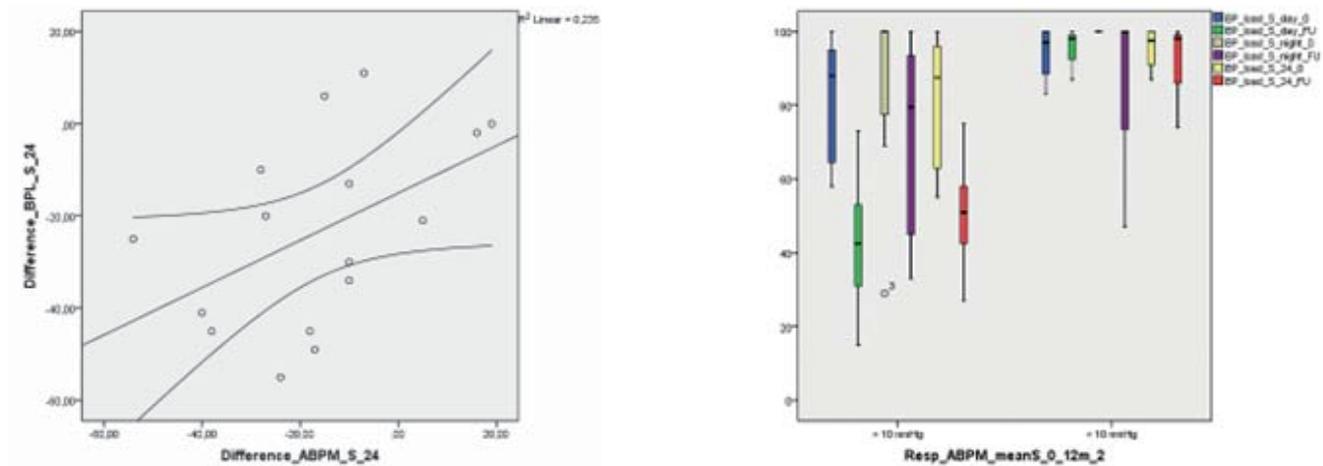
Fig. 6. Linear regression slope between the change in 24-hour systolic blood pressure and the change in systolic blood pressure load (left) and changes on systolic blood pressure load during the day, night and 24 h in responders and nonresponders during 12-month follow-up (right), 0-Baseline, FU – 12-month follow-up, p < 0.001 only for the responders group
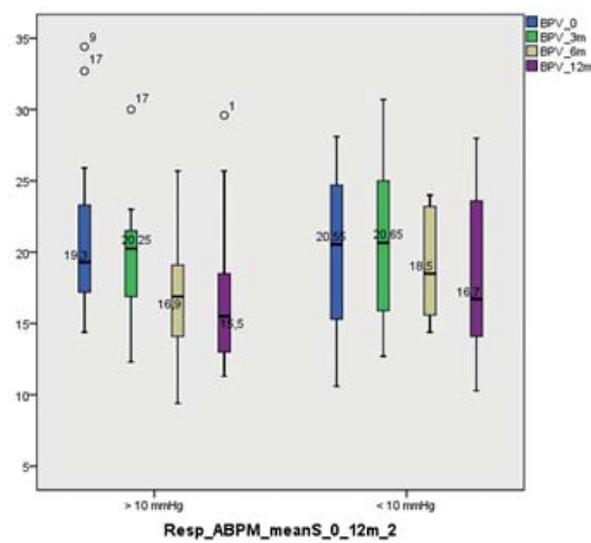
Fig. 7. Changes on blood pressure variability assessed by weighted 24 h SD (BPV) in responders and nonresponders during 12-month follow-up, 0 – Baseline, 3, 6 and 12 months respectively

DISCUSSION

Despite a stable global prevalence, the absolute number of people with hypertension increased from 648 million in 1990 to 1.28 billion in 2019 [22]. Disease awareness and BP control rates remain poor worldwide and in many on contemporary real-world data or registries not more than 50% of hypertensive have been controlled under medical treatment [22-24]. Over the last decades, device-based therapies and especially renal denervation have been investigated as additional treatment options for uncontrolled hypertension. Based on the data available to 2018 the ESC/ESH Guidelines for the Management of Arterial Hypertension provided the following recommendation: "Device-based therapies for hypertension are not recommended for the routine treatment of hypertension, unless in the context of clinical studies and randomized controlled trials, un-

til further evidence regarding their safety and efficacy becomes available" [25]. Based on the data available since then the new 2023 ESH Guidelines for the Management of Arterial Hypertension changes his recommendation for renal denervation to class of recommendation II, level of evidence B – „RDN can be considered as a treatment option in patients an eGFR > 40 ml/min/1.73 m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life" [26-27].

The main conclusions of our research can be grouped as follows: 1) In compliance with modern indications for diagnosis and management of resistant hypertension, renal denervation represents an additional reliable therapeutic method; 2) The effect of the procedure is durable and sustainable over time; 3) The beneficial reduction of blood pressure is achieved in all parameters of the 24-hour ambulatory ar-

terial pressure – daytime, nighttime and overall 24 h period; 4) in addition to the effect on the average values of the arterial pressure, a change in a favorable direction is also considered on blood pressure variability and blood pressure load; 5) in a multivariate regression analysis, high baseline nocturnal systolic blood pressure and low baseline pulse pressure were independent predictors of therapeutic success, defined by a 10 mm Hg reduction of 24-hour ABPM.

It is common practice in publications of large randomized trials in renal denervation to report procedure results on mean ambulatory monitoring values. Relatively less published data are available regarding blood pressure variability or effect on blood pressure load, two additional measures related to the burden of uncontrolled hypertension. An increased BPV provide prognostic information for cardiovascular risk prediction independent from average BP levels but the clinical significance and clinical implications of different BPV components may substantially differ. According to the position paper of the ESH on blood pressure variability several short term BP variability indices had a prognostic information [28]. Studies focused on daytime SD distribution suggest that systolic BPV > 15 mm Hg is associated with progression of vascular organ damage and cardiovascular mortality Nocturnal systolic SD > 12.2 mm Hg and diastolic SD > 7.9 mm Hg were proposed to identify a higher risk of cardiovascular events and death (outcome-based threshold levels). Twenty-four-hour systolic wSD > 12.8 mm Hg was proposed as marker of increased risk for cardiovascular events [28]. In the field of resistant hypertension several studies [29-33] proposed that RDN might decrease BP variability, as captured by the unadjusted or adjusted SD of mean 24-h ambulatory BP, ARV and coefficient of variation of 24-h ambulatory BP. Similar to the results of the published meta-analysis by Persu et al. [33], we report an effect of performed renal denervation on weighted 24 h SD, a parameter which is less influenced by the mean levels of blood pressure.

A challenging problem regarding RDN is the identification of the optimal candidate for RDN [13, 25-27]. Some of the identified predictors, such as high plasma renin activity and aldosterone, as well as higher heart rate appear to be promising indicators in patients not receiving drug therapy. The number of the ablation performed, a factor with clinical importance in first generation RDN studies was found to be predictor of response only in univariate analysis in our group of patients [41]. Overall, it may be difficult or even impossible to simplify the BP response to a single biomarker, since a large proportion of patients with true resistant hypertension have several additional comorbidities indicating a very heterogeneous patient population per se.

In the DENERHTN trial, Gosse et al found baseline average nighttime systolic BP and standard deviation as significant predictors of the systolic BP response in the denervation group [34]. We expand those data by adding additional predictor – lower pulse pressure and extending the period of follow-up to 12 months after denervation. In reality this is not the first study focusing on the importance of arterial stiffness evaluation in the time course of diagnosis and management of resistant hypertension [35-39]. Ott et al. [35] as well as Okon et al [36] published data on invasively measured pulse wave velocity and central pulse pressure as indicators and demonstrated that patients with low pulse wave velocity and clinical profile of isolated systolic hypertension responded with significant reduction in blood pressure. Fengler et al [37] demonstrated that the assessment of arterial stiffness can help improve patient preselection for renal sympathetic denervation and identify a subgroup of isolated systolic hypertension patients who benefit from sympathetic modulation. Brandt et al [38] focused on non-invasive assessment methods such as carotid-femoral pulse wave velocity and also found a link to a subsequent response to the procedure. The same is true for another promising indicator, such as the cardio-ankle vascular index (CAVI index) in patients with resistant arterial hypertension treated by renal denervation [40]. Although there is some cross-link between sympathetic activation and stiffness (decreased vasoconstriction with attenuated sympathetic drive), this interaction holds to be true only in the early stage of the disease. At a later stage, arterial stiffness is mainly driven by irreversible pathological remodeling of the vasculature. Unfortunately, a significant proportion of patients considered for RSD are probably beyond this point of no return.

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