Selda Murat[1], Bektas Murat[2], Halit Emre Yalvac[1],
Muhammet Dural[1], Kadir Ugur Mert[1], Yuksel Cavusoglu[1]

[1] Eskisehir Osmangazi University, Medical Faculty Department of Cardiology, Eskisehir, Turkey

[2] Eskisehir City Hospital, Department of Cardiology, Eskisehir, Turkey

Relationship between left atrial functions and ambulatory blood pressure variability in patients with heart failure and preserved ejection fraction

Aim	The aim of this study was to investigate the relationship between left atrial (LA) abnormalities and ambulatory blood pressure variability (BPV) in heart failure with preserved ejection fraction (HFpEF) patients.
Material and Methods	In this single-center, prospective study, we included 187 patients with HFpEF. Eighteen patients with poor image quality were excluded from the study. BPV was evaluated using 24-h ambulatory blood pressure (BP) monitoring. The standard deviation of systolic BP (SBP-SD) was calculated to assess BPV. The patients were classified into two groups according to median SBP-SD (10.5 mm Hg).
Results	Overall, 169 HFpEF patients (69.2% women, mean age 69.2±11 yrs) were evaluated. There were 98 patients (57.9%) with a SBP-SD greater than 10.5 mm Hg. Patients with higher SPB-SD had significantly higher left atrial stiffness (LASt) and lower LA reservoir strain (LASr) than those with low SPB-SD. LASt was correlated with 24 hr SBP-SD in both sinus rhythm (r=0.35, p=0.015) and atrial fibrillation patients (r=0.32, p=0.005). There were significant correlations between night-time SBP-SD and LASr (r= –0.23, p=0.045) in HFpEF with sinus rhythm. For all HFpEF patients, multiple regression analyses showed that 24-hr SBP-SD was correlated with LASt (coeff. =0.40, 95%CI = 0.52–5.25, p=0.017).
Conclusions	High BPV is associated with impaired LA function, especially for LASt and LASr. This study may provide insight for larger multicenter studies to evaluate the effects on outcomes in HFpEF.

Keywords	Blood pressure variability; heart failure with preserved ejection fraction; left atrial function; left atrial stiffness; left atrial strain
For citation	Selda Murat, Bektas Murat, Halit Emre Yalvac, Muhammet Dural, Kadir Ugur Mert, Yuksel Cavusoglu. Relationship between left atrial functions and ambulatory blood pressure variability in patients with heart failure and preserved ejection fraction. Kardiologiia. 2022;63(1):48–53. [Russian: Сельда Мурат, Бекташ Мурат, Халит Эмре Ялвач, Мухаммет Дурал, Кадир Угур Мерт, Юксель Чавушоглу. Взаимосвязь функции левого предсердия с вариабельностью артериального давления при амбулаторном измерении у больных с сердечной недостаточностью с сохранной фракцией выброса. Кардиология. 2022;63(1):48–53].

Corresponding author	Selda Murat. E-mail: selda.eraslan@hotmail.com

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common disease, accounting for about 50% of all patients with HF [1]. Although the pathogenesis of HFpEF is not fully understood, high blood pressure (BP) plays an etiological role and leads to left ventricular hypertrophy (LVH) and diastolic dysfunction [2]. Several cohort studies have revealed that variability (BPV) in systolic (SBP) and diastolic blood pressure (DBP) are closely associated with the risk of coronary heart disease, stroke, and both cardiovascular and all-cause mortality. However, the relationship of BPV with HFpEF is much less clear [3–6].

The influence of the BPV profile on left ventricular (LV) structure and mechanics was investigated previously, and several studies have reported that high BPV has a worse effect on LV remodeling [7]. Nevertheless, the effects of BPV on left atrial (LA) function have not been extensively investigated, especially in patients with HFpEF. LA function is significantly associated with LV systolic and diastolic function [8]. Assessment of LA function has recently emerged as an important parameter, particularly in evaluation of LV diastolic dysfunction and HFpEF [9, 10]. The aim of this study was to evaluate the relationship between BPV and LA structural and functional abnormalities in HFpEF.

Material and methods

Study population

This was a prospective, observational and, single-center study, and it was approved by the institutional ethics committee. All participants provided written, informed consent. A total of 187 patients with HFpEF were recruited, between December 2020 and December 2021. The diagnosis of HFpEF was based

ISSN 0022-9040. Кардиология. 2023;63(1). DOI: 10.18087/cardio.2023.1.n2118

on the European Society of Cardiology (ESC) guideline [11]. Patients with severe valvular heart disease, previous myocardial infarction and, sarcomeric hypertrophic cardiomyopathy were excluded. In addition, 18 patients were also excluded because the 2D imaging quality of the LA was inadequate.

Comprehensive echocardiography

Comprehensive echocardiography was performed by a physician using a commercially available system (EPIQ 7C, X5–1 transducer, Philips Medical Systems, Andover, USA). Raw echocardiographic data were stored digitally as DICOM and transferred for offline analysis to a workstation with Philips QLAB software. Echocardiographic measurements were performed following published guidelines [12, 13]. Four-chamber views were used to evaluate LA function. LA volume indexed to body surface area (BSA), and the LA volume index (LAVI) was calculated. Minimum LA volume at the QRS complex and pre-A LA volume preceding the P-wave were also calculated to assess LA phasic function by the volumetric method.

LA total emptying fraction (reservoir function) =
[(LA volumemax – LA volumemin) / LA volumemax] × 100

LA passive emptying fraction (conduit function) =
[(LA volumemax – LA volumepre-A) / LA volumemax] × 100

LA active emptying fraction (pump function) =
[(LA volumepre-A – LA volumemin) / LA volumepre-A] × 100

LA expansion index=
[(LA volumemax – LA volumemin) / LA volumemin] × 100

Calculations of peak atrial longitudinal strain (PALS) and LV global longitudinal strain (GLS) were performed by offline semiautomatic analysis. PALS was defined as the first peak of positive deflection, and it is representative of the LA reservoir (LASr) function. LA stiffness (LASt) was calculated as LASt=E/e' ratio/PALS) [14].

Ambulatory blood pressure monitoring

All of the subjects underwent 24 hr ambulatory BP monitoring (ABPM). According to the 24 hr BP measurements, BPV was evaluated through the calculations of standard deviation (SD), weighted SD (WSD) and average real variability (ARV) of the SBP and DBP during daytime, nighttime, and over 24 hr.

Weighted SD was calculated using the following formula:

WSD = [(daytime SD × 14) + (nighttime SD × 6)]/20 [15].

ARV was calculated as the average of the differences (in absolute value) between consecutive BP measurements [15, 16] (Figure 1). BPV was assessed by the SD of 24-hr SBP derived from ABPM. The patients were classified into two groups according to median SBP-SD (lower or higher than the median SD of 10.5 mm Hg).

Figure 1. Formula of the average real variability
(N is the number of BP readings and k – ranges from 1 to N-1)

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}|BP_{k+1} - BP_k|$$

Statistical analyses

Data are summarized as frequencies (percentages) for categorical variables, as mean±SD for normally distributed, continuous variables, or as median (interquartile (IRQ)

Table 1. Baseline clinical characteristics of the study population

Variable	Total (n=169)	Low BPV (24-hr SBP-SD), n=71	High BPV (24-hr SBP-SD), n=98	p value
Age, yrs	69.2±11	68.3±10.6	69.0±11.7	0.568
Male sex	52 (30.8)	19 (26.8)	33 (33.7)	0.400
BSA, m^2	1.88±0.20	1.89±0.21	1.88±0.20	0.756
Hypertension	126 (74.6)	51 (71.8)	75 (76.5)	0.592
Diabetes	63 (37.3)	24 (33.8)	39 (38.9)	0.264
Coronary artery disease	47 (28.4)	24 (33.8)	24 (24.5)	0.227
Atrial fibrillation	70 (41.4)	23 (32.4)	47 (48.0)	0.030
Chronic kidney disease	55 (32.5)	24 (33.8)	31 (31.6)	0.868
Office SBP, mmHg	119.8±17.4	119.1±17.3	120.3±18.2	0.649
Office DBP, mmHg	66.2±13.7	66.6±14.1	65.8±13.5	0.723
Heart rate, bpm	77.4±18.2	74.4±14.9	79.5±20.1	0.061
Beta-blocker	127 (75.6)	55 (77.5)	72 (74.2)	0.717
Calcium channel blockers	41 (24.4)	15 (21.1)	26 (26.8)	0.469
ACEI/ARB	82 (48.8)	41 (57.7)	41 (42.3)	0.034
Furosemide	104 (61.9)	46 (64.8)	58 (59.8)	0.525
MRA	33 (19.6)	18 (25.4)	15 (15.5)	0.082
Hemoglobin, g/dl	12.4±2.1	12.5±2.11	12.4±2.18	0.662
Glucose, mg/dl	135.9±64.4	135.1±60	136.6±67	0.886
Creatinine, mg/dl	1.2±0.7	1.19±0.79	1.2±0.70	0.964
Sodium, mmol/l	138.5±8.8	138.4±3.4	138.6±11	0.866
Albumin, g/dl	4.0±0.5	3.93±0.58	4.14±0.50	0.022
NT-proBNP, pg/ml	1113 (544-3200)	1008 (426-3266)	1259 (546-3108)	0.594

Data are n (%) or mean±SD or median (IQR). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensinogen receptor blocker; BPV, blood pressure variability; BSA, body surface area; DBP, diastolic blood pressure; NTproBNP, N-terminal prohormone of brain natriuretic peptide; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Echocardiographic data of patients with low versus high blood pressure variability

Variables	Total (n=169)	Low BPV (24-hour SBP-SD), n=71	High BPV (24-hour SBP-SD), n=98	p value
LVEF, %	60.1±4.9	60.2±5.1	60.1±4.9	0.855
LV-GLS, %	–14.4±3.2	–14.9±3.4	–14.1±3.0	0.142
LVH (≥12 mm)	118 (69.8)	46 (64.8)	72 (73.5)	0.148
TJV, m/sec	2.84±0.55	2.78±0.59	2.88±0.51	0.265
LA diameter, mm	44.7±6.05	44.0±4.9	45.2±6.7	0.198
LA area 4C, cm^2	21.6±5.6	20.7±4.9	22.3±6.0	0.078
LA volume, ml (area-length method)	74.8±32.8	69.7±25.1	78.5±37.1	0.087
LAVI, (ml/m^2)	39.4±15.7	37.1±13.7	41.1±16.9	0.104
LASr, (%)	17.6±8.9	19.1±8.3	16.5±9.2	0.046
LASt, (%)	0.97±0.72	0.54±0.06	0.80±0.09	0.004
sPAP, mm Hg	43.6±16.5	42.6±15.7	45.0±17.5	0.351
LAVmax, ml	85.9±30.8	77.5±29.7	92.3±30.2	0.007
LAVImax, ml/m	46.1±17.8	41.65±15.6	49.5±18.0	0.013
LAVpreA, ml	57.4 (44.8–77)	49.0 (38.3–76.1)	65.1 (48.1–79.2)	0.024
LAVIpreA, ml/m^2	32.6±12.5	29.7±11.8	35.1±12.7	0.35
LAVmin, ml	42.9 (29.2–62.3)	36.1 (22.9–58.1)	50.1 (32.2–64.7)	0.025
LAVImin, m/m^2	25.5±13.7	22.7±12.7	27.7±14.2	0.045
LA expansion index (%)	1.04±0.65	1.08±0.67	1.0±0.64	0.538
Total LA emptying fraction (%)	0.46±0.14	0.47±0.14	0.45±0.14	0.489
Active LA emptying fraction (%)	0.36±0.15	0.35±0.16	0.37±0.13	0.558
Passive LA emptying fraction (%)	0.22±0.098	0.23±0.10	0.22±0.095	0.389
Total LA emptying volume, ml	38.4±14.8	35.3±12.9	40.8±15.7	0.036
Active LA emptying volume, ml	19.9 (14.7–26.0)	18.1 (11.1–23.8)	22.3 (15.6–31.9)	0.014
Passive LA emptying volume, ml	17.4 (10.9–23.5)	16.8 (9.2–21.9)	17.9 (12.4–23.6)	0.528
LAVmax/LASr ratio	7.0±5.4	5.1±3.3	8.5±6.3	0.001

Data are n (%), mean±SD or median (IQR). LA, left atrium; LAVI, left atrial volume index;
LV-GLS, left ventricular global longitudinal strain; LASr, left atrial reservoir strain; LASt, left atrial stiffness index;
LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy, TJV, tricuspid jet velocity.

range) for non-normally distributed variables. Appropriate, continuous data were compared with two-tailed Student t tests, and discrete data were analyzed with chi-square tests. Pearson correlation and the simple regression analysis were used to assess the relationship between two variables. If the findings were significant, a multivariable regression analysis was performed. A significant difference was defined as p value <0.05 (2-tailed). The IBM SPSS Statistics 21.0 (IBM Corp.

Table 3. Univariate and multiple regression analysis of 24 hr SBP-SD

Variable	All HFpEF patients		
	Univariate analysis. Coeff. (95% CI) p-value		Multivariate analysis. Coeff. (95% CI) p-value
SBP	0.09	[(-0.01)-0.06)] p=0.272	–
DBP	0.18	(0.007-0.15) p=0.033	0.22(0.01-0.19) p=0.030
Heart rate	0.19	(0.007-0.09) p=0.024	0.01[(-0.05)-0.06] p=0.877
LAVmax	0.11	[(-0.01)-0.05)] p=0.248	–
LVMI	0.15	[(-0.002-0.03)] p=0.078	–
Age	0.07	[(-0.04)-0.10)] p=0.410	–
LASr	-0.22	[(-0.21)-0.02] p=0.016	0.23[(-0.08)-0.33] p=0.234
LA expansion index	-0.04	[(-1.69)-1.07] p=0.654	–
LA diameter	0.009	[(-0.12)-0.13)] p=0.921	–
LA area	0.07	[(-0.07)-0.21] p=0.368	–
LV-GLS	-0.22	[(-0.65)-(-0.05)] p=0.022	-0.14[(-0.65)-0.20] p=0.305
LASt	0.33	(1.12-3.48) p=0.000	0.40(0.52-5.25] p=0.017
LAVmax/LASr	0.302	(0.10-0.47) p=0.003	0.10[(-0.23)-0.44 p=0.557

DBP, diastolic blood pressure; LA, left atrium; LASr, left atrial reservoir strain; LASt, left atrial stiffness index; LAVmax, left atrial maximum volume index; LV-GLS, left ventricular global longitudinal strain; LVMI, left ventricular mass ındex; SBP, systolic blood pressure.

ISSN 0022-9040. Кардиология. 2023;63(1). DOI: 10.18087/cardio.2023.1.n2118

Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used for the analyses.

Results

187 patients were screened; 169 patients (69.2% female, mean age 69.2±11 yrs) were eligible for the study. Baseline clinical characteristics of the study population are shown in Table 1. The mean office SBP, DBP, and 24-hr ambulatory SBP were 119.8±17.4 mm Hg, 66.2±13.7 mm Hg, and 127.2±18.4 mm Hg, respectively. There were 98 patients (57.9%) with a SBP-SD value greater than 10.5 mm Hg. BPVs calculated by different methods and the relationships between the groups are summarized in Supplementary Table 1.

Detailed echocardiographic parameters are summarized in Table 2. We found significant correlations between 24-h-SBP SD and LASt (r =0.35, p=0.015) and between nighttime SBP-SD and LASr (r=–0.23, p=0.045) in HFpEF with sinus rhythm. We found significant correlations between 24-hours SBP-SD and LASt (r=0.32, p=0.005) and LASr (r= –0.40, p=0.005) in HFpEF with atrial fibrillation (AF). The LA variable that had the highest correlation with nighttime SBP-SD in patients with AF was LASt (Supplementary Table 2).

After adjusting the statistically significant variables in univariate regression analysis, multiple regressions analysis showed the highest correlation of 24-hrs SBP-SD with LASt (coeff.=0.40, 95%CI= 0.52–5.25, P= 0.017) (Table 3).

Discussion

This study comprehensively evaluated the relationship between BPV which is derived from ABPM and LA functions in patients with HFpEF. The main findings of this study are: 1. Higher BPV in 24-hrs SBP-SD is associated with LA dysfunction in HFpEF patients, independent of BP. 2. When BPV was evaluated according to the circadian rhythm, both day-time and night-time higher BPV was correlated with impaired LA function. 3. In HFpEF patients with AF, higher BPV is highly correlated with increased LASt. 4. Among LA structural and functional variables, BPV shows that the LA function was strongly associated with increased LASt, which is a more specific indicator of LA function.

BPV represents the fluctuation of BP during 24 hrs. Previous studies showed that an increase in the 24-hrs BPV assessed by 24-hrs BP monitoring and the visit-to-visit variability (VVV) in systolic blood pressure (VVV-SBP) was associated with increase in cardiovascular morbidity and mortality, independent of the mean BP values [17–19]. A study in healthy subjects also found that VVV-SBP over 5 yrs was significantly associated with LA function, particularly active EF, i.e., booster LA function. It has been reported that the increase in BPV and the decrease in active EF are correlated. The same study also emphasized that LA changes are independent of SBP [19]. In another study that investigated the relationship between BPV, obesity and LA phasic function in the hypertensive population, the researchers reported that BPV increases progressively and LA functions decrease in obese patients [7].

HFpEF is a multifaceted disease with a complex etiology and is often associated with several comorbidities, such as HT, diabetes mellitus, obesity, AF, and kidney disease [20]. Because of these complexities, the evaluation of BPV and LA function in HFpEF patients is challenging. Previous studies found that increased BPV is associated with impaired LA function and clinical outcomes in patients with HT and HF with reduced EF (HFrEF), independent of SBP [7, 21–25].

In the present study, although there was no significant difference between the higher BPV group and both mean office BP and mean ABPM compared to the lower BPV group, similar to previous studies, it was observed that BPV had a significant effect on LA function, independent of the mean SBP in HFpEF patients. There are some differences between our study and previous study populations. While previous studies included patients with HFrEF and patients with HT and other comorbid conditions, our study population was limited to patients with HFpEF with comorbid conditions. Moreover, LA remodeling and dysfunction are common in the HFpEF population. Impaired LA function has previously been noted in conditions associated with HFpEF, even in the presence of normal LA size [26–28]. In another study, which included hypertensive-diabetic patients, it was reported that there were no associations between BPV assessed through 24-hrs ABPM and echocardiographic variables related to diastolic function, LVH and cardiac chamber diameters [29]. Similarly, in our study, there was no significant relationship between higher BPV and LA enlargement, LA area, LVH, and LVEF.

In addition to the structural changes, LA cavity remodeling and dysfunction, volumetric variables, and strain assessment also play an important clinical role in HFpEF patients. In a previous study, it was reported that LASt, a marker of myocardial fibrosis and atrial dysfunction, is associated with deterioration in the functions of the LA cavity [25]. Chronic deterioration in LA pressure causes remodeling and ultimately fibrosis. These changes result in worsening of cavity function, including contraction and stiffness, which eventually causes elevation of cavity pressure and pulmonary venous hypertension [30]. Impairment in LA function was also shown to be associated with poor outcome in HF patients in previous studies [24]. Although recent studies have shown that BPV is associated with LA dysfunction, AF, and cardiovascular mortality in the general population and in patients with HFrEF, there is sparse data in patients with HFpEF [31–33]. In our study, higher BPV was associated with increased LASt and low LASr, which are important indicators of LA dysfunction. These findings indicate that BPV may affect LA functions in HFpEF patients, which may affect hospitalization and poor prognosis.

Furthermore, the relationship between the circadian rhythm of BPV and LA functions in patients with HFpEF has not been fully demonstrated in previous studies. However, there are studies reporting that night-time higher BPV is associated with LVH. In a study by R. Sega et al. it was shown that there is a correlation between BPV and LV mass index (LVMI) [34]. Also, in another study reported by Mustafa ER et al. it was shown that there is a significant correlation between the LVMI and nocturnal BPV [35]. In a study investigating the effect of circadian BP on cardiovascular outcomes in patients with HFpEF, it was reported that abnormal pattern of circadian BP rhythm is associated with cardiovascular outcomes and night-time BP values can be considered for the therapeutic target [36]. The present study has methodological differences from other studies, we did not directly evaluate the cardiovascular mortality or outcomes, but we evaluated whether circadian rhythm has an effect on LA function in HFpEF patients. When BPV was evaluated according to circadian rhythm, night-time SD-SBP was correlated with increased LASt. In light of these results, it may be important to consider the effect of nocturnal BPV on LA functions during treatment planning.

In addition, AF is both common and associated with adverse outcomes in HFpEF [37]. This complicates assessment of BPV and LA functions. Our study showed that BPV was highly correlated with LAVmax/LASr ratio and increased LASt in HFpEF patients with AF, despite similar mean BP. t It might be explained that AF leads at first to increased HR variability, which may cause labile BP. Another possibility is that patients who develop AF have an increased burden of traditional cardiovascular risk factors, which are associated with increased BPV. One of the most important reasons may be that, in HFpEF patients, the deterioration of LA function may trigger the development of AF by causing LA fibrosis, even in the presence of normal LA diameter. at first

Limitations

This study had a few limitations. First, there was a small population, and the results were obtained at a single center; therefore, it lacked the obvious advantages of a larger multicenter trial. Secondly, during echocardiographic assessment of HFpEF patients, AF represents a limitation for evaluation of LV diastolic function. Patients with AF have lost the atrial 'booster pump' phase, so the A wave and its derivate cannot be assessed. Hence, larger studies should confirm the association between BPV and atrial function in patients with HFpEF. In addition, its effect on mortality and hospitalizations in HFpEF patients should be confirmed by further study.

Conclusion

Our study showed that higher BPV with 24-hours SBP-SD is associated with LA dysfunction in HFpEF patients, independent of BP. Furthermore, among LA structural and functional variables, SBP variability shows that LA function was strongly associated with increased LASt, which is a more specific indicator of LA function. In addition, in HFpEF patients with AF, higher BPV is highly correlated with increased LASt which may depict LA dysfunction.

Funding

This research was supported by no specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study has not been presented or reported previously.

No conflict of interest is reported.

The article was received on 29/03/2022

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021;42(36):3599–726. DOI: 10.1093/eurheartj/ehab368
2. Selvaraj S, Claggett BL, Böhm M, Anker SD, Vaduganathan M, Zannad F et al. Systolic Blood Pressure in Heart Failure With Preserved Ejection Fraction Treated With Sacubitril/Valsartan. Journal of the American College of Cardiology. 2020;75(14):1644–56. DOI: 10.1016/j.jacc.2020.02.009
3. Suchy-Dicey AM, Wallace ER, Elkind MS, Aguilar M, Gottesman RF, Rice K et al. Blood Pressure Variability and the Risk of All-Cause Mortality, Incident Myocardial Infarction, and Incident Stroke in the Cardiovascular Health Study. American Journal of Hypertension. 2013;26(10):1210–7. DOI: 10.1093/ajh/hpt092
4. Arashi H, Ogawa H, Yamaguchi J, Kawada-Watanabe E, Hagiwara N. Impact of Visit-to-Visit Variability and Systolic Blood Pressure Control on Subsequent Outcomes in Hypertensive Patients With Coronary Artery Disease (from the HIJ-CREATE Substudy). The American Journal of Cardiology. 2015;116(2):236–42. DOI: 10.1016/j.amjcard.2015.04.011
5. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT et al. Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. Annals of Internal Medicine. 2015;163(5):329–38. DOI: 10.7326/M14-2803
6. Nuyujukian DS, Koska J, Bahn G, Reaven PD, Zhou JJ. Blood Pressure Variability and Risk of Heart Failure in ACCORD and the VADT. Diabetes Care. 2020;43(7):1471–8. DOI: 10.2337/dc19-2540
7. Tadic M, Cuspidi C, Ilic I, Suzic-Lazić J, Zivanovic V, Jozika L et al. The relationship between blood pressure variability, obesity and left atrial phasic function in hypertensive population. The International Journal of Cardiovascular Imaging. 2016;32(4):603–12. DOI: 10.1007/s10554-015-0822-8
8. Russo C, Jin Z, Homma S, Rundek T, Elkind MSV, Sacco RL et al. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. Heart. 2012;98(10):813–20. DOI: 10.1136/heartjnl-2011-301388
9. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC state-of the art review. Journal of the American College of Cardiology. 2019;73(15):1961–77. DOI: 10.1016/j.jacc.2019.01.059
10. Donal E, Lund LH, Oger E, Bosseau C, Reynaud A, Hage C et al. Importance of combined left atrial size and estimated pulmonary pressure for clinical outcome in patients presenting with heart failure with

preserved ejection fraction. European Heart Journal – Cardiovascular Imaging. 2017;18(6):629–35. DOI: 10.1093/ehjci/jex005
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiologia Polska. 2016;74(10):1037–147. DOI: 10.5603/KP.2016.0141
12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging. 2016;17(12):1321–60. DOI: 10.1093/ehjci/jew082
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging. 2015;16(3):233–71. DOI: 10.1093/ehjci/jev014
14. D'Ascenzi F, Pelliccia A, Natali BM, Cameli M, Andrei V, Incampo E et al. Increased left atrial size is associated with reduced atrial stiffness and preserved reservoir function in athlete's heart. The International Journal of Cardiovascular Imaging. 2015;31(4):699–705. DOI: 10.1007/s10554-015-0600-7
15. de la Sierra A, Pareja J, Armario P, Barrera Á, Yun S, Vázquez S et al. Renal Denervation vs. Spironolactone in Resistant Hypertension: Effects on Circadian Patterns and Blood Pressure Variability. American Journal of Hypertension. 2017;30(1):37–41. DOI: 10.1093/ajh/hpw085
16. Morrad S, Morrad B, Ata N. Blood Pressure Variability in Early and Late Period in Hypertensive Patients with Myocardial Infarction. MN Kardiyoloji. 2017;24(4):145–50. [Av. at: https://www.mnkardiyoloji.com.tr/sayfa.asp?Sayfa=Icindekiler&Bak=24]
17. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K et al. Prognostic Value of Reading-to-Reading Blood Pressure Variability Over 24 Hours in 8938 Subjects From 11 Populations. Hypertension. 2010;55(4):1049–57. DOI: 10.1161/HYPERTENSIONAHA.109.140798
18. Stolarz-Skrzypek K, Thijs L, Richart T, Li Y, Hansen TW, Boggia J et al. Blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. Hypertension Research. 2010;33(8):757–66. DOI: 10.1038/hr.2010.110
19. Tanaka S, Segawa T, Noda T, Tsugita N, Fuseya T, Kawaguchi T et al. Assessment of visit-to-visit variability in systolic blood pressure over 5 years and phasic left atrial function by two-dimensional speckle-tracking echocardiography. Heart and Vessels. 2021;36(6):827–35. DOI: 10.1007/s00380-020-01751-5
20. Miranda-Silva D, Lima T, Rodrigues P, Leite-Moreira A, Falcão-Pires I. Mechanisms underlying the pathophysiology of heart failure with preserved ejection fraction: the tip of the iceberg. Heart Failure Reviews. 2021;26(3):453–78. DOI: 10.1007/s10741-020-10042-0
21. Monzo L, Ferreira JP, Abreu P, Szumski A, Böhm M, McMurray JJV et al. Visit-to-visit blood pressure variation and outcomes in heart failure with reduced ejection fraction: findings from the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms trial. Journal of Hypertension. 2020;38(3):420–5. DOI: 10.1097/HJH.0000000000002275
22. Zhang Q, Zhou B, Ma Y, Hu Y, Li X, Cong H. Blood pressure visit-to-visit variability and outcomes in patients with heart failure with preserved ejection fraction. ESC Heart Failure. 2021;8(5):3984–96. DOI: 10.1002/ehf2.13542
23. Bytyçi I, Bajraktari G, Ibrahimi P, Berisha G, Rexhepaj N, Henein MY. Left atrial emptying fraction predicts limited exercise performance in heart failure patients. IJC Heart & Vessels. 2014;4:203–7. DOI: 10.1016/j.ijchv.2014.04.002
24. Rossi A, Dini FL, Agricola E, Faggiano P, Benfari G, Temporelli PL et al. Left atrial dilatation in systolic heart failure: a marker of poor prognosis, not just a buffer between the left ventricle and pulmonary circulation. Journal of Echocardiography. 2018;16(4):155–61. DOI: 10.1007/s12574-018-0373-9
25. Bytyçi I, D'Agostino A, Bajraktari G, Lindqvist P, Dini FL, Henein MY. Left atrial stiffness predicts cardiac events in patients with heart failure and reduced ejection fraction: The impact of diabetes. Clinical Physiology and Functional Imaging. 2021;41(2):208–16. DOI: 10.1111/cpf.12688
26. Kanagala P, Arnold JR, Cheng ASH, Singh A, Khan JN, Gulsin GS et al. Left atrial ejection fraction and outcomes in heart failure with preserved ejection fraction. The International Journal of Cardiovascular Imaging. 2020;36(1):101–10. DOI: 10.1007/s10554-019-01684-9
27. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. Journal of the American Society of Echocardiography. 2011;24(8):898–908. DOI: 10.1016/j.echo.2011.04.014
28. Hoit BD. Left Atrial Size and Function: role in prognosis. Journal of the American College of Cardiology. 2014;63(6):493–505. DOI: 10.1016/j.jacc.2013.10.055
29. Massierer D, Leiria LF, Severo MD, Ledur PDS, Becker AD, Aguiar FM et al. Blood pressure variability and its association with echocardiographic parameters in hypertensive diabetic patients. BMC Cardiovascular Disorders. 2016;16(1):4. DOI: 10.1186/s12872-015-0183-1
30. Bytyci I, Bajraktari G, Fabiani I, Lindqvist P, Poniku A, Pugliese NR et al. Left atrial compliance index predicts exercise capacity in patients with heart failure and preserved ejection fraction irrespective of right ventricular dysfunction. Echocardiography. 2019;36(6):1045–53. DOI: 10.1111/echo.14377
31. Kwon S, Lee S-R, Choi E-K, Lee S-H, Han K-D, Lee S-Y et al. Visit-to-visit variability of metabolic parameters and risk of heart failure: A nationwide population-based study. International Journal of Cardiology. 2019;293:153–8. DOI: 10.1016/j.ijcard.2019.06.035
32. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D et al. Visit-to-Visit Variability of Blood Pressure and Cardiovascular Disease and All-Cause Mortality: A Systematic Review and Meta-Analysis. Hypertension. 2014;64(5):965–82. DOI: 10.1161/HYPERTENSIONAHA.114.03903
33. Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The Relationship Between Visit-to-Visit Variability in Systolic Blood Pressure and All-Cause Mortality in the General Population: Findings From NHANES III, 1988 to 1994. Hypertension. 2011;57(2):160–6. DOI: 10.1161/HYPERTENSIONAHA.110.162255
34. Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G et al. Blood Pressure Variability and Organ Damage in a General Population: Results from the PAMELA Study. Hypertension. 2002;39(2):710–4. DOI: 10.1161/hy0202.104376
35. Mustafa ER, Istrătoaie O, Muşetescu R. Blood Pressure Variability and Left Ventricular Mass in Hypertensive Patients. Current Health Sciences Journal. 2016;42(1):47–50. DOI: 10.12865/CHSJ.42.01.07
36. Komori T, Eguchi K, Saito T, Hoshide S, Kario K. Riser Pattern Is a Novel Predictor of Adverse Events in Heart Failure Patients With Preserved Ejection Fraction. Circulation Journal. 2017;81(2):220–6. DOI: 10.1253/circj.CJ-16-0740
37. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial Dysfunction in Patients with Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. Journal of the American College of Cardiology. 2020;76(9):1051–64. DOI: 10.1016/j.jacc.2020.07.009