Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Original Article
J Hypertens Res (2021) 7(2):69-78

Cardio-ankle vascular index (CAVI) as a marker for arterial stiffness predicts outcome of renal sympathetic denervation in patients with resistant arterial hypertension

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Received: April 19, 2021, Accepted: May 31, 2021

Abstract

This study aimed to examine arterial stiffness using the cardio-ankle vascular index (CAVI) in patients with resistant arterial hypertension and to assess the predictive value of the parameter in the identification of responders from renal denervation. The study included 62 patients with treatment-resistant hypertension; after out-of-office blood pressure measurement and intensification of therapy, renal denervation was performed in 32 cases. Patients with increased arterial stiffness were older, with a larger waist circumference and previous cardiovascular events. Despite similar baseline out-of-office and office blood pressure and concomitant antihypertensive therapy, patients with lower arterial stiffness had a more significant blood pressure effect after renal denervation, a result that persisted within 12 months of follow-up. In contrast, the effect of the procedure was clinically insignificant among patients with baseline CAVI values above 8.3.

Keywords: resistant hypertension, cardio-ankle vascular index (CAVI), arterial stiffness, predictors.

Introduction

High blood pressure (BP) is the strongest modifiable risk factor for global death and disability from cardiovascular disease [1]. Resistant hypertension (RH) is a multifactorial chronic condition in which antihypertensive medications fail to lower raised BP or whereby many medications are required to lower BP below hypertensive thresholds. RH is clinically defined as BP ≥140/90 mmHg despite adherence to three or more different classes of antihypertensive drugs at optimal doses, one of which is a diuretic, or BP <140/90 mmHg with the use of four or more antihypertensive drugs [2]. Among people treated for hypertension, approximately 1 in 50 will develop RH. These individuals are at higher risk of target organ damage [3] and cardiovascular events than those whose treatment can control BP levels [4].

Over recent years, percutaneous renal sympathetic denervation (RSD) has been developed as an interventional treatment option for patients with

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treatment-resistant hypertension. Mechanistically, modulation of efferent and afferent renal sympathetic nerve fibers is believed to improve renal regulatory functions and blood flow and attenuate the central sympathetic activity [5, 6].

As the genesis of arterial hypertension is multifactorial, uniform treatment response to RSD in all patients cannot be expected. Given the invasiveness with potential side effects and the cost of the therapy, it is highly desirable to identify patients who will benefit from RSD prior to the intervention. So far, analyses of markers predicting treatment response have focused mainly on such factors as patients' medical history, technical aspects of the procedure, and the quantification of sympathetic activity [7–10].

Another factor influencing the presence and time course of arterial hypertension is arterial stiffness (AS). Reduction in vessel distensibility is based on a progressive remodeling of the vascular wall and predisposes to increased cardiovascular mortality and morbidity [11, 12]. The role of stiffness in the pathogenesis of hypertension is of critical importance as data point to the fact that increased AS is not solely a consequence but one of the main contributors to the development of arterial hypertension [13–16]. Pulse wave velocity (PWV) has been shown to be the most reliable parameter, but in the last years, there have been proposed different new noninvasive methods for the quantification of AS. Only a few data exist on the role of vascular factors in patients treated with RSD, and the value of AS to predict the response to RSD is unclear [17–20].

Therefore, the aim of the present study was to determine the clinical characteristics of patients with increased AS undergoing RSD and examine the role of noninvasive cardio-ankle vascular index (CAVI) measurement as a surrogate for AS in predicting the outcome of RSD.

Material and Methods

Study population

Consecutive patients with resistant hypertension who underwent RSD 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 mmHg or diastolic BP ≥90 mmHg in 24-hr ambulatory blood pressure measurement (ABPM) despite the intake of at least three antihypertensive agents, including one diuretic. Patients with renal anatomy unsuitable for denervation, severe renal artery stenosis, or an estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2 (using the Modification of Diet in Renal Disease equation) were excluded. This study was performed according to the 1975 Declaration of Helsinki and the Good Clinical Practice guidelines; it was approved by the local ethics committee (approval ID: 163/11.12.2013) and all patients provided written informed consent.

Ambulatory blood pressure measurement

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 latest European Society of Cardiology (ESC) guidelines [21].

Cardio-ankle vascular index

The cardio-ankle vascular index (CAVI) was measured and automatically calculated using the VaSera system (Fukuda Denshi Co, Japan) as per the manufacturer's recommendations. CAVI requires the placement of ECG electrodes on both wrists, a microphone for phonocardiography on the sternum, and four BP cuffs wrapped around the four limbs. The upper arm and ankle pulse waves, as well as BP, were measured. CAVI is disregarded if the ankle-brachial index (ABI) is less than 0.9 [22].

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 [7, 8]. 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 fentanil 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 the 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.

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

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, was conducted for a period of 4 years between 2014 and 2018 in the Excellence Center of Arterial Hypertension at Cardiology Clinic of St. Anna University Hospital, Sofia. For this purpose, a predefined protocol was created, including the history of hypertension; risk profile assessment; accompanying cardiovascular diseases; lipid profile; renal function; office, home, and 24-hour ambulatory blood pressure monitoring; noninvasive assessment of arterial stiffness, renovasography, and renal denervation in the absence of contraindications. The follow-up group consisted of 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 months 1 and 3. In the third group – 3.2% (n=2) of patients, the performed renovasography identified renovascular hypertension with significant renal artery stenosis, which was successfully intervened upon. In 51.6% (n=32) the resistant hypertension was confirmed, and renal denervation was performed in the absence of contraindications. Office, home, and ABPM measurements were repeated every 3 months after RSD. Response to RSD was defined as a reduction of 10 mmHg in systolic 24-hr blood pressure (ABPM) at month 12. Any patient who did not fulfill this criterion was considered a non-responder.

Arterial stiffness assessment in patients with resistant hypertension

The mean values of CAVI in the whole group of patients with resistant hypertension were 8.19±0.21 on the right and 8.17±0.23 on the left with a median of 8.3 (minimum and maximum values of 4.4 and 10, respectively) (Figure 1).

The characteristics of patients with AS, defined as CAVI greater than the median of 8.3, are shown

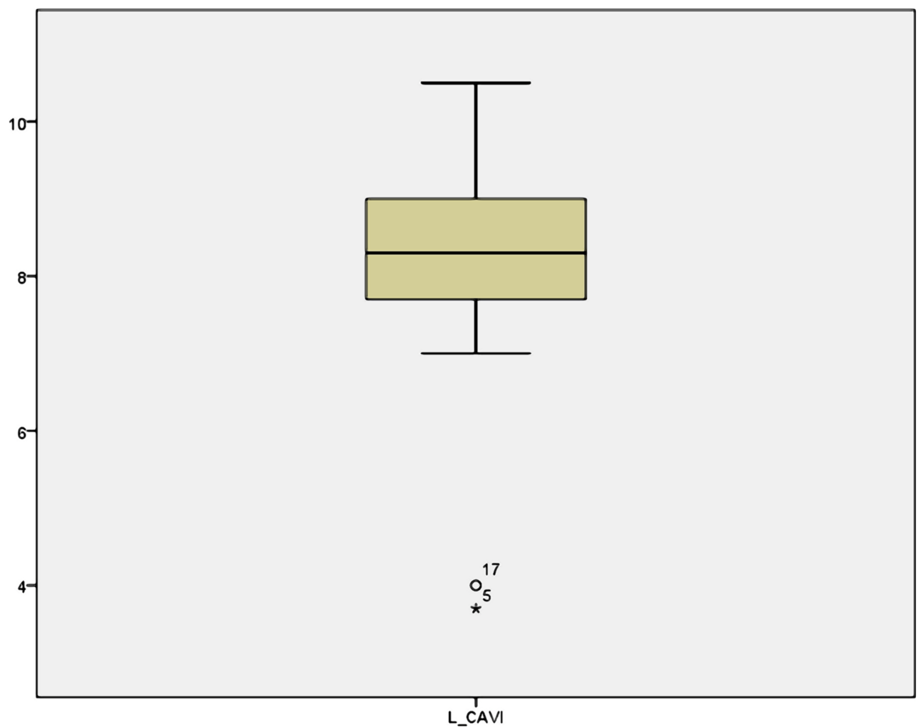

Figure 1. Mean values of CAVI in the group of patients with resistant hypertension.

Table 1. Characteristics of patients stratified according to the CAVI value.

CAVI		Mean	Std. Deviation	Std. Error Mean	P-value
Age	<8.3	60.11	8.622	2.032	0.04
	>8.3	63.35	12.394	3.006	
Total cholesterol	<8.3	4.9507	1.26352	.32624	0.36
	>8.3	4.5475	.93331	.26942	
LDL-C	<8.3	2.9064	1.21961	.32595	0.38
	>8.3	2.5133	.98605	.28465	
HDL-C	<8.3	1.1986	.29866	.07982	0.46
	>8.3	1.1142	.27914	.08058	
TG	<8.3	1.9220	1.25392	.32376	0.9
	>8.3	1.9192	1.14251	.32982	
Fasting blood sugar	<8.3	6.534	1.7566	.4695	0.8
	>8.3	6.711	2.4872	.7180	
BMI	<8.3	30.39	5.553	1.309	0.34
	>8.3	32.20	5.031	1.299	
Waist circumference	<8.3	100.36	12.289	3.284	0.08
	>8.3	108.69	10.950	3.037	
Baseline number of antihypertensive drugs	<8.3	4.83	1.150	.271	0.8
	>8.3	4.75	1.000	.250	
Number of antihypertensive dugs at month 12	<8.3	5.73	1.421	.428	0.9
	>8.3	5.80	.837	.374	
eGFR	<8.3	90.79	21.470	5.738	0.75
	>8.3	87.25	35.271	10.182	

eGFR – estimated glomerular filtration rate.

in Table 1. Compared to patients with a CAVI lesser than the median, patients with CAVI greater than the median were significantly older, had a higher waist circumference, and received significantly more vasodilators with comparable biochemical parameters of lipid profile, carbohydrate metabolism, and renal function. We found a significantly higher number of previous cardiovascular events with an increase in arterial stiffness – 29.4% vs. 17.6%, p=0.03, and the difference was significant both in terms of previous myocardial infarction – 11.8% vs. 2.9%, p=0.04, and previous strokes 17.6% vs. 8.8%, p=0.04 (Figure 2).

There was no difference between the two groups at baseline and during the study in terms of antihypertensive therapy and baseline office and out-of-office (home and ABPM) blood pressure values – Tables 1 and 2. The proportion of patients with increased arterial stiffness was higher among patients with a profile of isolated systolic hypertension (64.3%) versus those with systolic-diastolic hypertension (38.1%), a result which, despite the pronounced trend, did not reach statistical significance (p=0.120).

Predictive value of cavi for response to renal sympathetic denervation

In the study, renal denervation was performed in 32 patients (51.6%) as part of the treatment regimen. A long-term effect of the procedure reported as a reduction in the 24-hour systolic blood pressure greater than 10 mmHg was found in 22 patients (68.8%). The median of the observed reduction of the 24-hour systolic blood pressure was -16 mmHg at a 95% confidence interval (from -9.1 to -21 mmHg). Despite the very high baseline levels of blood pressure and the number of antihypertensive medications, the procedure was related with satisfactory long term results – the percentage of patients nor-

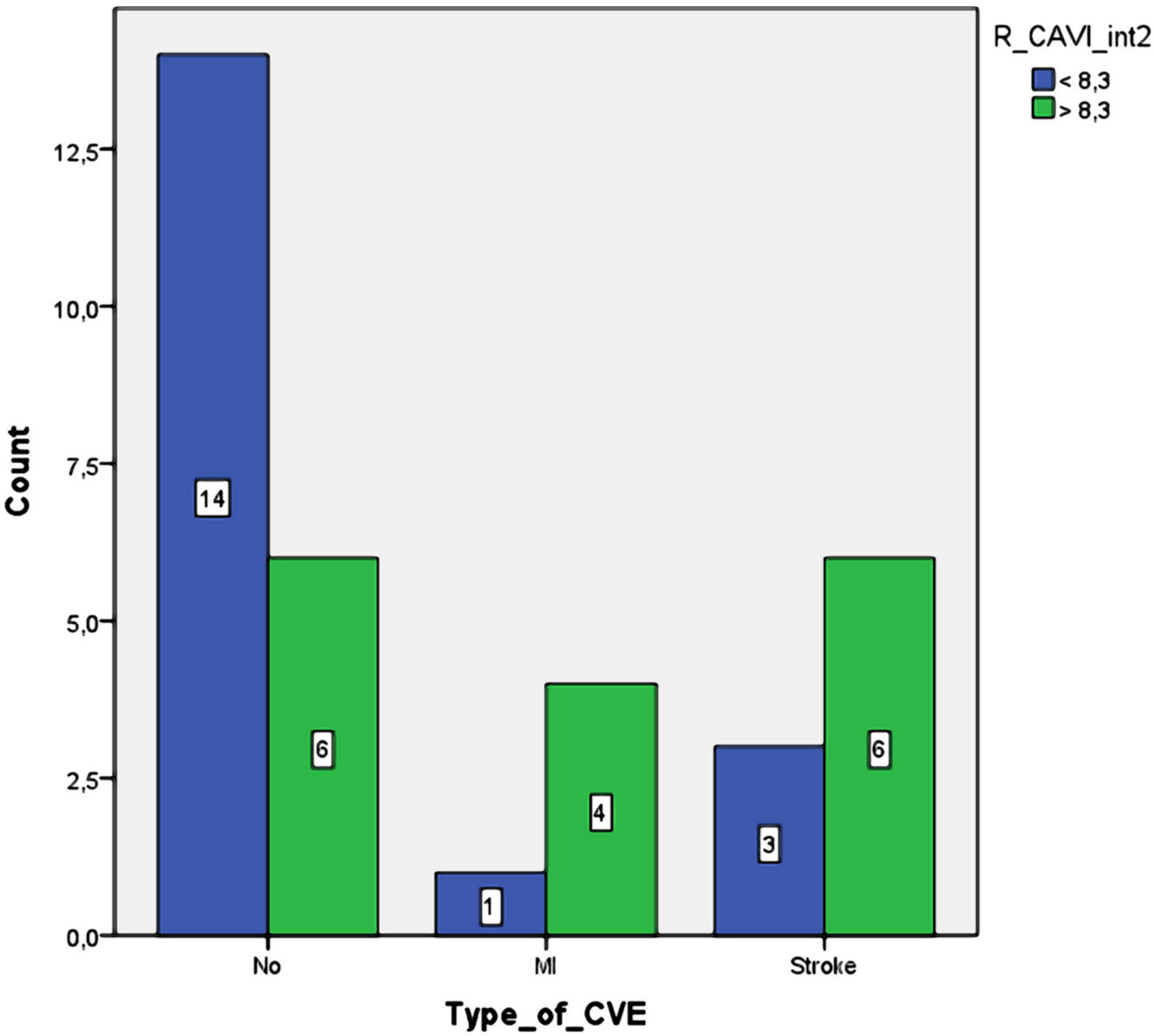

Figure 2. Previous cardiovascular events according to CAVI values.

malizing office blood pressure 12 months after the procedure – 46.9%, normalizing home blood pressure values below 135/85 mmHg – 18.8% and 24h ABPM<130/80 mmHg – 15.6%.

In our series of patients, several noninvasive indicators demonstrated the potential to predict the long-term outcome after renal denervation – baseline higher systolic office blood pressure, lower nocturnal heart rate, lower pulse pressure and lower CAVI index. Figure 3 gives an idea of the median of the reported effect in the reduction of systolic 24-hour blood pressure among patients with lower or high arterial stiffness.

In the present study, we found a statistically significant reduction of both office and out-of-office blood pressure values only among patients with baseline low vascular stiffness (Table 3). In contrast, the effect of the procedure among the patients with high baseline AS was insignificant from a statistical and clinical point of view (Figure 3).

Discussion

The main result of the present study was the reduction of office and out-of-office blood pressure values in a significant proportion of patients with resistant arterial hypertension. Based on an established protocol including the sequential inclusion of out-of-office techniques for blood pressure monitoring, correction, and intensification of antihypertensive therapy, a group of patients in whom the performed renal denervation was associated with a significant blood pressure reduction was selected. The result obtained was clinically important and persistent

Table 2. Baseline values of office and off-office blood pressure depending on arterial stiffness. Data are presented as mean±SD. BP – blood pressure; O – office, H – Home, S – Systolic, D – Dyastolic.

CAVI		Mean	Std. Deviation	P-value
sOBP	<8.3	169.89	19.629	.651
	>8.3	166.65	22.400	
dOBP	<8.3	94.61	12.113	.387
	>8.3	90.59	14.967	
ABPM_meanS	<8.3	155.94	15.498	.310
	>8.3	162.88	23.696	
ABPM_meanD	<8.3	87.22	10.276	.930
	>8.3	86.76	19.113	
ABPM_dayS	<8.3	160.44	15.523	.344
	>8.3	167.06	24.458	
ABPM_dayD	<8.3	90.33	11.072	.846
	>8.3	89.29	19.377	
ABPM_nightS	<8.3	148.89	16.827	.458
	>8.3	154.06	23.523	
ABPM_night	<8.3	82.06	10.344	.850
	>8.3	81.06	19.492	
sHBP	<8.3	159.83	15.124	.170
	>8.3	168.18	19.844	
dHBP	<8.3	89.50	7.501	.570
	>8.3	91.76	14.847	

Table 3. Difference in office and out-of-office BP measurements between the baseline values and those at month 12 after renal denervation in patients with low arterial stiffness.

Differences after 12 months in Office, home and 24-hr ABPM	Mean difference	SD	P-value
Δ office systolic BP	-29.818	19.969	.001
Δ office diastolic BP	-9.909	10.406	.010
Δ 24-hr systolic BP	-24.273	15.395	.000
Δ 24-hr diastolic BP	-13.545	11.510	.003
Δ daytime systolic BP	-24.182	16.036	.001
Δ daytime diastolic BP	-17.727	10.574	.000
Δ night-time systolic BP	-25.909	18.229	.001
Δ night-time diastolic BP	-15.545	14.929	.006
Δ 24-hr pulse pressure	-11.636	8.891	.001
Δ 24-hr heart rate	.364	9.739	.904
Δ dipping systolic	2.455	9.543	.414
Δ dipping diastolic	3.727	12.191	.334
Δ home systolic BP	-27.909	20.868	.001
Δ home diastolic BP	-12.727	10.130	.002

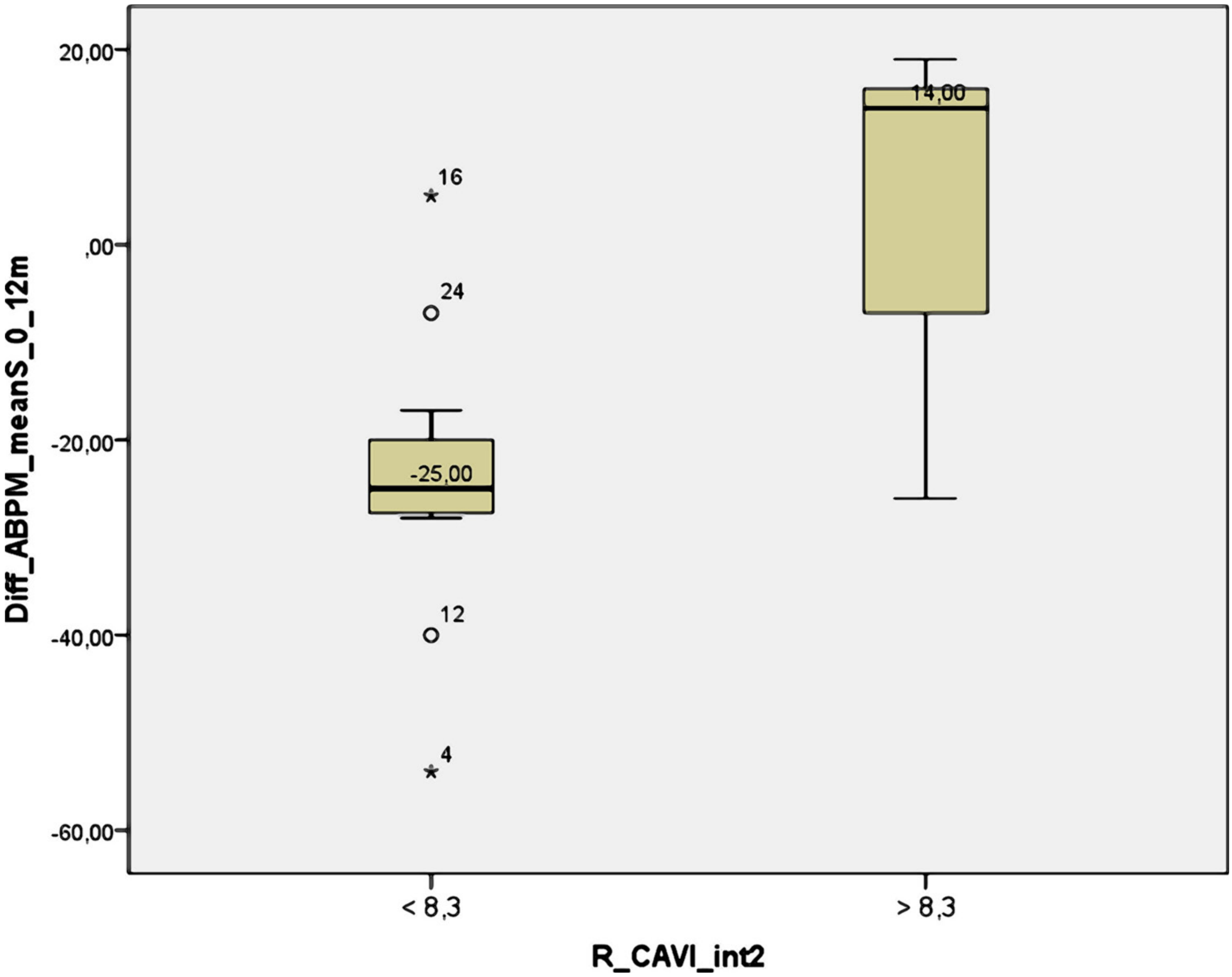

Figure 3. Reduction in the values of the systolic 24-hour arterial pressure after renal denervation according the initial values of arterial stiffness.

in the larger group of patients. Another potential result of the study is the identification of potential predictors of successful renal denervation.

In our opinion, the reported results are one of the few published that focus on the importance of initial assessment of arterial stiffness as a tool of successful identification of the patients who will respond to the treatment. Among the predominant patient profile of systolic-diastolic resistant arterial hypertension, we could establish values of arterial stiffness, which identify future responders from the conducted denervation.

The question of potential predictors of successful renal denervation is especially relevant after the published results of the SIMPLICITY 3, SPYRAL HTN-OFF MED, RADIANCE-HTN SOLO studies and the data from the global SIMPLICITY registry [23–26]. The lack of clearly identifiable clinical, procedural and laboratory indicators to differentiate patients who will demonstrate a clinically significant effect of renal denervation is the reason for the low class of recommendations in the current guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension, as well as the restriction of the methodology to centers with extensive experience from its implementation [21].

A challenging problem regarding RDN is the identification of the optimal candidate for RDN. Published rates of BP response due to RDN, arbitrarily defined as BP reduction of at least 10 mmHg, differ widely [14, 26]. Hence, in the various published clinical studies on the effects of RDN, analyses have been performed to delineate predictors of BP response. Most of these approaches have focused on patient factors and potential biomarkers.

Indeed, previous studies have suggested that cardiac baroreflex sensitivity (BRS), levels of soluble fms-like tyrosine kinase-1 (sFLT-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) predict the response to RDN [17, 18]. Overall, it may be difficult or even impossible to simplify the BP response to a single biomarker since a large proportion of patients with treatment-resistant hypertension have several additional comorbidities indicating a very heterogeneous patient population per se.

As pointed out by others, AS resembles a measure of the cumulative and time-dependent pathological alterations of the vascular bed [11–13]. It is believed to be more robust and stable than most other measures of cardiovascular health. Although there is some cross-link between sympathetic activation and stiffness (decreased vasoconstriction with attenuated sympathetic drive), this interaction holds true only in the early stage of the disease. At a later stage, AS 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.

To date, there is only a minimal number of studies investigating the predictive value of arterial stiffness in patients with resistant hypertension. Ott *et al.* [27], as well as Okon *et al.* [28], 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 a significant reduction in blood pressure. Fengler *et al.* demonstrated that the assessment of arterial stiffness could help improve patient preselection for renal sympathetic denervation and identify a subgroup of isolated systolic hypertension patients who benefit from sympathetic modulation [29]. Brandt *et al.* focused on noninvasive assessment methods such as carotid-femoral pulse wave velocity and also found a link to a subsequent response to the procedure [20].

In the present study, we extend these data by demonstrating a significant effect of denervation among the group of patients with a profile of systolic-diastolic hypertension, as well as by reporting specific data and by examining another promising indicator such as the CAVI index in patients with resistant arterial hypertension. CAVI measures the arterial stiffness index beta from the origin of the aorta to the ankle. This approach has potential advantages over the conventional measurement of PWV. The derivation of b (CAVI) as an arterial stiffness index appears to be independent of BP at the time of measurement. Thus, it could be used to determine independent pressure changes in arterial stiffness.

CAVI is an innovative noninvasive method for assessing arterial stiffness, which is characterized by good reproducibility of measurements and is easily applicable in everyday clinical practice [22]. An interesting question for future clarification, especially in the field of resistant hypertension and renal denervation, is the integration of the predictive value of the parameter with those provided by 24h ABPM.

Conclusion

Our results add to the growing evidence of increased AS as a predictor for less favorable outcomes following RSD and promote CAVI as a suitable way to measure AS. These findings hold the promise that AS might be used as a selection criterion for RSD, thereby improving outcomes following RSD.

Conflict of interest

The author confirms that there are no conflicts of interest.

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