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# Association between Heart Rate and Global Left Ventricular Longitudinal Strain and Left Atrium Structural and Functional Changes in Hypertensive Patients with Normal Left Ventricular Ejection Fraction (A Speckle Tracking Study)

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## Abstract

**Background and Aim:** The structure and function of the left heart cavity have important prognostic value in heart diseases, and heart rate (HR) control is an important treatment goal. In this study, we investigated the effects of HR on left heart structure and function in hypertensive patients with normal left ventricular (LV) systolic function.

**Materials and Methods:** This was a single-center, prospective, observational (case-control) study. A total of 153 patients were included in the study. Patients were divided into two groups according to their HR (70 beats/min and below and above 70 beats/min). LV and atrial strain analyses were performed during echocardiographic evaluation.

**Results:** Patients with a resting HR of 70 beats/min or less were included in group 1 (64.2±4.5) and patients with a resting HR above 70 beats/min were included in group 2 (79.1±6.8). There is a significant difference between group 1 and group 2 in left atrial maximum volume (60.8±15.5 mL vs. 52.9±16.3 mL  $P = 0.007$ ), left atrial minimum volume (28.8±9.5 vs. 22.6±7.9  $P < 0.001$ ), left atrial emptying fraction (52.8±8.5% vs. 56.1±8.5%  $P = 0.035$ ), left atrial expansion index (1.19±0.44 vs. 1.36±0.47  $P = 0.044$ ), pLASRcd (-1.3±0.38 vs. -1.5±0.61  $P = 0.031$ ), and global longitudinal strain (-19.3±3 vs. -18.2±2.7  $P = 0.07$ ). In the multivariable regression analysis, beta-blocker [odds ratio (OR): 0.291, 95% confidence interval (CI) 0.105-0.810,  $P = 0.018$ ], mean high diastolic blood pressure (OR: 1.054, 95% CI 1.009-1.101,  $P = 0.018$ ), left atrial minimum volume (OR: 0.870, 95% CI 0.809-0.938,  $P < 0.001$ ), S' (OR: 10.6, 95% CI 1.1-104,  $P = 0.041$ ), left atrial expansion index (OR: 0.870, 95% CI 0.809-0.930,  $P < 0.033$ ) were determined as independent predictors of high resting HR.

**Conclusion:** HR control is an important goal in patients with hypertension who have preserved LV systolic function. Mortality and morbidity can also be improved by HR control.

**Keywords:** Heart rate, hypertension, strain, preserved left ventricular systolic function

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## INTRODUCTION

Hypertension is an important risk factor with a high prevalence worldwide, and its role in adverse cardiovascular (CV) events is well known. The damage caused by hypertension to the heart can be detected by echocardiography.<sup>[1]</sup> Impaired left ventricular (LV) systolic function is an important independent predictor of adverse CV events, such as heart failure and CV death.<sup>[2]</sup> In patients with long-standing hypertension, impaired LV function, LV hypertrophy, and myocardial fibrosis are markers of end-organ damage.

The heart rate (HR) is an important and easily observable indicator that does not require advanced technical equipment. High HR is associated with increased CV events in the general human population and individuals with CV risk factors.<sup>[3]</sup> In the Framingham Study, HR was found to be associated with mortality in men and women who are patients with hypertension.<sup>[4]</sup> Therefore, it is important to quantify the potential risks associated with the resting HR of patients. In this context, the resting HR and its structural and functional effects on the heart should be well defined.

Speckle tracking echocardiography has emerged as a non-invasive and sensitive method for detecting early regional and global myocardial dysfunction that is undetectable by conventional two-dimensional (2D) echocardiographic imaging in both symptomatic and asymptomatic patients with CV disease (CVD). Subclinical systolic dysfunction can be detected using global longitudinal strain (GLS), which is beyond conventional echocardiographic evaluation.<sup>[5]</sup>

The left atrium (LA) has an important role in the regulation of LV filling and has been identified as an important biomarker of CVD and adverse CV outcomes.<sup>[6]</sup> The role of LA function as a biomarker is increasingly being evaluated, both alone and in conjunction with the LA dimension. Strain parameters, which are less dependent on the load than the traditional parameters of LA structure and function, are becoming increasingly important.<sup>[7]</sup>

In this study, we aimed to reveal the relationship between the HR of patients with hypertension with preserved ejection fraction (EF), who are at risk of adverse CV events, and subclinical LV dysfunction and LA function with strain, which is a sensitive method for demonstrating subclinical dysfunction. We believe that determining the safest target HR in this risky patient group will contribute to preventing adverse CV events.

## MATERIALS AND METHODS

### Participants and Data

This single-center, prospective, observational (case-control) study. A total of 325 patients who were admitted to the

cardiology outpatient department of our hospital with a diagnosis of hypertension between January 2019 and February 2019 were included in the study. We planned to invite patients for echocardiography evaluation between April 15, 2022, and May 15, 2022. Informed consent was obtained from all patients. The study design was approved by the University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital's Ethics Committee in accordance with good clinical practice, and the study was conducted in accordance with the Declaration of Helsinki (decision no.: 2022/26, date: 11.04.2022).

The exclusion criteria of our study; previously known CVD history (coronary artery disease, peripheral artery disease, arrhythmia, moderate and advanced valvular disease), clinically diagnosed heart dysfunction (EF <50%), oncology disease, advanced kidney, and liver failure. Patients were analyzed according to the exclusion criteria. One hundred fifty-three patients who met all the criteria were included in the study, and the demographic data of these patients were recorded.

The body mass index (BMI) is defined as the body mass divided by the square of the body height and is expressed in units of kg/m<sup>2</sup>. Smoking was defined as "current smokers" and "non-smokers". Drugs used by patients receiving hypertension treatment were determined by categorizing them into groups. Patients with glucose levels of 126 mg/dL or above and who were on medication for diabetes mellitus (DM) were classified as diabetic. Patients with total cholesterol levels of 200 mg/dL or higher and who were on medication for hypercholesterolemia were classified as hypercholesterolemic patients.

### Laboratory and Echocardiographic Evaluations

Blood tests were performed using venous blood. As routine tests in the cardiology outpatient department; complete blood count (BC-5800 automatic hematology analyzer, Mindray Medical electronics Co. Shenzhen, China), fasting blood glucose level, kidney function test, lipid panel, and C-reactive protein (CRP) (AU680 Clinical Chemistry Analyzer System; Beckman Colter K.K.) were assessed. The glomerular filtration rate was calculated using the Cockcroft-Gault formula. Total cholesterol, low-density-lipoprotein, high-density-lipoprotein, and triglyceride levels were studied as lipid panels.

Echocardiographic studies, including two-dimensional, M-mode, pulsed Doppler, and pulsed tissue Doppler imaging (TDI) examinations, were performed using an echocardiography machine (VIVID S-5 General Electric Medical System Vingmed Ultrasound AS, Horten, Norway) equipped with a 3.6-MHz transducer and TDI. Parasternal and apical (standard 2- and 4-chamber images were taken with a 5.1-MHz sector transducer. LVEF was calculated using Simpson's method. The LV end-diastolic septal and posterior wall thicknesses

were calculated using the M-mode in the parasternal long-axis view. Early and late mitral filling flow were recorded by Doppler echocardiography. The systolic, early diastolic, and late diastolic tissue velocity waves obtained from the annulus were recorded by TDI. The isovolumetric relaxation time and E-wave deceleration time were also measured by Doppler echocardiography.

LA volumes were calculated using the formula of  $0.85 \times (A1 \times A2 / L)$ , where A1 is the planimeter LA area in the apical 4-chamber view, A2 is the planimeter LA area in the apical 2-chamber view, and L is the LA long-axis length determined as the distance of the perpendicular line measured from the middle of the plane of the mitral annulus to the superior aspect of the LA. With measurements taken at the end of ventricular systole, just before mitral valve opening, LA maximum volume; at the end of ventricular diastole when the mitral valve was closed, the minimum LA volume was calculated. Using these parameters, the LA emptying volume ( $LAV_{max} - LAV_{min}$ ), LA emptying fraction  $[(LAV_{max} - LAV_{min}) / LAV_{max}]$ , and LA expansion index  $[(LAV_{max} - LAV_{min}) / LAV_{min}]$  were calculated.

Transthoracic images were processed to assess left atrial and ventricular deformation through speckle-tracking imaging using 2D strain software (EchoPAC 108.1.12, General Electric Medical Systems, Horten, Norway, featuring software for speckle-tracking of the left ventricle) by two cardiologists who were blinded. LA and LV endocardial boundaries were selected with automatic contour tracking and optimized using manual adjustment as needed. LV-GLS analysis was calculated by taking apical 4-chamber, apical 3-chamber, and apical 2-chamber images. LA-GLS analysis was calculated using apical 4 and apical 2 chamber images. The strain and strain rates were calculated and recorded separately during ventricular systole, early peak diastole, and atrial systole.

Strain echocardiography parameters were named as follows;

LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, LASct: Strain during contraction phase, pLASRr: Peak strain rate during reservoir phase, pLASRcd: Peak strain rate during conduit phase, pLASRct: Peak strain rate during contraction phase, GLSLV: Left ventricular global longitudinal strain rate.

### Heart Rate and Blood Pressure Measurements

In general, guidelines recommend a HR below 70 beats/min for patients with heart failure and coronary artery disease. For this reason, we used 70 beats/min as the cut-off value for the study. Rest electrocardiography (ECG) was performed on the patients in the supine position. ECG parameters were evaluated using a 0.01 mm graduated ruler. The mean HR was calculated by measuring 3 different RR intervals. The resting HR was set at 70

beats/min. People with a resting HR above 70 beats/min were categorized as group 2 (n=89), and people with a resting HR of 70 beats/min and below were categorized as group 1 (n=64). Blood pressure measurements were obtained separately with an office and 24-hour blood pressure holter. A 24-hour ambulatory blood pressure monitoring was performed using an Agilis-CDABPM (ELA Medical, France, 2002) device, a non-invasive ambulatory blood pressure monitoring instrument. Blood pressure was measured at 15 minute intervals during the day and at 30 minute intervals during the night. Among all the readings,  $\geq 80\%$  was considered valid.

### Statistical Analysis

SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnov and homogeneity of variance tests were performed to examine the normal distribution of the data. The independent samples t-test was used for a two-group comparison of normally distributed variables, and variables were expressed as mean standard deviation. The Mann-Whitney U test was used for two-group comparisons of variables that did not show normal distribution, and variables were expressed as median, minimum, and maximum values. Categorical variables were compared using the chi-square test, and the number was presented as a percentage. All variables were evaluated by univariate regression analysis. Independent variables that were statistically significant in the univariate analysis were carried out in the multivariate analysis. The predictors were determined using a multivariate logistic regression test.  $P < 0.05$  was considered statistically significant.

## RESULTS

One hundred fifty-three patients were included in the study. Patients with a resting HR of 70 beats/min and below were named group 1 (n=64). Patients with a resting HR above 70 beats/min were named group 2 (n=89). Average age is 72.8 years. The demographic characteristics of the individuals included in the study, drug treatments they used, blood pressure monitoring, and blood parameters are presented in Table 1. A significant difference was detected between the two groups in age ( $P < 0.001$ ), DM ( $P = 0.034$ ), mean diastolic blood pressure (DBP) ( $P = 0.004$ ), beta-blocker (BB) use ( $P = 0.036$ ), oral antidiabetic use ( $P = 0.039$ ), and statin use ( $P = 0.004$ ). There was no statistical difference between the BMI indexes of the patients in both groups. However, the average BMI of the patients in both groups was  $>30$ ; thus, they were determined as preobese and 1<sup>st</sup> degree obese. There was no statistical difference in the hemoglobin, CRP, triglyceride, high-density lipoprotein, low-density lipoprotein (LDL), total cholesterol, estimated glomerular filtration rate, creatinine, fasting blood sugar, insulin, oral hypoglycemic agents, diuretics, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor,

angiotensin II receptor blockers, use, average office systolic blood pressure (SBP), office DBP, smoking, hyperlipidemia, and sex. Routine echocardiographic data of the patients are shown in Table 2, and strain echocardiographic data are given in Table 3. Evaluation of echocardiographic data showed that LAV<sub>max</sub> (60.8±15.5 mL vs. 52.9±16.3 mL *P* = 0.007), LAV<sub>min</sub> (28.8±9.5 mL vs. 22.6±7.9 mL *P* < 0.001), left atrium empty fraction (LAEF) (52.8±8.5% vs. 56.1±8.5, *P* = 0.035), left atrium expansion index (LAEI) (1.19±0.44 vs. 1.36±0.47, *P* = 0.044), pLASRcd (-1.3±0.38 vs. -1.5±0.61, *P* = 0.031) were significantly different between group 1 and group 2, respectively. There was no statistical difference between other parameters.

In the univariable regression analysis, age (*P* < 0.001), DM (0.049), using BB (0.049), using statin (*P* = 0.005), mean diastolic blood pressure (*P* = 0.005), LAV<sub>max</sub> (*P* = 0.009), LAV<sub>min</sub>

(*P* = 0.001), *S'* (*P* = 0.018), LAEF (*P* = 0.038), LAEI (*P* = 0.048), and pLASRcd (*P* = 0.04) were associated with a higher resting HR. In the multivariable regression analysis, BB (OR: 0.291, 95% CI 0.105-0.810, *P* = 0.018), mean diastolic blood pressure (OR: 1.054, 95% CI 1.009-1.101, *P* = 0.018), LAV<sub>min</sub> (OR: 0.870, 95% CI 0.809-0.938, *P* < 0.001), Sm (OR: 10.6, 95% CI 1.1-104, *P* = 0.041), LAEI (OR: 0.870, 95% CI 0.809-0.930, *P* = 0.033) were determined as independent predictors of high resting HR. Data are presented in Table 4.

## DISCUSSION

As a result of this study, we found that, in hypertensive patients with preserved LV function, LAV<sub>min</sub>, LAEI, BB use, mean diastolic blood pressure, and LV-*S'* were associated with HR, independent of other factors.

**Table 1: Demographics and laboratory data**

Variables	Group 1 (n=64)	Group 2 (n=89)	P-value
Heart rate (beats/min)	64.2±4.5	79.1±6.8	<0.001
Age (years)	57.06±9.4	51.1±9.2	<0.001
Sex (male, %)	29 (45.3)	40 (44.9)	0.547
BMI (kg/m <sup>2</sup> )	31.3±4.6	32.6±4.9	0.121
Diabetes mellitus (%)	44 (68.8)	47 (52.8)	0.034
Hyperlipidemia (%)	47 (73.4)	54 (62.1)	0.098
Smoke (%)	9 (14.1)	21 (24.1)	0.091
Office SBP (mmHg)	152.1±13.2	149.9±16.6	0.379
Office DBP (mmHg)	92.1±9.3	94.5±11.5	0.173
Average SBP (mmHg)	140.7±15	143.4±15.5	0.313
Average DBP (mmHg)	81.5±12.5	87.9±13.2	0.004
Beta blocker (%)	24 (37.5)	20 (22.7)	0.036
ACEI (%)	25 (39.7)	31 (35.2)	0.348
ARB (%)	24 (37.5)	29 (33)	0.341
Diuretic (%)	27 (42.2)	31 (35.2)	0.241
Calcium channel blockers (%)	20 (31.2)	18 (20.7)	0.099
Oral hypoglycemic agents (%)	42 (65.6)	44 (50)	0.039
Insulin (%)	2 (3.1)	10 (11.4)	0.056
Fasting blood glucose (mg/dL)	128.8±50.2	129.6±54.4	0.928
Statin (%)	26 (40.6)	17 (19.3)	0.004
Creatinine (mg/dL)	0.8±0.16	0.78±0.17	0.464
eGFR	85.6±19	88.3±14.4	0.489
Total cholesterol (mg/dL)	197.1±44.2	210±41.1	0.055
LDL-C (mg/dL)	128.3±35	136±34	0.144
HDL-C (mg/dL)	45.9±9.6	47.2±12.9	0.501
Triglyceride (mg/dL)	170.6±93	169.4±83	0.934
C-reactive protein (mg/dL)	0.25 (0.11-0.47)	0.32 (0.15-0.60)	0.127
Hemoglobin (mg/dL)	13.5±1.2	13.8±1.5	0.225

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blockers, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol

Cardiac remodeling in hypertension involves an imbalance in the production of collagen types 1 and 3, which carry the main stress in the extracellular matrix.<sup>[8]</sup> Increased stress, particularly in the subendocardial region causes heterogeneous myocardial fibrosis to form and enlarge. This irregular collagen production and myocardial fibrosis are associated with decreased GLS and cause early deterioration of systolic function in hypertensive patients.<sup>[9]</sup> Hypertension is also associated with morphological and functional abnormalities in LA. LA size increase and tissue Doppler LA strain fluctuations are common findings in strain imaging in hypertensive patients.<sup>[10]</sup>

In the literature, HR was associated with survival in both healthy individuals and individuals with different underlying CVDs. A high HR can cause poor outcomes by affecting the

CV system in many ways (ventricular workload, myocardial oxygen consumption, endothelial stress, increase in aortic/arterial stiffness, and decrease in myocardial oxygen delivery). Therefore, treatment approaches aim to decrease the HR and increase survival.<sup>[11]</sup>

Sardana et al.<sup>[12]</sup> showed in their study that BB use among hypertensive individuals without heart failure was significantly associated with deterioration in LA reservoir, conduit, and contraction function, which is consistent with the findings of the present study. However, the negative effects of high diastolic blood pressure and DM on LA strain parameters are known.<sup>[13]</sup> In our study, BB use and DM incidence were higher in group 1; diastolic blood pressure elevation was higher in group 2. Therefore, it cannot be clearly said that the data we obtained

**Table 2: General echocardiography data**

Variable	Group 1 (n=64)	Group 2 (n=89)	P-value
LVEF (%)	60.4±7.1	61.7±5.9	0.223
IVS (mm)	12.1±1.7	11.8±2	0.378
PW (mm)	11.4±1.6	11.1±1.8	0.196
LAV <sub>max</sub> (mL)	60.8±15.5	52.9±16.3	0.007
LAV <sub>min</sub> (mL)	28.8±9.5	22.6±7.9	<0.001
E (cm/s)	74.9±16.2	71.9±19.2	0.323
A (cm/s)	85.2±19.7	84.9±20.1	0.933
EDT (ms)	207.8±53	197±45	0.228
S' (cm/s)	8.8±2	9.6±2.1	0.015
E' (cm/s)	10.2±3.7	10.5±5	0.640
A' (cm/s)	12±3.4	12±3.5	0.958
IVRT (ms)	66.1±24	70±26	0.336
E/A	0.9±0.29	0.88±0.27	0.366
E/E'	5.62±4.29	4.38±3.92	0.073
LAEV (mL)	31.7±9.06	28.7±8.7	0.081
LAEF (%)	52.8±8.5	56.1±8.5	0.035
LAEI	1.19±0.44	1.36±0.47	0.044

LVEF: Left ventricular ejection fraction, IVS: Interventricular septum, PW: Posterior wall, LAV: Left atrial volume, EDT: E-wave deceleration time, E': Early diastolic tissue velocity, S': Systolic tissue velocity, A': Late diastolic tissue velocity, IVRT: Isovolumic relaxation time, LAEV: Left atrium empty volume, LAEF: Left atrium empty fraction, LAEI: Left atrium expansion index

**Table 3: Strain echocardiography data**

Variable	Group 1 (n=64)	Group 2 (n=89)	P-value
LASr, %	35.1±9.9	34.9±7.4	0.972
LAScd, %	-17.1±4.7	-18.01±4.3	0.914
LASct, %	-17.9±4.7	-18.01±4.3	0.979
pLASRr	1.3±0.34	1.54±0.42	0.056
pLASRcd	-1.3±0.38	-1.5±0.61	0.031
pLASRct	-2.3±0.64	-2.43±0.55	0.315
GLSLV, %	-19.3±3	-18.2±2.7	0.071

LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, LASct: Strain during contraction phase, pLASRr: Peak strain rate during reservoir phase, pLASRcd: Peak strain rate during conduit phase, pLASRct: Peak strain rate during contraction phase, GLSLV: Left ventricul global longitudinal strain



**Table 4: Multivariate regression analysis of factors predicting heart rate differences**

Variable	Univariate			Multivariate		
	OR	CI 95%	P-value	OR	CI 95%	P-value
Age (years)	0.939	0.898-0.969	<0.001			
Diabetes mellitus	0.509	0.260-0.997	0.049			
Beta blocker	0.490	0.241-0.997	0.049	0.291	0.105-0.810	0.018
OHA	0.524	0.270-1.017	0.056			
Statin	0.350	0.169-0.724	0.005			
Average DBP	1.040	1.012-1.069	0.005	1.054	1.009-1.101	0.018
LAV <sub>max</sub>	0.970	0.949-0.992	0.009			
LAV <sub>min</sub>	0.922	0.881-0.966	0.001	0.870	0.809-0.938	<0.001
S'	7.496	1.417-39.65	0.018	10.6	1.1-104	0.041
LAEF	1.050	1.003-1.099	0.038			
LAEI	2.399	1.008-5.712	0.048	0.870	0.809-0.930	0.033
pLASRcd	3.113	1.056-9.179	0.040			
Costant			0.030	7.905		

OHA: Oral hypoglycemic agents, DBP: Diastolic blood pressure, LAV: Left atrial volume, S': Systolic tissue velocity, LAEF: Left atrial emptying fraction, LAEI: Left atrial expansion index, pLASRcd: Peak strain rate during the conduit phase, OR: Odds ratio, CI: Confidence interval

are related to a single variable. However, the use of BBs plays a significant role in positively affecting strain parameters by reducing HR.

When the baseline characteristics of the groups were examined in our study, it is noteworthy that DM and age parameters, which are the most important risk factors in determining CV risk score, were higher in the group with low HRs. DM and age are the most important risk factors in many CV risk-scoring systems. In a meta-analysis by Al Saikhan et al.<sup>[14]</sup>, GLS was defined as a prognostic marker for CV mortality and morbidity, and its worsening was defined as a conventional risk factor. Risk factors affecting GLS, such as aging, hypertension, and CVD, are common features of longitudinal population-based elderly samples. Even if the LVEF is normal in elderly patients, GLS changes with the effect of these risks factors.<sup>[15,16]</sup> In the study by Enomoto et al.<sup>[17]</sup>, there was no difference between the age and HR groups. Strain values were found to be better in the control group without DM and hypertension than in the group with hypertension only. Although the strain value of the group with only DM tended to be better than that of the group with both DM and hypertension, this difference did not show statistical significance.<sup>[17]</sup> In a study by Kraigher-Krainer et al.<sup>[18]</sup>, high HR was found to negatively affect GLS. In our study, parallel to the aforementioned result, despite DM and advanced age, which adversely affect GLS, the GLS value in the group with a low HR tended to be better than that in the group with a high HR ( $-19.3 \pm 3$  vs.  $-18.2 \pm 2.7$   $P = 0.07$ ). The reason for this may be that the BB group was chosen as an additional drug in the possible long-term follow-up of hypertension (37.5% vs. 22.7%  $P = 0.036$ ). When evaluated together with the results of our study, HR should also be considered when reaching the

target blood pressure for the treatment of hypertension, with or without DM. For this purpose, the BB and non-dihydropyridine CCB groups should also be considered in our minds, especially in drug selection in patients with advancing age.

The LA plays an important role in the regulation of LV filling and contributes to one-third of the cardiac output.<sup>[19]</sup> LA has also been identified as an important biomarker of CVD-associated adverse outcomes.<sup>[6,20]</sup> Although LA size was previously used as a biomarker, LA function is increasingly being evaluated along with it.<sup>[21]</sup> Strain parameters are relatively independent of coupling effects and are less load dependent than conventional parameters of the LA function.<sup>[7]</sup> Poor LA strain is associated with advanced age, high frequency of atrial fibrillation, left ventricle hypertrophy, poor left and right ventricular systolic function, and poor left and right ventricular diastolic function.<sup>[22]</sup> However, the relationship between HR and LA strain parameters was not directly demonstrated. In our study, the reason for the poor left atrial size and strain values in the group with low HR may be explained by the direct effects of advanced age and DM, as well as the direct effects of its negative effects on diastolic dysfunction. There are many studies supporting this situation. There are only few studies showing the relationship between age and LA strain and strain rate. In the study of Boyd et al.<sup>[23]</sup>, which had results consistent with our study, it has been shown that LA systolic strain and strain rates decrease significantly with aging. DM affects LA enlargement and dysfunction independently of other risk factors. In many studies, it has been shown that LA reservoir and conduit function is impaired in diabetic patients.<sup>[24]</sup> In the study by Kadappu et al.<sup>[25]</sup>, 73 patients with type 2 DM

were compared with the control group according to age and gender. In the diabetes group, hypertension and the LA volume index were increased independent of the effect of diastolic dysfunction. LA global strain value was found to be decreased in the diabetes group compared with the control group, and this effect did not change in the increased diastolic dysfunction group.<sup>[25]</sup> These findings were also confirmed by Muranaka et al.<sup>[26]</sup> in which strain evaluation of LV and LA functions in patients with diabetes was performed. In our study, results consistent with the literature were obtained, and the pLASRcd value in the first group was found to be lower than that in the second group ( $-1.3 \pm 0.38$  vs.  $-1.5 \pm 0.61$   $P = 0.031$ ), whereas the pLASRr value tended to be lower in the first group ( $-1.3 \pm 0.34$  vs.  $-1.5 \pm 0.42$   $P = 0.056$ ). In our study, it was observed that low HR cannot prevent the negative changes in LA structure and function that develop with the effects of DM and age.

LV diastolic dysfunction occurs as a result of hypertension. Changes in the size and function of the LA are associated with the severity of LV diastolic dysfunction.<sup>[27]</sup> In addition to hypertension, obesity, female sex, DM, and age factors also affect LV diastolic dysfunction. In our study, the LA size function and LV diastolic status were consistent with the literature. Diastolic parameters in the first group tended to be worse than those in the second group (E/Em,  $5.62 \pm 4.29$  vs.  $4.38 \pm 3.92$ ,  $P = 0.073$ ), LA dimensions increased ( $LAV_{max}$ ,  $60.8 \pm 15.5$  vs.  $52.9 \pm 16.3$ ,  $P = 0.007$ ,  $LAV_{min}$ ,  $28.8 \pm 9.5$  vs.  $22.6 \pm 7.9$ ,  $P < 0.001$ ) and worsening of functions was detected (LAEF,  $52.8 \pm 8.5$  vs.  $56.1 \pm 8.5$ ,  $P = 0.035$ , LAEI,  $1.19 \pm 0.44$  vs.  $1.36 \pm 0.47$ ,  $P = 0.044$ ). In the study of Salako et al.<sup>[28]</sup>, it was shown that there was no improvement in cardiac structural changes despite antihypertensive treatment. Similarly, a study by Chen et al.<sup>[27]</sup> showed that LA dimensions did not regress to normal levels by keeping blood pressure within normal limits with anti-hypertensive treatment. In our study, it was observed that the positive effect of HR on LV GLS was not apparent in LA strain parameters (pLASRr,  $1.3 \pm 0.34$  vs.  $1.54 \pm 0.42$ ,  $P = 0.056$ , pLASRcd,  $-1.3 \pm 0.38$  vs.  $-1.5 \pm 0.61$ ,  $P = 0.031$ , GLSLV,  $-19.3 \pm 3$  vs.  $-18.2 \pm 2.7$ ,  $P = 0.071$ ). Therefore, with opportunistic blood pressure measurements and detection of hypertension at an early stage, adverse events can be prevented or delayed with the use of different targets, such as GLS.

Many studies have shown the effects of HR control and strain values on mortality and morbidity.<sup>[29]</sup> Here, we aimed to evaluate the relationship between HR control and strain. Our study did not include mortality or morbidity data.

Statin use and presence of DM were associated with a lower HR in the univariate analysis, but were not found to be independent predictive factors in the multivariate analysis. The association between statin use and DM and low HR may be related to BB use in group 1 rather than the effect of statin use and DM itself. Therefore, statin use and DM can be considered confounding

factors. The reason why statin use was higher in group 1 was that the LDL level required to start statin medication in patients with DM was lower.

Some studies have shown that patients with isolated systolic hypertension are less sensitive to h HR-lowering drugs. There are even studies showing that BBs, which are drugs that reduce HR, increase SBP.<sup>[30]</sup>

Beta blocker use was significantly more frequent in group 1 than in group 2. However, the use of all antihypertensive drugs was proportionally higher in group 1. Why diastolic blood pressure in group 1 is lower than in group 2. This may be due to the collective effect of all these medications. Although there was a statistical difference in diastolic blood pressure between the 2 groups, it was not thought to be a parameter that would affect the main purpose of our study since it was in the normal and high-normal categories.

In the multivariate analysis, although there was no difference between the groups in LA strain values; LAEI and  $LAV_{min}$ , which showed structural and functional changes, differed in favor of the group with high HR. This condition, as mentioned before, was caused by poor LV diastolic function caused by DM and aging, as well as their independent negative effects. In particular, in the early period, aiming to control the HR along with the blood pressure target may have a positive effect on the functional and structural changes in LA. Preventing or reversing structural and functional deterioration in LA can also prevent atrial arrhythmia that may occur in the future and possible cerebrovascular stroke.

### Study Limitations

The single-center nature of the study and the limited number of patients are our primary limitations. The other limitations are the lack of randomization and long-term follow-up. More reliable results can be obtained using multicenter studies with larger patient populations.

### CONCLUSION

There are no known medical treatments that affect mortality in heart failure patients with preserved LV systolic function. Some drugs are partially effective against morbidity. As observed in our patient groups with preserved LV systolic function, it is necessary to reveal systolic and diastolic parameters, the status of LA structure, and functions to determine the appropriate intervention. It was observed that diastolic dysfunction cannot be corrected with HR control, and LA structure function cannot be positively affected by HR control. However, it is important that the LV GLS value, which affects mortality and morbidity, improves with HR control. HR control is an important goal in hypertension patients with preserved LV systolic function.

With the positive effect of HR control on GLS, mortality and morbidity can also be improved.

## Ethics

**Ethics Committee Approval:** The study design was approved by the University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital's Ethics Committee in accordance with good clinical practice, and the study was conducted in accordance with the Declaration of Helsinki (decision no.: 2022/26, date: 11.04.2022).

**Informed Consent:** Informed consent was obtained from all patients.

## Authorship Contributions

Surgical and Medical Practices: M.G.Y., A.Ö., F.K., G.U., H.K., E.K., Concept: M.G.Y., E.E., E.K., Design: M.G.Y., E.E., E.K., Data Collection or Processing: M.G.Y., A.Ö., F.K., G.U., H.K., Analysis or Interpretation: T.T., E.K., M.Ç., Literature Search: M.G.Y., E.E., K.H., Writing: M.G.Y., E.E., O.T., E.K.

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