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Hypertension-mediated organ damage regression associates with blood pressure variability improvement three years after successful treatment initiation in essential hypertension

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Abstract

Blood pressure variability (BPV) has been associated with the development, progression, and severity of cardiovascular (CV) organ damage and an increased risk of CV morbidity and mortality. We aimed to explore any association between short-term BPV reduction and hypertension-mediated organ damage (HMOD) regression in hypertensive patients 3-year post-treatment initiation regarding BP control. 24-h ambulatory blood pressure monitoring (24 h ABPM) was performed at baseline in 180 newly diagnosed and never-treated hypertensive patients. We measured 24 h average systolic (24 h SBP) and diastolic BP (24 h DBP) as well as 24 h systolic (sBPV) and diastolic BPV (dBPV). Patients were initially evaluated and 3 years later regarding arterial stiffness (PWV), left ventricular hypertrophy (LVMI), carotid intima-media thickness (cIMT), 24 h microalbumin levels (MAU), and coronary flow reserve (CFR). Successful BP treatment was defined as 24 h SBP/DBP < 130/80 mm Hg based on 2nd ABPM and subsequently, patients were characterized as controlled ($n = 119$, age = 53 ± 11 years) or non-controlled ($n = 61$, age = 47 ± 11 years) regarding their BP levels. In the whole population and the controlled group, 24 h SBP/DBP, sBPV/dBPV, LVMI, and IMT were decreased. Additionally, LVMI improvement was related with both sBPV ($p < .001$) and dBPV reduction ($r = .18$, $p = .02$ and $r = .20$, $p = .03$, respectively). In non-controlled hypertensives, PWV was increased. In multiple linear regression analysis, sBPV and dBPV reduction predicted LVMI improvement in total population and controlled group independently of initial office SBP, mean BP, and 24 h-SBP levels. In middle-aged hypertensive patients, a 3-year antihypertensive treatment within normal BP limits, confirmed by 24-h ABPM, leads to CV risk reduction associated with sBPV and dBPV improvement.

1 | INTRODUCTION

Arterial hypertension (AH), is one of the most common diseases worldwide with a 30%–45% prevalence among several regions which increases with advanced age.[1,2] It represents a well-established risk factor for cardiovascular disease (CVD) with significant morbidity and mortality and often coexists with other cardiovascular (CV) risk factors (dyslipidemia, glucose intolerance, diabetes mellitus) which all together contribute further to increased total CV risk.[3,4] AH leads to a wide spectrum of subclinical organ damages (hypertension-mediated organ damage, HMOD) or overt clinical diseases (ie coronary artery disease, heart failure, stroke, and chronic kidney disease).[2] HMOD refers to a subclinical intermedium stage of the cardiovascular continuum affecting various target-organs[2] and leading to left ventricular hypertrophy (LVH), reduced coronary flow reserve (CFR), increased carotid intima-media thickness (cIMT), retinopathy, microalbuminuria increased aortic stiffness and endothelial dysfunction.[5] As HMOD relates to increased morbidity and mortality, blood pressure (BP) treatment targets to HMOD prevention and/or regression besides BP control.[2,5]

BP is characterized by continuous and significant changes (blood pressure variability, BPV) beat-to-beat (very short-term BPV), over 24-h (short-term BPV), day-to-day (mid-term BPV) and from visit-to-visit (long-term BPV). AH diagnosis is usually based on 24 h ambulatory blood pressure monitoring (24 h ABPM), which provides a variety of information during a 24-h period apart from single blood pressure (BP) measurements, like nocturnal BP recording, dipping status and BPV, useful for AH diagnosis as well as for treatment evaluation.[2,6,7] BPV has been associated with the development, progression, and severity of CV organ damage and an increased risk of cardiovascular morbidity and mortality.[8] However, the actual size of its independent contribution to CV risk remains unknown.[9] Accordingly, we aimed to explore any existing relationship between short-term BPV improvement, derived by 24 h ABPM, and HMOD regression in recently diagnosed and never-treated hypertensive patients 3 years after medical treatment initiation.

2 | PATIENTS AND METHODS

2.1 | Study population

We studied 350 consecutive Caucasian hypertensive patients with recently diagnosed and never-treated stage I-II essential hypertension according to the 2018 guidelines of the European Society of Hypertension (ESH) visiting our outpatient ESH Excellence Centre.[2] All patients were subjected to the following examinations within 2 weeks: (1) The average of three (3) office BP measurements taken in the hypertension outpatient clinic was considered as office BP (systolic and diastolic); (2) blood and urine sampling for routine blood chemistry (lipid profile included) and urine examination; (3) standard 12-lead electrocardiogram; (4) 24 h ABPM in order to confirm hypertension diagnosis based on office BP measurements; (5)

transthoracic echocardiogram (TTE) in order to evaluate LVMI as well as CFR of left anterior descending artery (LAD), (6) carotid ultrasonography for cIMT measurement, (7) carotid-femoral pulse wave velocity (PWV) to evaluate arterial stiffness and (8) microalbumin levels measurement (MAU) in 24 h urine collection.

Informed consent was obtained during the initial visit of the study which was approved by the ethical committee of our hospital.

Patients with secondary hypertension, congestive heart failure, previous myocardial infarction, stroke, cardiac valve diseases, history of coronary artery by-pass grafting, atrial fibrillation, renal insufficiency, overt proteinuria, anemia or other hematologic disorder, as well as those patients on medication for cardiovascular (except statins for hyperlipidemia treatment) or non-cardiovascular diseases or hormonal replacement for any reason were excluded from the study. Conclusively, the participants in our study neither had any concomitant disorders nor received any cardio-metabolic medications and subsequently they constitute a homogenous group of newly diagnosed hypertensives.

2.2 | Diagnostic work-up

The protocol of the study has been described in details in a previous study by our research group.[10] However, a short description follows:

2.2.1 | Office BP measurement

Morning office BP was measured in the hospital outpatient clinic, approximately at the same morning hour, by the same cardiologist using a mercury sphygmomanometer {first and fifth phases of Korotkoff sounds taken as systolic (SBP) and diastolic (DBP) blood pressure, respectively} after the patients had rested for 5–10 min in the sitting position while they were advised to avoid smoking or drinking coffee for at least 2 h before examination. Three measurements were taken at 1 min intervals, and the average was used as the office SBP and DBP. Hypertension was diagnosed as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg.[2] PP was defined as SBP-DBP while mean BP as DBP + PP/3.

2.2.2 | Ambulatory BP monitoring

ABPM was carried out 1–4 days after the first evaluation of each patient in the hypertension outpatient clinic on the non-dominant arm using validated Spacelab 90207 (Spacelab) recorders. The ABPM device was set to obtain BP readings at 15 min intervals during the day (07.00–23.00) and at 20 min intervals during the night (23.00–07.00). The time of application and the type of the device were the same in all patients. The patients were instructed to attend their usual day-to-day activities but to keep still at the times of measurements. While ABP monitoring was obtained during working days (Monday–Friday), patients were asked to go to

bed not later than 23.00 and to stay in bed until 07.00. If this was not acceptable, information from their diaries was taken in order to correctly obtain data from daily and night activities according individual patient's schedule. Recordings were analyzed to obtain 24 h, daytime and nighttime average SBP, DBP, PP and heart rates. Systolic readings >260 or <70 mm Hg and diastolic readings >150 or <40 mm Hg were discarded. In order to define ABPM as valid, each patient had to have no fewer than 3 successful readings per hour during daytime and 2 during night-time and ≥70% of successful readings. In only six patients (3.3%), ABPM did not meet the above definition of validity and the patient had to repeat it during the next day. Systolic and diastolic BPV (sBPV, dBPV) were defined as the standard deviation of 24 h average SBP and DBP.[2] ΔsBPV (or ΔdBPV) was defined as sBPV at baseline minus sBPV at 3-year post-treatment initiation (or dBPV at baseline minus dBPV at 3-year post-treatment initiation).

2.3 | Hypertension-mediated organ damage (HMOD) evaluation

a. Left ventricular hypertrophy (LVH) was estimated by LVMI, using the Devereux formula according to the Penn Convention Protocol with a Vivid 7 system (GE Medical Systems). LV hypertrophy was defined as LVMI index >115 g/m² in men and >95 g/m² in women.[11] ΔLVMI was defined as LVMI at baseline minus LVMI at 3-year post-treatment initiation.

b. Coronary flow reserve was estimated by coronary velocity profiles in the left anterior descending artery obtained by color-guided pulse wave Doppler from long axis apical projections after adenosine infusion (140 µg/kg/min) for 3 min. CFR_D < 2 has been considered as abnormal, 2–2.5 as borderline normal and >2.5 as normal.

c. Carotid intima-media thickness (cIMT) was measured by ultrasonography in 3 paired segments of both carotid arteries (at the level of the common carotid artery, the carotid bulb and the internal carotid artery). In each segment, 3 measurements of the maximal cIMT in the far wall were averaged. The average cIMT of all 6 segments was calculated; a cIMT < 0.09 cm was considered as normal.

d. Carotid-femoral PWV: Aortic stiffness was estimated by an automatic carotid-femoral PWV measurement using a Complior SP (Artech Medical), a computerized device that permits automatic calculation of PWV. The same examiner, who was blinded to the patient's history, performed all measurements. Patients were advised to avoid smoking or coffee at least for 2 h before examination. PWV < 12 m/s was considered as normal.[2]

e. e.MAU levels in 24 h urine collection: MAU was analyzed by nephelometry (Immunochemical assay, BN, Prospec, Dade Behring). Patients were classified as normoalbuminuric (NA) when microalbuminuria levels were <30 mg/24 h and microalbuminuric (MA) when microalbuminuria levels were between 30 and 300 mg/24 h.[2]

When baseline evaluation was completed, antihypertensive treatment was initiated. The latter included RAAS inhibitors (angiotensin converting enzyme inhibitors or sartans) alone or in double combination with calcium blockers or hydrochlorothiazides or in triple combination (RAAS inhibitors plus calcium blockers plus hydrochlorothiazides). Patients were followed by our ESH Excellence Centre every 3–6 months during scheduled visits. At baseline 350 hypertensive patients were recruited. However, only 200 (57%) were re-evaluated at 3 years after treatment initiation following the same protocol as at baseline evaluation (office BP measurements, ABPM, assessment of HMOD). The rest 150 patients were lost during the follow-up period or they refused to be submitted in the re-evaluation protocol. Finally, we present results from 180 patients, since we found incomplete diagnostic documentation at re-evaluation in 20/200 patients.

2.4 | Statistical analysis

The Shapiro-Wilk test was used to assess the normality of distribution. Almost all variables were normally distributed and are expressed as mean ± SD or % incidence. However, weight, BMI, HDL-C, 24-h average SBP, PWV, MAU, E/Ea, LVMI, IMT, CFR (both at baseline and after 3 years) as well as sBPV after 3 years were not normally distributed and were presented as median value plus 25%–75% interquartile range (IQR). Categorical variables are expressed as absolute values and percentages. Paired sample *t* test and Wilcoxon signed-ranked test were used for comparisons regarding normally and non-normally distributed parameters, respectively between the same group of patients at baseline and 3 years after treatment. Independent sample *t* test and Mann-Whitney test were used for normally and non-normally distributed parameters, respectively in order to compare differences between two different groups of patients. Finally, chi-squared test was used for the comparison of categorical variables.

Pearson's analysis was used to identify any existing relationships between changes regarding sBPV/dBPV and HMOD (LVMI, E/Ea, CFR, MAU, IMT, and PWV) at 3-year post-treatment initiation. Multiple linear regression analysis, using backward method, was performed in order to explore any independent relationships between differences in sBPV (ΔsBPV) or dBPV (ΔdBPV) and LVMI (ΔLVMI) in the whole population and controlled hypertensives, separately. Age, BMI, cholesterol, BP, and smoking at baseline evaluation were forced in the model as independent variables. Due to collinearity between office and 24-h BP parameters, three models were examined (Models A, B, C); in each one we used another method of baseline BP evaluation (office SBP, office mean BP, and 24-h SBP). The level of significance was determined as two-sided *p* < .05. Statistical analysis was performed on a SPSS 23 version (SPSS Inc).

3 | RESULTS

Demographic and clinical characteristics of the total population (*n* = 180) and studied groups (controlled and non-controlled hypertensives) at

TABLE 1 Study population demographic and clinical characteristics at baseline and 3 years after treatment initiation

Characteristics	Total population			Controlled hypertensives			Non-controlled hypertensives			Controlled vs. non-controlled at baseline	Controlled vs. non-controlled at re-evaluation
	Baseline	Re-evaluation	p	Baseline	Re-evaluation	p	Baseline	Re-evaluation	p	p	P
N	180	180	-	119	119	-	61	61	-	-	-
Sex (M/F)	116/64	116/64	-	66/53	66/53	-	50 (82%)	50 (82%)	-	-	-
Age (years)	51 ± 12	54 ± 12	-	53 ± 11	56 ± 11	-	47 ± 11	50 ± 11	-	.001	.001
Weight (kg)	84 (74–96)	83 (74–95)	.79	82 (73–94)	82 (73–94)	.49	86 (78–99)	87 (76–98)	.64	.081	.09
BMI (kg/m^2)	29 (27–32)	29 (27–32)	.51	29 (27–33)	29 (27–32)	.36	29 (26–32)	29 (26–32)	.89	.486	.42
Current smokers (%)	39 (22%)	29 (16%)	.08	19 (16%)	13 (11%)	.26	20 (33%)	16 (26%)	.18	.01	.03
Cholesterol (mg/dl)	214 ± 34	200 ± 32	.001	214 ± 35	193 ± 32	.01	214 ± 33	205 ± 33	.02	.917	.04
LDL-C (mg/dl)	136 ± 34	124 ± 29	.002	135 ± 33	118 ± 28	.008	137 ± 35	134 ± 29	.29	.634	.04
HDL-C (mg/dl)	48 (42–58)	50 (42–62)	.90	51 (44–63)	53 (43–64)	.57	44 (40–51)	46 (41–57)	.35	.001	.04
Blood pressure and blood pressure variability parameters											
Office SBP (mm Hg)	145 (135–160)	131 (125–140)	<.001	145 (135–160)	130 (124–140)	<.001	145 (135–160)	135 (125–144)	<.001	.730	.23
Office DBP (mm Hg)	90 (85–100)	82 (80–90)	<.001	90 (80–95)	80 (77–85)	<.001	95 (85–100)	85 (80–90)	<.001	.08	.003
24-h SBP (mm Hg)	137 (131–144)	122 (117–129)	<.001	134 (130–140)	119 (114–123)	<.001	142 (136–150)	132 (127–138)	<.001	<.001	<.001
24-h DBP (mm Hg)	87 ± 9	75 ± 8	<.001	86 (77–95)	72 (68–76)	<.001	91 (82–100)	83 (81–87)	<.001	<.001	<.001
24-h HR (beats/min)	77 ± 8	73 ± 7	<.001	77 ± 8	72 ± 8	<.001	78 ± 8	75 ± 7	.005	.28	.002
sBPV (mm Hg)	15 ± 3	13 (11–15)	.002	15 ± 3	13 ± 3	<.001	14 ± 3	13 ± 3	0.01	.08	.51
dBPV (mm Hg)	13 ± 3	11 ± 2	<.001	11 ± 2	11 ± 2	<.001	13 ± 3	11 ± 3	<.001	.96	.31
Hypertension-mediated organ damage											
LVMI (g/m^2)	76 (67–92)	73 (64–89)	.01	76 (68–92)	71 (63–89)	.01	76 (67–93)	79 (69–90)	.36	.94	.04
E/Ea	6.7 (5.4–8.7)	6.7 (5.4–8)	.32	6.7 (5.5–8.7)	6.7 (5.4–8.2)	.68	6.7 (5.2–8.6)	6.7 (5.3–7.7)	.27	.58	.38
PWV (m/s)	10.8 (9.3–12.5)	10.8 (9.4–12.1)	.35	10.8 (9.3–12.6)	10.7 (9.3–12)	.60	10.8 (9.3–11.8)	11 (10–13)	.01	.68	.09
MAU (mg/24 h)	10 (7–16)	8 (6–12)	<.001	9 (6–14)	7 (5–11)	.002	11 (8–20)	9 (6–16)	.09	.01	.11

TABLE 1 (Continued)

Characteristics	Total population			Controlled hypertensives			Non-controlled hypertensives			Controlled vs. non-controlled at baseline	Controlled vs. non-controlled at re-evaluation
	Baseline	Re-evaluation	p	Baseline	Re-evaluation	p	Baseline	Re-evaluation	p	p	p
CFR	2.5 (2–3)	2.6 (2–3.2)	.55	2.5 (2–2.9)	2.6 (2–3.2)	.23	2.6 (2.3–3.2)	2.7 (2.1–3.4)	.53	.06	.54
cIMT (cm)	0.1 (0.08–0.12)	0.09 (0.08–0.11)	<.001	0.1 (0.08–0.12)	0.09 (0.08–0.10)	.002	0.1 (0.09–0.12)	0.09 (0.08–0.11)	.03	.31	.23

Note: Data are presented as mean ± SD or % or median (25−75 IQR).

Abbreviations: BMI, body mass index; LDL-C/HDL-C, low/high density lipoprotein cholesterol; SBP/DBP, systolic/diastolic blood pressure variability; LVMI, left ventricular mass index; E/Ea, E wave (transmitral)/to Ea wave (Tissue Doppler Imaging ratio) ; PVW, pulse wave velocity; MAU, microalbumin; CFR, coronary flow reserve; 8 cIMT, carotid intima-media thickness.

Italics indicate statistical significance.

baseline and 3-year post-treatment initiation are listed in Table 1. Patients in the whole population were middle-aged (age = 51 ± 12 years), mostly males (64%), non-smokers (78%), over-weighted (BMI = 29 kg/m^2) with a minor prevalence of diabetes mellitus (7%).

Successful BP treatment was defined as 24 h SBP/DBP < 130/80 mm Hg based on 2nd ABPM and subsequently, patients were characterized as controlled (n = 119, age = 53 ± 11 years, 56% males) or non-controlled (n = 61, age = 47 ± 11 years, 82% males) regarding their BP levels. We compared the two groups of controlled and non-controlled hypertensives regarding their baseline characteristics. It appears that controlled hypertensives, were older (p = .001) with similar BMI, Cholesterol and LDL, office SBP and DBP levels, sBPV and dBPV, PWV, LVMI, E/Ea, cIMT, CFR compared to the "non-controlled hypertensives". However, controlled hypertensives had lower baseline 24-h SBP (p < .001), 24-h DBP (p < .001) and MAU (p = .01) and higher HDL-C levels (p = .001) compared to non-controlled ones. 15 controlled hypertensives (6/9 males/females) and 6 non-controlled ones (5/1 males/females) had LVH at baseline evaluation.

At re-evaluation, controlled hypertensives had similar BMI, office SBP levels, sBPV and dBPV, PWV, LVMI, E/Ea, cIMT, CFR compared to non-controlled hypertensives. However, controlled hypertensives had lower office DBP (p = .003), 24-h SBP (p < .001), 24-h DBP (p < .001), Cholesterol, LDL (p < .05) and LVMI (p < .05) and higher HDL-C levels (p < .05) compared to non-controlled ones.

When we studied the 3-year post-treatment changes in the whole population, we found that Cholesterol (p = .001), LDL-C (p = .002), office SBP and DBP, 24-h SBP and 24-h DBP (p < .001), MAU levels (p < .001), cIMT (p < .001), and LVMI (p = .01) were improved. Additionally, sBPV (p = .002) and dBPV (p < .001) were also reduced. Similar results were found in controlled hypertensives, that is Cholesterol (p = .01), LDL-C (p = .008), office SBP and DBP, mean 24 h SBP and 24-h DBP (p < .001), sBPV and dBPV (p < .001), MAU levels and cIMT (p = .002) and LVMI (p = .01) were decreased. However, in non-controlled hypertensives, Cholesterol (p = .03), office SBP/DBP, 24-h SBP/DBP (p < .001), sBPV (p = .01) and dBPV (p < .001) and IMT (p = .04) were decreased while PWV was increased (p = .02).

We have to mention that at re-evaluation, white coat hypertension phenomenon (WCH) was found in 34/119 (29%) controlled hypertensives. On the other hand, the masked hypertension phenomenon was revealed in 36/61 (59%) non-controlled hypertensives.

In turn, we performed Pearson's correlation analysis and we found the following relationships between:

a. Differences in LVMI (ΔLVMI) and sBPV (ΔsBPV) as well as dBPV (ΔdBPV) (r = .25, p = .001 and r = .18, p = .02, respectively) in the whole population and
b. ΔLVMI and ΔsBPV as well as ΔdBPV (r = .29, p = .001 and r = .20, p = .03, respectively) in controlled hypertensives (Table 2).

Finally, we performed multiple regression analysis, using the backward method, in order to investigate any associations between ΔLVMI and ΔsBPV or ΔdBPV in the whole population and the

controlled hypertensives. Age, BMI, cholesterol, BP, and smoking at baseline evaluation were inserted in the model as independent variables. We examined three models (Models A, B, C) using in each one a different method of baseline BP evaluation; office SBP in Model A, office mean BP in Model B and 24-h SBP in Model C. We found that, ΔsBPV was independently related with ΔLVMI (in all models) in the whole population and the controlled hypertensives, (Figure 1). Additionally, ΔdBPV was associated with ΔLVMI (in models A and B) in the whole population as well as the controlled hypertensives. Initial 24-h SBP was also associated with ΔLVMI in the whole population and well-controlled hypertensive patients.

4 | DISCUSSION

In the present prospective study, we investigated the role of the short-term BPV reduction regarding HMOD regression in hypertensive patients at 3 years after initiation of medical treatment. The primary endpoint of the study is that both systolic and diastolic BPV decrease associate with LVMI regression only in well-controlled hypertensive patients, the latter confirmed by 24-h ABPM.

BPV reflects a dynamic hemodynamic parameter, which depicts marked BP fluctuations across time. These variations can be measured over a period of seconds or minutes (very short-term BPV), 24 h (short-term BPV), between days (mid-term BPV) and between months or years (long-term BPV).[8] Under physiological conditions, BPV largely represents a response to environmental stimulations and challenges of daily life. It aims at maintaining the so-called BP "homeostasis" which in turn is necessary to guarantee adequate organ perfusion in response to changing metabolic and physiologic demands (ie during physical exercise) or to changing environmental conditions (ie during exposure to high-altitude hypobaric hypoxia or weather-related temperature changes). However, sustained increases in BPV may also reflect alterations in the mechanisms responsible for cardiovascular homeostasis or underlying pathological conditions and may represent a source of damage to

TABLE 2 Multiple linear regression analysis regarding independent associations between differences in LVMI and BPV (systolic and diastolic)

| Independent variables	Left ventricular mass index differences (ΔLVMI)						
	Total population (n = 180)				Controlled hypertensives (n = 119)		
Model A (Office SBP)							
ΔsBPV	β = 0.20, p = .01	ΔdBPV	β = 0.17, p = .04	ΔsBPV	β = 0.26, p = .01	ΔdBPV	β = 0.22, p = .01
Age	–	Age	–	Age	–	Age	–
Smoking	–	Smoking	–	Smoking	β = 0.19, p = .06	Smoking	–
BMI	–	BMI	–	BMI	–	BMI	β = −0.20, p = .05
Cholesterol	–	Cholesterol	–	Cholesterol	–	Cholesterol	–
Office SBP	–	Office SBP	–	Office SBP	–	Office SBP	–
Model B (Office mean BP)							
ΔsBPV	β = 0.20, p = .01	ΔdBPV	β = 0.17, p = .04	ΔsBPV	β = 0.26, p = .01	ΔdBPV	β = 0.22, p = .02
Age	–	Age	–	Age	–	Age	–
Smoking	–	Smoking	–	Smoking	β = 0.19, p = .06	Smoking	–
BMI	–	BMI	–	BMI	–	BMI	β = −0.20, p = .05
Cholesterol	–	Cholesterol	–	Cholesterol	–	Cholesterol	–
Office mean BP	–	Office mean BP	–	Office mean BP	–	Office mean BP	–
Model C (24-h SBP)							
ΔsBPV	β = 0.20, p = .01	ΔdBPV	–	ΔsBPV	β = 0.19, p = .04	ΔdBPV	–
Age	–	Age	–	Age	–	Age	–
Smoking	–	Smoking	–	Smoking	–	Smoking	–
BMI	–	BMI	–	BMI	β = −0.20, p = .03	BMI	β = −0.20, p = .03
Cholesterol	–	Cholesterol	–	Cholesterol	–	Cholesterol	–
24-h SBP	β = 0.29, p < .001	24-h SBP	β = 0.30, p < .001	24-h SBP	β = 0.35, p < .001	24-h SBP	β = 0.39, p < .001
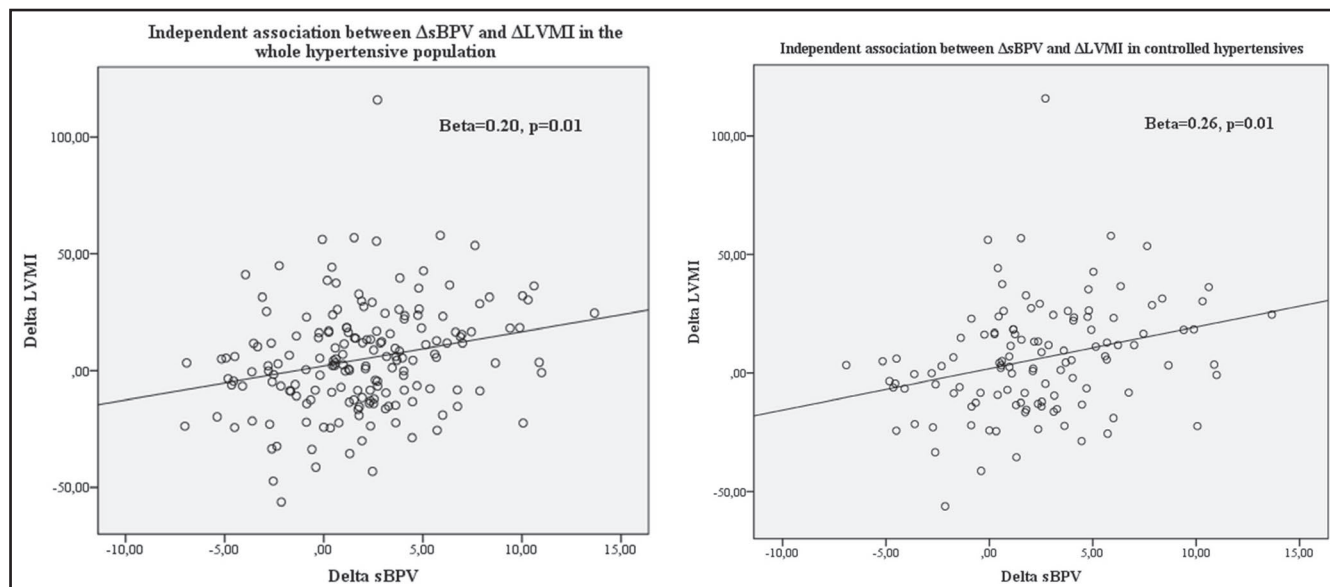
FIGURE 1 Relationship between LVMI regression and sBPV decrease in the whole population and controlled hypertensives

the cardiovascular system.[12] Each type of BPV shares a different underlying mechanism, although not fully revealed.[12,13] Very short-term and short-term BPV are mainly determined by increased central sympathetic drive, reduced arterial reflexes and behavioral and emotional factors while long-term variability should be shaped mainly by reduced arterial compliance, seasonal changes as well as improper dosing or poor adherence to antihypertensive treatment.[14] Despite the different substrate, both short- and long-term BPV are associated with the development, progression and severity of cardiovascular and renal complications independently of mean pressure elevation.[14] However, clinical trials have shown that long-term BPV is associated with cardiovascular events to a greater degree compared to short-term BPV.[15-17]

ABPM has been long recognized as the gold standard method for diagnosing AH compared to office BP measurement, providing data on BP during patient's activities and uniquely during sleep.[18,19] Since it is the only method for nocturnal BP dipping measurement, it may also calculate both day and night BP fluctuations and subsequently BPV (ABPV).[20,21] Increased ABPV is associated with AH, carotid artery disease, progression of small vessel disease, left ventricular hypertrophy (LVH) and CV events.[20] Consequently, ABPV is considered as an independent CV risk factor compared to 24-h average BP levels derived by ABPM.[20] Various methods have been used for BPV measurement (continuous beat-to-beat recordings, office BP, home BP measurement, 24-h ABPM). Moreover, there are different indices for BPV evaluation (ie standard deviation [SD], coefficient of variation, weighted 24-h SD, average real variability [ARV]). Since there is no clear indication as to which method or index should be preferred, the choice should be supported by the strongest outcome evidence.[9] A recent meta-analysis [8] pointed to the use of SD, derived by 24-h ABPM, as one of the preferred indices for 24-h BPV evaluation, which was also investigated in our study.

Hypertension-mediated organ damage shows increased prevalence among patients even in the early stages of hypertension disease.[2,21-23] HMOD is due to BP levels as well as variable concomitant conditions, neurohormonal alterations and life style (ie increased salt consumption[24]) involved in structural and functional alterations of arterial bed, heart, kidneys and central nervous system.[5]

The clinical significance and prognostic implications of BPV have been demonstrated by a series of recent studies in which increased BPV has been associated with a higher risk of CV mortality in the general population,[25] future CV events[26] or contributed modestly to CV risk stratification.[27] However, 24 h ambulatory BP level remained the most valuable CV predictor for use in clinical practice.[28] Additionally, 24-h BPV has been recognized as a useful index of HMOD in hypertensive and general population, pointing to carotid artery wall alterations and LVH,[29-31] the latter representing, at cardiac level, the main factor associated with worse CV prognosis.[32] Likewise, increased BPV has been associated with arterial stiffness and LV mass and dysfunction in treated and untreated hypertensive population, suggesting that BPV may be an important determinant of HMOD.[33-35] In a group of elderly hospitalized patients, 24-h SBPV could reflect the degree of HMOD as it was associated with IMT, LVMI and MAU.[36] In a 7-year follow-up study of a small hypertensive group (n = 73), Frattola et al reported that the BP level achieved by treatment, the degree of HMOD at baseline evaluation and the long-term BPV were the most important determinants of future end-organ damage related to hypertension throughout the years of follow-up.[37] Importantly, a recent meta-analysis showed a weak positive correlation between several 24-h ABPM-derived BPV measurements (24-h SD, diurnal SD, weighted SD and 24-h ARV) and LVMI.[38] On the other hand, Veloudi et al concluded that BPV appeared with limited clinical utility over a 12-month period in patients with uncomplicated hypertension since the changes in average 24-h

SBP, but not BPV, were most relevant to changes in HMOD (LVMI, PWV).[39]

In our study, we examined a population with recently diagnosed, never-treated and uncomplicated hypertension using 24-h ABPM at baseline and after 3 years of treatment initiation. We pointed out associations between ΔsBPV (and ΔdBPV) and ΔLVMI (independent from initial levels of office SBP, mean BP and 24-h SBP) as well as between 24-h SBP at baseline and ΔLVMI in the whole population and well-controlled hypertensive patients. Our results underscore the prognostic significance of initial ABPM-derived data (BP levels and fluctuations) regarding LVMI regression. However, no other correlation was revealed between ΔsBPV (and ΔdBPV) and the other HMOD indices studied (PWV, LVMI, E/Ea, IMT, CFR).

In non-controlled hypertensive patients, no relationship was found between ΔsBPV (or ΔdBPV) and ΔLVMI or changes of any of the other HMOD indices studied (PWV, LVMI, E/Ea, IMT, CFR). On the contrary, we noticed that PWV was increased at 3-year post-treatment even though BP was reduced from baseline levels in that group of hypertensives patients. Thus we re-confirmed that PWV increases over time in those hypertensive patients under treatment who do not achieve the optimal BP levels since vascular aging and life style besides BP levels are also powerful variables over time regarding arterial stiffness increase.[10]

This is the first study which takes into account the outcome of a 3-year successful antihypertensive treatment, evaluated by ABPM results, in order to explore the significance of BPV (systolic and diastolic) as a predictor index of HMOD regression. The achievement of BP control within normal limits should be the primary goal of our antihypertensive treatment and if this happens, then short-term sBPV reduction over time is able to predict the subsequent LVMI regression.

4.1 | Study limitations

Our clinical prospective study has several limitations. Arterial hypertension has a high prevalence in population worldwide and subsequently the moderate number of our Caucasian patients, overall and in each study group as well as the absence of co-morbidities like diabetes mellitus or chronic kidney disease, does not support us to generalize our results in all treated hypertensive patients. A greater number of patients are needed in future studies in order to expand our results. However, our group of 180 untreated hypertensive patients was relatively homogenous and it was re-evaluated after an adequate time period of 3-year post-treatment. Another limitation might be that our results were based on single ABPM at baseline and 3-year post-treatment. However, recent ESH guidelines do not support the need of a second ABPM application. Finally, the absence of severe HOMD is probably explained by the status of our patients at baseline (newly diagnosed, never-treated, and hypertension stage I-II) since a recent initiation of hypertension disease was recorded and the hypertension burden was not severe.

In conclusion, our study provides substantial evidence that in middle-aged hypertensive patients, systolic and diastolic BPV improvements, associated with cardiovascular risk reduction (left ventricular mass regression), occur only in the setting of BP treatment within normal limits as it is confirmed by ABPM.

AUTHOR CONTRIBUTIONS

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