Relationship between variability of arterial blood pressure from ambulatory 24-hour monitoring of arterial blood pressure with echocardiographic parameters in patients under antihypertensive therapy

Dušan Bastać (1), Igor Đorđioski (2), Zoran Joksimović (1), Anastasija Raščanin -Stamenković (1), Bratimirka Jelenković (2), Brankica Vasić (2), Mila Bastać (3), Vojkan Čvorović (4), Ljiljana Čvorović (5), Maja Mladenović (2)

(1) INTERNAL MEDICINE PRACTICE "DR. BASTAĆ", ZAJEČAR; (2) HEALTH CENTER ZAJEČAR, ZAJEČAR; (3) "MEDSCAN TADIĆ DIAGNOSTICS", ZAJEČAR; (4) PRIVATE GENERAL HOSPITAL BELMEDIC, BELGRADE; (5) CLINIC FOR ENT AND MAXILLOFACIAL SURGERY, CLINICAL CENTER OF SERBIA

Summary: Introduction: Variability of systolic daytime arterial pressure was until recently a controversial parameter but is now recognized as an independent prognostic risk factor for stroke in hypertensive patients. Blood pressure variability is a quantitative index of spontaneous daily and nocturnal variations in systolic and diastolic arterial blood pressure and has been proposed as a risk factor for inducing subclinical damage to target organs in arterial hypertension. Besides varying degrees of left ventricular myocardial hypertrophy (LVH), patients with hypertension also exhibit accompanying diastolic dysfunction of the left ventricle as an early sign of hypertensive damage, even when myocardial hypertrophy does not develop. The variability of pressure over 24 hours in Ambulatory Blood Pressure Monitoring (ABPM) has not been sufficiently studied in terms of correlation with echocardiographic parameters in controlled hypertension. Methods: A total of 196 adequately treated patients with stage 2 hypertension, with a target of achieving normotension less than 140/90, were examined. The total of 196 patients, 109 males and 87 females, with a mean age of 49.3 ± 8.4 years, untreated or inadequately treated patients with stage 2 hypertension (mean BP before treatment 167/106 mmHg) were divided into three groups according to blood pressure variability parameters. Alongside standard methods: medical history, clinical examination, and electrocardiogram (ECG), 24-hour ambulatory arterial pressure monitoring (ABPM, so-called blood pressure holter) was performed with 24-hour, daytime, and nighttime variability of systolic and diastolic blood pressure as well as Color and Tissue Doppler echocardiography after adequate treatment. Results: Elevated blood pressure variability was observed in 66/196 patients (34%) in group V despite good pressure regulation, while 130/169 (66%) had normal variability - group C (control). A subgroup ExtV was particularly highlighted within group V with extreme variability of daytime systolic BP (SD>20 mmHg) - 15/66 patients (8%). Evaluation of left ventricular myocardial mass index (LVMI) showed no difference in the degree of LVH between groups C and V. In the subgroup ExtV (from group V with extreme blood pressure variability), comprising 15/66 patients (8%), a significant difference in the degree of left ventricular myocardial hypertrophy was found between groups C and V regarding extreme variability ($p<0.01$). There was no difference concerning gender and age structure. Statistical analysis of investigated 24-hour blood pressure parameters and echocardiographic parameters did not show significant correlation through calculation of the linear correlation coefficient between mean arterial pressure measured by 24-hour ambulatory pressure monitoring and standard deviations of daytime and nighttime pressure and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r <0.20$), as expected. However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, E/E' ratio, and variability of daytime systolic pressure: $r= 0.41$. Only the subgroup with extreme variability ExtV in terms of daytime systolic pressure has a statistically significant correlation with the degree of LVMI myocardial hypertrophy, $r=0.51$. Conclusion: One-third of the examined patients, 66/196 patients (34%) in group V, had elevated blood pressure variability despite good pressure regulation. There was no significant difference in the degree of left ventricular myocardial hypertrophy between the investigated parameters of 24-hour blood pressure and echocardiographic indices, except in extreme variability ExtV ($P<0.01$). However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function,

E/E' ratio, and variability of daytime systolic pressure: r= 0.41. Only the subgroup with extreme variability ExtV in terms of daytime systolic pressure has a statistically significant correlation with the degree of LVMI myocardial hypertrophy, r=0.51.

Keywords: arterial hypertension, systolic and diastolic blood pressure, daytime and nighttime blood pressure, early morning pressure, left ventricular hypertrophy, mean 24-hour arterial pressure, 24-hour ambulatory blood pressure monitoring (ABPM), 24-hour blood pressure variability, left ventricular myocardial mass index, diastolic dysfunction of the left ventricle, extreme blood pressure variability.

INTRODUCTION

Blood pressure variability refers to changes in blood pressure (BP) values over a certain period of time. By definition, blood pressure variability (BPV) is a quantitative index of spontaneous daily and nocturnal variations in systolic and diastolic arterial BP and has been proposed as a risk factor for inducing subclinical damage to target organs mediated by hypertension (HMOD) [1]. Older studies of ambulatory invasive intra-arterial pressure have shown that BP is highly variable during the day and to a lesser extent at night [2,3] due to the interplay of central neuro factors, humoral influences, local vasoactive mechanisms, and the buffering effect of baroreflexes [4,5].

While it's normal for blood pressure to vary throughout the day, excessive variability, i.e., high blood pressure variability, may be associated with an increased risk of heart disease, stroke, and other complications [1]. It is well known that besides reducing the mean arterial pressure measured by 24-hour ambulatory blood pressure monitoring (ABPM), reducing blood pressure variability under therapy has prognostic significance as an independent factor in stroke prevention [1]. Episodic elevated blood pressure is associated with more frequent cardiovascular (CV) events.

Short-term BPV is quantitatively related to the level of elevated BP and is therefore greater in arterial hypertension than in normotension [3] and has a detrimental effect on the development of hypertension-mediated subclinical organ damage (HMOD) [6]. Interestingly, significant differences in blood pressure variations exist between human and animal studies, with BPV being much lower in experimental animals [7]. Non-invasive studies with ABPM have shown that 24-hour BP variability has a detrimental effect on CV outcomes, independent of 24-hour mean BP [8,9,10,11].

Left ventricular hypertrophy (LVH) as one of the most important HMODs is a sensitive index for the level of elevated mean arterial pressure (MAP) [12]. LVH and aortic dilation are also sensitive indices for the level of blood pressure variability MAP [12].

Table 1. Models and mechanisms of elevated blood pressure variability (BPV). [4,5]

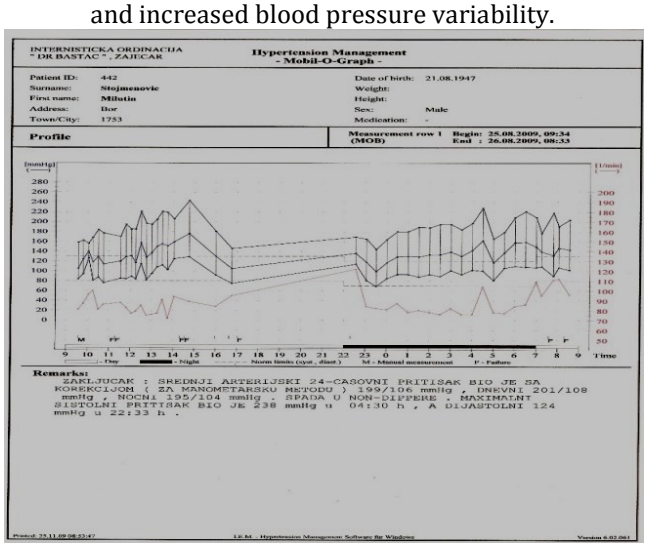
variability model	region/tissue	clinical example
increased variability at rest	baroreflex afferent nerves brain stem centers	autonomic dysfunction age morning BP surge
increased vasoreactivity	endothelium vascular muscle	dyslipidemia, insulin, resist hypertension
behavioral response (fear, anger)	hypothalamus brain stem centers	

The complex topic of short-term and long-term blood pressure variability (BPV) is a factor that introduces some confusion in the diagnosis, classification, and treatment of hypertension. The true pathophysiological variation in blood pressure is associated with heart rate, respiration, complex sympathetic nervous system responses, vascular reactivity, and arterial stiffness [4,5]. Measurement errors (systematic and random errors) further complicate the analysis of BPV. Most studies use serial clinical blood pressure values in the office, 24-hour ambulatory blood pressure monitoring (ABPM), or home blood pressure values (HBPM) with standard statistical indicators (standard deviation, variance, or coefficient of variation) (Figure 1 and 2).

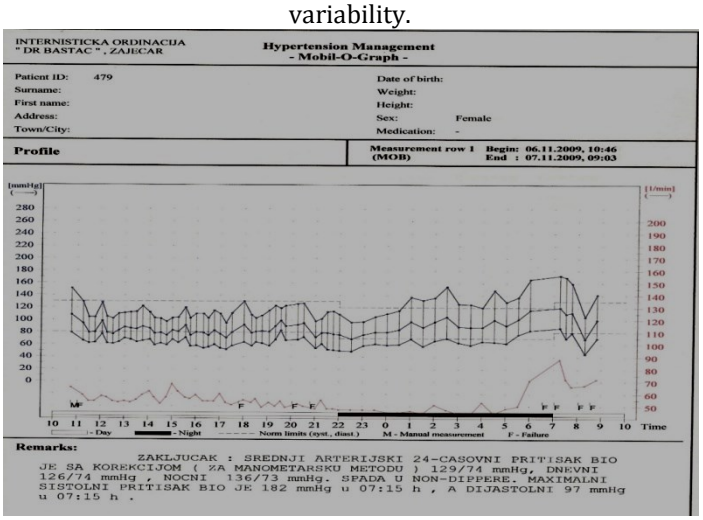
Various studies have found that BPV is reduced to a small extent with calcium antagonists and diuretics therapy and even increased with ACE inhibitors, beta-blockers, and alpha-blockers [13,14], but no interventional study has addressed whether reducing blood pressure variability provides protection

from cardiovascular disease risk [11]. BPV is not specifically mentioned in the latest ESH guidelines and practical recommendations from 2023 [15], but it is tacitly confirmed by recommendations for repeated blood pressure measurements, standardization of techniques, and confirmation of hypertension diagnosis by home or ambulatory blood pressure monitoring to explain the "white coat effect," masked hypertension, time spent in normotension during treatment, and to avoid problems in hypertension classification. There is no formal consensus on how to quantify or treat elevated blood pressure variability despite the real need for better diagnostic and therapeutic guidelines. Therefore, doctors should focus on controlling mean blood pressure using combinations of medications that improve cardiovascular disease (CVD) outcomes. Future consensus guidelines should directly address blood pressure variability and should include educational materials for both physicians and patients [15].

Picture 1. Example of elevated mean 24-hour blood pressure on ABPM graph with stage 3 hypertension and increased blood pressure variability.



Picture 2. Ambulatory 24-hour ABPM monitoring of blood pressure under antihypertensive therapy that is well-regulated shows normal average arterial 24-hour BP, but there is still increased blood pressure variability.



PATIENTS AND METHODS

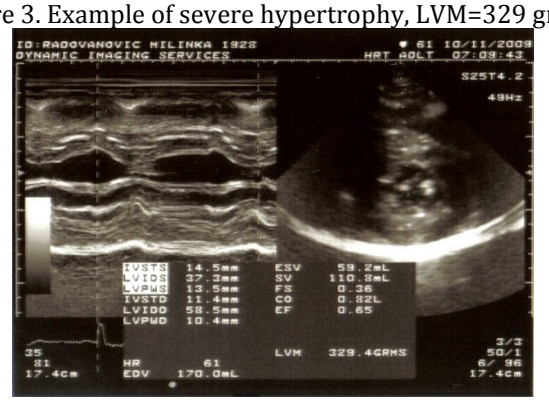
This retrospective cross-sectional study included 196 hypertensive patients under adequate therapy who underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean 24-hour arterial pressure for the entire group was normal at 123/76 mmHg on ambulatory blood pressure

monitoring. A total of 196 patients were examined, 109 males and 87 females, with a mean age of 49.3 ± 8.4 years, untreated or inadequately treated patients with stage 2 hypertension (mean BP before treatment 167/106 mmHg) who were divided into three groups according to blood pressure variability parameter. Elevated blood pressure variability was present in 66/196 patients (34%) - group V despite good pressure control, while 130/169 (66%) had normal variability - group C, control. A subgroup ExtV was specifically identified within group V with extreme blood pressure variability (SD>20 mmHg) - 15/66 patients (8%). In addition to routine clinical methods, ECG, office blood pressure measurements, and 24-hour ABPM, all patients underwent echocardiography using a GE Vivid 7 DIMENSION PRO machine with an emphasis on myocardial hypertrophy: left ventricular mass (LVM) and left ventricular mass index (LVMI) and parameters of left ventricular diastolic function via pulse (PW), continuous (CW), and tissue (TDI) Doppler.

Normal geometry assumes normal LVMI (less than 134 g/m2 for males and 110 for females), normal relative wall thickness (RWT less than 0.45), normal left ventricular end-diastolic dimension index (LVDDI less than 3.1 cm/m2), and normal septal eccentricity index (less than 1.3). Two-dimensional echocardiography was performed for precise measurements on M-Mode and qualitative analysis of standard two-dimensional (B-mode) cross-sectional planes. All parasternal longitudinal and transverse sections, apical sections with two and four cardiac chambers, as well as subcostal and suprasternal sections, were routinely performed. Visual analysis of the appearance of valvular echo apparatus, endocardium, and pericardium was performed. Regional myocardial motion analysis was also performed: presence or absence of hypokinesia, akinesia, or dyskinesia, and motion nonuniformities, taking into account normal variations. Diastolic parameters were determined by PW and TDI Doppler, including the E and A wave velocities ratio (E/A), the deceleration time of the A wave (DTA) representing myocardial relaxation, and the E wave transmitral velocity/mitral annulus E' velocity ratio on tissue Doppler representing left ventricular compliance and indirectly left ventricular filling pressure.

Statistical analysis was performed using the Statgraphics computer program, and the following parametric tests were used to test the hypothesis: Student's t-test, linear correlation coefficient, and nonparametric chi-square test.

Picture 3. Example of severe hypertrophy, LVM=329 grams.



‘ Increased blood pressure variability is represented as the standard deviation (±SD) of blood pressure values in mmHg. Reference threshold values for increased blood pressure variability are categorized according to blood pressure standard deviation (±SD).

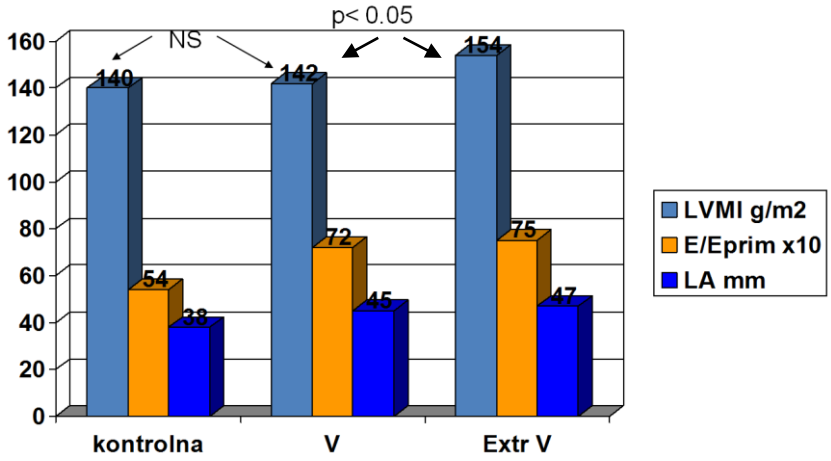
- daily systolic: >17 mmHg,
- daily diastolic: >13 mmHg,
- nocturnal systolic: >13 mmHg,
- nocturnal diastolic: >10 mmHg,
- extreme daily systolic variation: >20 mmHg.

RESULTS:

One-third of the examined patients, 66 out of 196 (34%), had increased blood pressure variability - group V despite good pressure control, while two-thirds of the patients, 130 out of 169 (66%), had normal variability - group C, which served as the control group. A subgroup ExtV was specifically identified within

group V with extreme blood pressure variability - consisting of 15 out of 66 patients (8%). Left ventricular mass index (LVMI) was elevated in groups C (140 g/m2) and V (142 g/m2) but without statistically significant difference (NS). Only in the group with extreme variability of daily systolic blood pressure, the left ventricular mass index was significantly higher compared to groups C and V ($p<0.05$) (Graph 1). There was no difference regarding gender and age structure.

GRAPH 1. Myocardial mass and diastolic function

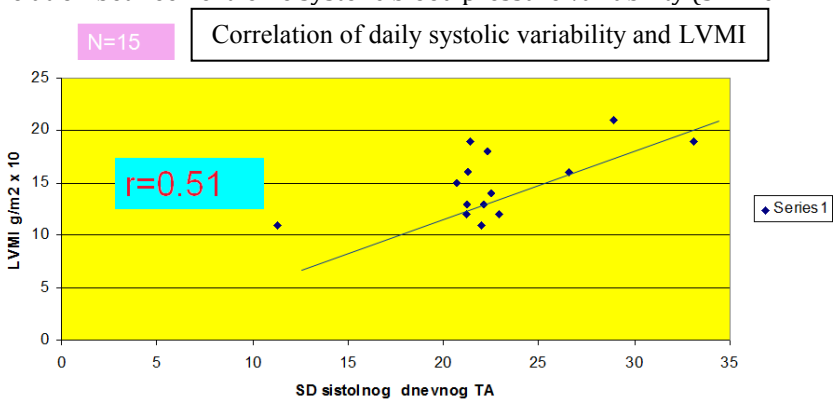


The mean left atrial (LA) dimension, as a parameter of cardiac diastolic function, was normal in the control group C (LA=38 mm, normal up to 40 mm), and statistically significantly higher ($p<0.01$) in groups with increased blood pressure variability (group V - LA=45mm and ExtV - LA=47mm), but without significant differences between them. The diastolic function, expressed as the ratio of transmitral early diastolic filling velocity E to the average mitral annulus velocity E' (E/E'), was normal in group C (E/E' = 5.4 x 10) and statistically significantly higher in groups V (E/E'=7.2) and ExtV (E/E'=7.5) compared to the control group C ($p<0.01$), although all mean E/E' values were within the normal range.

Statistical analysis of the examined parameters of 24-hour ambulatory blood pressure monitoring and echocardiographic parameters did not reveal significant correlation through calculating the coefficient of linear correlation between mean arterial pressure measured by 24-hour ambulatory blood pressure monitoring and standard deviation of daily and nocturnal blood pressure, and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r <0.20$), as expected. However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, the E/E' ratio, and the variability of systolic daily blood pressure: r=0.41. A weak correlation was found between the E/E' ratio and the variability of nocturnal diastolic blood pressure (r=0.30). There is no correlation between E/E' and the variability of diastolic daily blood pressure (r=0.01) and nocturnal systolic blood pressure (r=0.16).

Early morning systolic pressure determined by ambulatory blood pressure monitoring, as an important prognostic factor, only has a weak correlation with LVMI (r=0.39). Only the subgroup with extreme variability ExtV in terms of daily systolic blood pressure has a statistically significant good correlation with the degree of left ventricular myocardial hypertrophy LVMI, r=0.51 (Graph 2).

GRAPH 2. Correlation between extreme systolic blood pressure variability (SD>20mmHg) and LVMI



DISCUSSION

The pronounced variability in arterial blood pressure (ABP) is intertwined and overlaps with the diagnosis of hypertension, presenting a challenge for clinicians, as standard antihypertensive drugs only modestly reduce ABP fluctuations, as they are a consequence of pathophysiological changes or behavioral factors. Clinically, ABP variability is classified into 4 main types based on the duration of monitoring: ultra-short-term (beat-to-beat), short-term (within 24 hours), medium-term (within a few days), and long-term (over one month or year). Blood pressure variability is a strong risk factor for cardiovascular disease, chronic kidney disease, cognitive decline, and mental illness. The diagnostic and therapeutic value of measuring and controlling blood pressure variability can provide critical targets alongside reducing average blood pressure in hypertensive populations. [14].

Although some studies have shown that treatment reduces 24-hour blood pressure variability (BPV), there are no studies to date demonstrating that lowering BPV through treatment reduces cardiovascular risk. [8,9,16,17].

Numerous studies have focused on other types of BPV. Conflicting results have been published regarding the prognostic value of BP variability in-office between physician visits (inter-visit variability) [18], while some studies have reported an association between day-to-day variability when BPV was assessed through home blood pressure monitoring (HBPM) and the risk of cardiovascular outcomes [19,20]. However, the largest body of evidence for BPV relates to office BP variability, from visit to visit over the course of one or more years (long term). Post-hoc analyses of antihypertensive treatment studies have shown that long-term BPV, measured as differences between office BP readings at 6 or 12 months, is associated with cardiovascular risk in treated hypertensive patients. In a post-hoc analysis of three studies, an increased number of physician visits resulting in office BP being lowered to recommended levels was associated with a proportional reduction in cardiovascular outcomes and mortality, independent of the average office BP achieved during the treatment period. [21-23].

Furthermore, in studies or treated cohorts of patients with various demographic and clinical characteristics, BP variations between physician visits are associated with cardiovascular and renal risk, independent of mean BP values over years of treatment [24-26]. In one study, combining the mean BP during treatment with BPV between physician visits identified a safer cardiovascular risk profile in treated hypertensive patients than any individual measurement [27]. These data suggest that in treated patients, protection depends on the time spent under controlled pressure, as evidenced by the recent confirmed relationship between cardiovascular events and the calculated time spent within the therapeutic BP range (TTR) or other BP burden ratios in patients undergoing renal denervation and treated diabetics, respectively. [28,29].

From a clinical practice perspective, these data justify recommendations to pay attention to the consistency or regularity of BP regulation in patients on therapy, as the absence of regulation in a given physician visit does not represent "innocent" BP elevation without consequences, as it indicates a prolonged period of high pressure in previous months. Evidence from the ELSA study shows that inconsistent BP regulation is common in treated hypertensive patients [30]. Few studies have explored the relationship between blood pressure variability and echocardiographic parameters of myocardial

mass, systolic and diastolic function indices [31,32,33]. Multivariable logistic regression showed that the trend of 24-hour systolic blood pressure burden on ABPM acts independently as a critical risk factor for LVH development [31]. A correlation was observed between systolic blood pressure burden and the severity of LVH in pediatric patients with hypertension, and 24-hour SBP burden acts as a critical early prognostic parameter for LVH [31]. Shin et al. [32] found that patients with higher blood pressure variability showed a significantly increased left ventricular myocardial mass index (LVMI) and late mitral inflow velocity (A), as well as a reduced E/A ratio (early mitral inflow velocity/late mitral flow velocity) compared to those with lower BP variability (LVMI: $p = 0.02$; velocity: $p < 0.001$; E/A ratio: $p < 0.001$;). Additionally, increased blood pressure variability was associated with higher pulse wave velocity (PWV) and augmentation index ($p < 0.001$). Even among patients whose blood pressure was well controlled, blood pressure variability correlated with LV mass, diastolic dysfunction, and arterial stiffness [32]. Increased blood pressure variability was associated with LV mass and dysfunction, as well as arterial stiffness, suggesting that blood pressure variability may be an important determinant of target organ damage in patients with hypertension [32].

Variability in systolic blood pressure from visit to visit is associated with increased cardiac events [33]. Recent advances in imaging deformation via speckle tracking allow analysis of left atrial volume at various phases (2-DSTE) and easy measurement of left atrial phase function (LA). However, the relationship between BP variability and left atrial functional deformation with patient clinical outcomes has not been sufficiently explored. Findings by Tanaka et al. [33] suggest that high VVV-SBP is associated with cardiovascular risk, including worsening LA function in clinical practice.

Recent technological advancements through practical ambulatory systems without cuffs will enable continuous, non-invasive monitoring of blood pressure (BP), heart rate, and cardiac rhythm on both longitudinal 24-hour measurement scales and high-frequency blood pressure variability from beat to beat, along with synchronous heart rate variability (HRV) and changes in baseline heart rhythm[11,34].

CONCLUSION:

Variability in daytime systolic arterial blood pressure is now recognized as an independent prognostic risk factor for stroke in hypertensive patients. One-third of the examined patients, 66 out of 196 (34%), had elevated blood pressure variability (BPV) - group V despite good pressure regulation. Comparing the examined parameters of 24-hour ambulatory pressure and echocardiographic indexes, no significant difference was found in the degree of left ventricular myocardial hypertrophy, except in extreme variability (ExtV) ($P<0.01$).

The left ventricular myocardial mass index (LVMI) was elevated in groups C (140 g/m2) and V (142 g/m2) but without statistically significant difference (NS). Only in the group with extreme variability of daytime systolic blood pressure was the LVMI significantly higher compared to groups C and V ($p<0.05$). The mean value of left atrial dimension (LA) as a parameter of cardiac diastolic function was normal in the control group C (LA=38 mm, normal up to 40 mm), but statistically significantly higher ($p<0.01$) in groups with elevated BPV (group V - LA=45mm and ExtV - LA=47mm), although without significant difference between them.

Diastolic function, represented by the E/E' ratio (the ratio of early diastolic transmitral velocity to early diastolic mitral annulus velocity), was normal in group C (E/E' = 5.4 x 10) but statistically significantly higher in groups V (E/E'=7.2) and ExtV (E/E'=7.5) compared to control group C ($p<0.01$), although all mean values of E/E' were within normal limits.

However, there is a moderate but significant correlation between the best echocardiographic parameter of diastolic function, the E/E' ratio, and the variability of daytime systolic blood pressure: $r= 0.41$. Only the subgroup with extreme variability (ExtV) regarding daytime systolic blood pressure has a statistically significant strong correlation with the degree of left ventricular myocardial hypertrophy (LVMI), $r=0.51$.

Statistical analysis of the examined parameters of 24-hour ambulatory pressure and echocardiographic parameters did not find a significant correlation through the calculation of the linear correlation coefficient between the mean arterial pressure measured by 24-hour ambulatory pressure monitoring and the standard deviation of daytime and nighttime blood pressure and the degree of left ventricular myocardial hypertrophy (linear correlation coefficients $r <0.20$), as expected.

Arterial blood pressure variability has a strong correlation with a representative echocardiographic parameter of diastolic function derived from tissue Doppler: the E/E' ratio r=0.41, which best represents left ventricular diastolic dysfunction as subclinical organ damage. Only the subgroup with extreme variability (ExtV) regarding daytime systolic blood pressure has a statistically significant strong correlation with the degree of left ventricular myocardial hypertrophy (LVMI), r=0.51.

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